Norwegian University of Life Sciences
Faculty of Veterinary Medicine
Department of Companion Animal Clinical Sciences

Philosophiae Doctor (PhD)
Thesis 2019:78

Epidemiology of orthopaedic conditions in companion animals with emphasis on cranial cruciate ligament disease

Epidemiologiske aspekt ved ortopediske smådyrsjukdomar med fokus på korsbandskadar

Gudrun Seeberg Boge

Epidemiology of orthopaedic conditions in companion animals with emphasis on cranial cruciate ligament disease

Epidemiologiske aspekt ved ortopediske smådyrsjukdomar med fokus på korsbandskadar

Philosophiae Doctor (PhD) Thesis

Gudrun Seeberg Boge

Norwegian University of Life Sciences
Faculty of Veterinary Medicine
Department of Companion Animal Clinical Sciences

Adamstuen 2019

Thesis number 2019:78
ISSN 1894-6402
ISBN 978-82-575-1638-3

“The greater the number of surgical techniques available for treatment of a particular orthopaedic disease, the more one should question their effect.” Lars Lønaas

Table of Contents

Acknowledgements

The work of this PhD-project was carried out at the Department of Companion Animal Clinical Sciences, Faculty of Veterinary Science, at the Norwegian University of Life Sciences (NMBU) in cooperation with the Department of Clinical Sciences at the Swedish University of Agricultural Science (SLU). I would like to thank everyone who contributed in some way to this thesis:

- My supervisors for their help and support:
    - Annika Bergström, my dear main supervisor; always encouraging, supportive and able to put the brakes on with her calm Swedish politeness whenever necessary. Thank you for trusting me with this project. Although working full time in Stockholm and Uppsala, you were always there when I needed you, and you even managed to make orthopaedics fun!
    - Elena Regine Moldal, my always-enthusiastic and bright co-supervisor; the reason behind my engagement in this project, always standing up for me and always finding time. Thank you for all the inspiring discussions, swift replies and for ensuring an appropriate level of not-so-scientific procrastination. Together we have introduced Snapchat as an arena for manuscript feedback.
    - Eystein Skjerve, my steady, and a little bit crazy, other co-supervisor; at all times encouraging and supportive. Your door has always been open, the enthusiasm never-ending. Thank you for introducing me to the endless possibilities of epidemiology while playing jokes along the way.
- My Swedish co-authors at SLU, especially the other half of this two-piece cruciate puzzle and PhD-partner in crime, Karolina Engdahl. Working with you has been a sincere joy! I await the next chapter with excitement.
- A special thanks to Ingrid Toftaker for valuable inputs and thoughts in the final stage of manuscript preparation.
- Former Head of Department, Anna Eggertsdottir; for believing in me at a time when I didn’t - you found a solution and reopened the academic door that I though was closed for good.

- The motley, joyful crew at "EPI-senteret" during the past year; Adis, Anki, David, Erik, Eystein, Ingrid, Marit and Rolf. Thank you for taking on the role as couple therapists every day during lunch, I promise to pay you back in ice cream.
- The nurses and veterinarians at the NMBU Small animal clinic: This thesis is practically built upon your everyday enthusiastic and loving patient care.
- All my great colleagues at the internal medicine service; a special thanks for taking me under your supportive wings during vet. school and afterwards, from my first clinical experience as a very pregnant newly graduate and to this day. It has meant a lot!
- The final year veterinary students, Constance Bakke and Isabelle Brown at NMBU and Caroline Mason, Karin Rantén and Yusi Fang at SLU. Without your help the completion of my PhD would have been a distant dream, since I would likely still be plotting data into Excel.
- My dear colleagues, office-mates and friends at "Quisten": from the beginning with Linda, Heidi and Kristin PA, to Kristin H., Malin, Josefin and Annelin. Thank you for all the giggles, interruptions and support, and for sidetracking me to the point where I had to move office to be able to complete this work.
- Mr. Lee & Ms. Littlegood for ensuring essential nutritional support and keeping me going. Always there when I needed you the most.
- All of my friends for ensuring mental soundness: Lille-Marte, must our countless far-to-long lunches never end; Store-Marte, all your "Hakuna Matatas" are invaluable; Ola, please continue keeping fun so fun; Kristin, very much looking forward to our next wine-hiking; Malin and Sigrun, I miss you and wish you were here; Julie, so glad to have you back.
- Finally, I am indebted to my family for their encouragement and practical support: my mother and father for being such caring parents and grandparents; my kids Sondre and Johanna for their love and patience with a (sometimes) tired and stressed mom, and; my dearest, kindest Sveinung for your enthusiasm and everlasting support.

Adamstuen, August 2019

Gudrun Seeberg Boge

List of papers

Paper I

Boge, G.S., Moldal, E.R., Dimopoulou, M., Skjerve, E., Bergström, A., 2019. Breed susceptibility for common surgically treated orthopaedic diseases in 12 dog breeds. Acta Vet. Scand. 61, 19. http://dx.doi.org/10.1186/s13028-019-0454-4

Paper II

Boge, G.S., Engdahl, K., Moldal, E.R., Bergström, A., 2019. Cranial cruciate ligament disease in cats: an epidemiological retrospective study of 50 cats (2011–2016). J. Feline Med. Surg. 0, 1098612X19837436. http://dx.doi.org/10.1177/1098612x19837436

Paper III

Engdahl K., Boge G.S., Bergström A., Emanuelson U., Hanson J., Höglund O., Moldal E.R., Skjerve E., Krontveit R., 2019. The effect of treatment strategy on long-term outcome in dogs with cranial cruciate ligament disease, an epidemiological study of 333 dogs. Submitted Vet. Comp. Orthop. Traumatol. April 2019, under review

Selected abbreviations

CrCL	Cranial cruciate ligament
CdCL	Caudal cruciate ligament
CCLD	Cranial cruciate ligament disease
ED	Elbow dysplasia
ES	Extra-articular stabilisation
LFS	Lateral fabellotibial suture
MMP	Modified Maquet procedure
MPL	Medial patellar luxation
OA	Osteoarthritis
OC	Osteochondrosis
TPA	Tibial plateau angle
TPLO	Tibial plateau leveling osteotomy
TTA	Tibial tuberosity advancement

Summary

Lameness caused by orthopaedic disease is an important reason for owners to take their dog or cat to the veterinarian. Many diagnoses, such as cranial cruciate ligament disease (CCLD), considered the most common cause of hindlimb lameness in dogs, usually require expensive and complicated surgical interventions. Information regarding risk factors and treatment methods influencing disease outcome is consequently relevant for both pet owners and veterinarians. Although various studies had assessed the pathophysiology, epidemiology and treatment outcome of CCLD in dogs when this thesis was initiated, knowledge about inherent risk factors for development of the disease was limited. Moreover, there was a paucity of information regarding breed susceptibility for orthopaedic diseases in Norway and Sweden, and the scientific literature concerning CCLD in cats was sparse.

The overall aim of this thesis was to expand the understanding of orthopaedic diseases in dogs and cats, in particular related to breed susceptibility and risk factors with a potential influence on the prognosis of CCLD. To reach this aim, retrospective data from medical records at two university animal hospitals, the Norwegian University of Life Sciences and the Swedish University of Agricultural Science, were utilised, in addition to owner questionnaires and data from the national pet ID-registers.

Firstly, a case-control study was performed to estimate breed susceptibility for common surgically treated orthopaedic conditions in popular Norwegian and Swedish dog breeds. The Labrador retriever, Rottweiler, German shepherd dog and Staffordshire bull terrier were identified to have increased risk of elbow dysplasia compared to mixed breed dogs. Susceptibility for CCLD was found for the Rottweiler, but not the Labrador retriever, although this breed has commonly been regarded as predisposed. The Chihuahua was the only breed with increased risk of medial patellar luxation.

In the second study, characteristics and long-term outcome of CCLD were described in a cohort of 50 cats followed for a median of 41 months. According to a standardised *quality of life* questionnaire, the conservatively treated cats experienced less chronic pain at long-

term follow-up compared to cats surgically treated with the lateral fabellotibial suture technique.

Finally, survival analysis was used to assess long-term outcome after CCLD treatment in dogs. Cranial cruciate ligament disease was a contributing cause to the decision of euthanasia in 18.3% of the 333 dogs included. Both treatment strategy, age, weight and orthopaedic comorbidities were identified as risk factors for CCLD-related euthanasia in the final multivariable Cox proportional hazard model. Dogs surgically treated by osteotomy techniques had a lower hazard of CCLD-related euthanasia compared to dogs receiving conservative treatment.

Altogether, this thesis elucidates central aspects of orthopaedic diseases in dogs and cats. However, it is important to acknowledge the uncertainty of the results; causality cannot be inferred with complete certainty. Such ambiguity is typical for retrospective studies, emphasising the urgent need for well-designed prospective studies within the field of veterinary orthopaedic research.

Samandrag (Summary in Norwegian)

Haltheit grunna ortopediske sjukdommar er ein viktig årsak til at hunde- og katteeigarar søkjer veterinærhjelp. Skadar på det fremre korsbandet i kneet, såkalla korsbandskade, vert rekna som den vanlegaste årsaka til bakbeinshaltheit hos hundar. For korsbandskadar og mange andre ortopediske sjukdommar er det ofte naudsynt med avansert og kostbar kirurgisk behandling. Informasjon om samanhengen mellom risikofaktorar, behandlingsalternativ og utfall er følgjeleg verdifull for både veterinærar og dyreeigarar. Då dette doktorgradsprosjektet vart igangsett hadde mange studiar undersøkt faktorar kring patofysiologi, epidemiologi og behandlingsresultat hos hundar med korsbandskadar. Likevel var det sparsamt med tilgjengeleg informasjon knyta til medfødde risikofaktorar og sjukdomsutvikling. Ein visste dessutan lite om rasepredisposisjon for ortopediske sjukdommar bland norske og svenske hundar, og det var mangel på kunnskap om korsbandskadar hos katt.

Hovudmålet med denne avhandlinga var bidra til å auke kunnskapen om ortopediske sjukdommar hos hundar og kattar, då særleg spørsmål kring rasepredisposisjon og risikofaktorar med potensiell påverknad på prognose etter korsbandskadar. For å nå dette målet nytta vi retrospektive journaldata frå smådyrsjukehusa ved Noregs miljø- og biovitskaplege universitet og Sveriges lantbruksuniversitet, i tillegg til spørjeskjema til eigarar og data frå dei nasjonale ID-registera for kjæledyr.

Ein kasus-kontrollstudie vart utførd for å estimere rasedisposisjonar for vanlege kirurgisk behandla ortopediske sjukdommar blant populære norske og svenske hunderasar. Vi fann ein auka risiko for olbogeledd-dysplasi hos labrador retriever, rottweiler, schæfer og Staffordshire bull terrier samanlikna med blandingshundar. Analysane viste også at rottweiler var predisponert for korsbandskade, men vi fann ingen auka risiko hos labrador retriever, til trass for at rasen ofte vert omtala som predisponert. Chihuahua var den einaste rasen kor ein auka risiko for medial patellaluksasjon vart identifisert.

Signalement, sjukdomstrekk og langtidsutfall hos 50 kattar med korsbandskade vart skildra i ein kohortstudie med ei gjennomsnittleg oppfølgingstid på 41 månader. Ved oppfølginga

vart eit standardisert spørjeskjema om livskvalitet hos kattane sendt ut til eigarane. Resultata indikerte at kattane som hadde fått konservativ behandling hadde mindre teikn på kronisk smerte enn kattane som hadde blitt kirurgisk behandla med ein lateral fabellotibial suturteknikk.

I den siste studien vart overlevingsanalyse nytta for å vurdere langtidsutfallet etter behandling av korsbandskade hos hundar. Av dei 333 inkluderte hundane var korsbandskade ein medverkande årsak til avliving i 18,3 % av tilfella. Både behandlingsmetode, alder, vekt og andre samtidige ortopediske sjukdommar vart identifiserte som risikofaktorar i den endelege multivariable Cox proporsjonal hasard regresjonsmodellen. Det var også ein lågare hasard for korsbandsrelatert avliving hos hundar som var kirurgisk behandla med ein osteotomiteknikk samanlikna med dei som berre hadde fått konservativ behandling.

Arbeidet i denne avhandlinga kastar lys over sentrale sider ved ortopediske sjukdommar hos hundar og kattar. Det er likevel viktig å vere klar over at det er usikkerheit kring resultata som kompliserer tolkinga av årsaksamanhengane. Slik usikkerheit er vanleg førekommande i retrospektive studiar og illustrerer at det trengs godt designa, prospektive studiar innanfor framtidig veterinærmedisinsk ortopediforsking.

Introduction

Thesis background

Orthopaedic disease can impact affected dogs and cats through life by causing pain and disability, as well as having substantial economical and emotional implications for the owners. Lameness caused by orthopaedic disease is an important reason for dog and cat owners to take their pet to the veterinarian, and many diagnoses require complicated surgical interventions. For example, cranial cruciate ligament disease (CCLD) was estimated to cost American dog owners 1.32 billion US Dollars in 2003 (Wilke et al., 2005). Considering the rapid development of veterinary care and treatment options for companion animals over the last decades, it is reasonable to assume this impact to be much higher today. In Norway, Sweden and Denmark, the disease accounts for 3-4% of the total reimbursement in dogs and 0.7-1% in cats insured in the largest Scandinavian pet insurance company, Agria (Agria Pet Insurance, 2019).

Joint diseases and traumatic fractures are the most commonly encountered orthopaedic conditions in both dogs and cats. Although studies have identified radiographically visible osteoarthritis (OA) in over 90% of cats without clinical signs of polyarthropathy (Lascelles et al., 2010), the literature concerning orthopaedic disorders in cats is generally sparse. In contrast, many peer reviewed studies concerning treatment of such diseases in dogs have been published. Compared to the number of studies providing detailed descriptions of surgical treatment techniques and biomechanical limb function, relatively little emphasis has been placed on the relationship between inherent patient-related factors and long-term functional outcome in dogs. The optimal treatment regime for common conditions such as CCLD and elbow dysplasia (ED) is still not agreed upon (Burton and Owen, 2008; Bergh et al., 2014; Vannini, 2015).

Animal welfare is a topic that engages people more than ever. With an animal welfare legislation that supersedes the EU regulations, the legal requirements in Norway and Sweden are stringent and sets a higher standard for animal welfare than most other European countries (Veissier et al., 2008). Moreover, informal policies initiated from nongovernmental organisations aid the continuing development of animal welfare measures across Europe. In joint effort with the United Kingdom (UK), Norway and Sweden tend to lead the way in matters initiated to improve animal welfare (Veissier et al., 2008). This is illustrated by issues spanning from the banning of battery cages for laying hens decades before the rest of Europe and, more recently, to the development of breed-specific breeding strategies and implementation of targeted scoring systems for prevention of breed-related problems such as the brachycephalic obstructive airway syndrome (BOAS) in dogs (NKK, 2019). Animal companionship is an integral aspect of many Norwegian and Swedish households, and the well-being of dogs and cats are of uttermost importance for most owners. The growing awareness of the impact of animal breeding strategies and management on welfare issues has led to a reduced tolerance for conditions perceived as unsatisfactory. Expanding our understanding of common orthopaedic conditions in dogs and cats can elucidate the implications of such diseases on animal health and well-being. By further development of preventive measures and treatment options, one can improve the long-term prognosis and thereby ensure better animal welfare.

The Norwegian and Swedish dog and cat population

Animal welfare is not the only matter where the northernmost parts of Europe have preceded most others regions. A Norwegian system with on-farm cattle health cards was established in the seventies and central registries for most production animals and pets followed over the next years (Olsson et al., 2001). In Norway and Sweden, comprehensive national ID-registries containing searchable information of all ID-marked pets (DyreID and DjurID, respectively) have been available for many years. ID-marking (microchipping) is mandatory for all dogs and cats holding a passport in Europe and is required for enrolment of purebred dogs into the Swedish and Norwegian kennel clubs' registers, a prerequisite for participating in activities such as dog shows. In addition, ID-marking of dogs and cats is a legal requirement in Sweden (Näringsdepartementet, 2018). According to the most recent estimates, more than 92% of the 784000 Swedish dogs are marked (SCB, 2012). Although ID-marking is not compulsory for mixed breed dogs in Norway, estimates from 2016 indicated that 84% of the approximately 520000 dogs living in Norway were marked (DyreID, 2018). Corresponding estimates for cats suggest that 660000 cats live in Norway and more than a million in Sweden. Although cats outnumber dogs in both countries, the percentage of ID-marked cats is lower (41 and 62% in Sweden and Norway, respectively) (SCB, 2012; DyreID, 2018). In total, approximately every fourth Swedish family owns a dog or cat, 13% a dog and 17% a cat (SCB, 2012). The estimated numbers for Norway are 18 and 32%, respectively (FEDIAF, 2017).

Dogs typically gain more attention, both in media, research and everyday life, than cats. Although it is still common for cats to serve a primary purpose as mouse deterrents in rural areas, today more than half of Swedish cats live mostly indoors (SCB, 2012). The population of stray cats has been estimated to be as high as 100000 in both Norway and Sweden. This contrasts the situation for dogs, as uncontrolled reproduction is not a problem in Scandinavia. The absence of stray dogs could partly explain why the neutering practice and legislation in the northernmost European countries differ from most of the world. Norway and Sweden have a custom not to neuter dogs, and most dogs are entire (Sallander et al., 2001). In Norway, neutering is regulated by the Norwegian Animal Welfare Act (2009) and is only legal when it is considered necessary due to medical reasons or animal welfare.

Data from USA, UK, Germany and Australia indicate that approximately 30-50% of dogs are mixed/cross breeds (AVMA, 2012; VDH, 2012; PDSA, 2013; AMA, 2016). Although corresponding Norwegian or Swedish estimates are absent, numbers from the national ID-registries imply a percentage of mixed breed dogs below 30%. Moreover, comparisons between the numbers of ID-marked and Norwegian kennel club (NKK) registered dogs of three brachycephalic breeds have been conducted. Although a fair share of illegal import from Eastern Europe was suspected for these breeds, 62% of all ID-marked dogs claiming to be French bulldogs were registered in NKK. The corresponding percentages for English bulldogs and pugs were 71 and 73%, respectively (Prestrud, 2019). These figures indicate that most purebred dogs are registered in the national kennel club and contrasts the situation in many other developed countries where a smaller portion of the purebred dog population have a registered pedigree (ACAC, 2010; Asher et al., 2011; Keijser et al., 2017). Unfortunately, comparable Swedish surveys have not been conducted.

The popularity of dog breeds tend to be influenced by trends much in the same way as fashion (Ghirlanda et al., 2013). Although some breeds seem to never go out of fashion, fluctuating trends result in a continuously changing breed profile of the dog population. With registration numbers going up more than 500% in Norway from 2006 to 2017, the Staffordshire bull terrier is a good example of a breed with a rapid increase in popularity. A similar, but less pronounced trend has been seen for the breed in Sweden over the same time period (NKK, 2017; SKK, 2018). Although the overall breed profile differ somewhat between the Norwegian and Swedish canine populations, registration numbers from the national kennel clubs and ID-registries reveal that regional variations are more pronounced than overall differences between the countries (Jordbruksverket, 2018; NKK, 2018). Bearing the close geographical, cultural and historical relations between the countries in mind, it seems reasonable for local demographic and geographic factors to be of greater importance than the overall country-wise difference.

Although dogs and cats typically are regarded as family members, Norwegian and Swedish dogs often serve multiple purposes; as shepherds, hunting companions, working- and sporting dogs. In a survey by Sallander et al. (2001), 16.7% of Swedish dog owners reported hunting as the primary purpose for having a dog. Moreover, dog shows, obedience and agility are highly appreciated hobbies for many Norwegian and Swedish dog owners; Swedish obedience and agility competitions had 153 400 participates in 2015, while 128 200 attended one of the more than 630 dog shows (SKK, 2015). In addition, many Scandinavian dogs perform valuable jobs in the police and military and aid people with disabilities. The importance of working dogs is also reflected in the breed profile of the dog population. The Border collie has been the most popular breed in Norway for several years and retrievers and gun dogs are among the most popular breeds in both countries (NKK, 2017; SKK, 2018). Hunting, skiing and hiking are popular recreational activities in Norway and Sweden. Thus, it is not surprising for high endurance dog breeds to be popular. However, due to lack of literature addressing the importance of sports- and working dogs across countries, no direct comparisons with the activity levels of other countries can be made.

Importance of orthopaedic diseases in dogs and cats

Diseases related to muscle, bones and/or joints were the 2nd most common group of disorders in a newly published survey of purebred dogs in the UK (Wiles et al., 2017). In general, orthopaedic diseases are considered a more important problem in dogs than in cats. Although a variety of different orthopaedic conditions are diagnosed in both species, a mid-90s survey from small animal practices in the UK reported the 10 most common diagnoses to account for as much as 75% of encountered orthopaedic cases, fractures being the most prevalent (Ness et al., 1996).

With the exception of traumatic fractures, most of the common orthopaedic diseases affect the appendicular joints. Canine orthopaedic joint diseases are often considered multifactorial in origin, with physical conformation and genetics as predisposing factors (LaFond et al., 2002; Bellumori et al., 2013). Many diseases, such as patellar luxation, canine hip dysplasia (CHD) and ED, affect dogs at a young age. Thus, they can have a life-long impact. While CHD and ED are most often diagnosed in large, fast-growing dogs (Michelsen, 2013; King, 2017), medial patellar luxation (MPL) is more common in smaller dogs (Alam et al., 2007).

To increase the animal welfare in a population, research efforts and selective breeding strategies should aim at reducing the impact of severe and commonly occurring diseases (Collins et al., 2011). Orthopaedic diseases which often lead to severe lameness, can potentially cause greater problems for a working dog trained in sports or hunting, than for a dog mainly going for shorter walks on a leash. The welfare implications of orthopaedic joint diseases could consequently be of particular importance for high endurance dogs. Already back in 1963, CHD, ED and patellar luxation were identified as conditions of concern at a British Small Animal Veterinary Association symposium on abnormalities and defects in purebred dogs (Hodgman, 1963). Although the issue of inherited diseases in dogs has been acknowledged throughout the modern history of dog breeding, the magnitude of the problem has become apparent in recent years. Specific breeding strategies such as closed stud books, use of popular sires and structural inbreeding, resulting in increased homozygosity, have been implicated in the high prevalence of inherited disorders in purebred dogs (Wayne and Ostrander, 2007; Leroy, 2011).

Some dog and cat breeds have a higher prevalence of some particular diseases than others. While feline prevalence estimates for orthopaedic diseases are rarely published, a substantial number of scientific papers have reported such estimates in dogs. Although a large number of studies have been conducted, direct comparisons of published results should be avoided due to large variations in sampling frames, eligibility criteria, data quality and geographical areas between studies. Traditionally, dogs and cats have been considered as predisposed or protected against disease by comparing the relative prevalence and odds ratio (OR), often using mixed breed dogs as a reference. A recent study from primary-care practices in the UK reported a prevalence of 1.3% for patellar luxation and identified several small-sized breeds, including the Chihuahua, the Cavalier King Charles spaniel, the French bulldog, the Jack Russel terrier, the Pomeranian and the Pug, as breeds with an increased risk of the disease compared to mixed breed dogs (O'Neill et al., 2016). The German shepherd, the Labrador retriever, the Newfoundland and the Rottweiler are well-known breeds at risk of ED, and the latter three are also commonly reported with an increased risk of CCLD (LaFond et al., 2002; Witsberger et al., 2008; Adams et al., 2011; Bellumori et al., 2013; Taylor-Brown et al., 2015). Although some breeds are consistently reported as susceptible for certain diseases, such as patellar luxation in the Chihuahua and ED and CCLD in the Rottweiler, predispositions also tend to vary between studies. For example, both an increased, same as reference level and a decreased risk of CCLD have been reported for the Golden Retriever (Whitehair et al., 1993; Duval et al., 1999; Taylor-Brown et al., 2015). Cranial cruciate ligament disease is considered the most common cause of hind-limb lameness in dogs, and prevalence estimates ranging between 0.53 and 2.55% have been described in recent years (Witsberger et al., 2008; Adams et al., 2011; Taylor-Brown et al., 2015). Although the prevalence of the disease in cats is unknown due to a lack of epidemiological studies, CCLD is regarded as a less common disease in cats than in dogs (Umphlet, 1993; Harasen, 2005; Wessely et al., 2017).

Cranial cruciate ligament disease in dogs and cats

Structure and function of the cranial cruciate ligament

The stifle joint functions as a hinge joint. Although the motion of the joint is mostly restricted to flexion and extension, some compression, rotation, angulation and cranial and caudal displacement is evident during movement (Arnoczky and Marshall, 1977; Korvick et al., 1994b). In dogs, the joint is flexed in the standing position and is never fully extended during the gait cycle (Korvick et al., 1994b). Four femorotibial ligaments provide primary

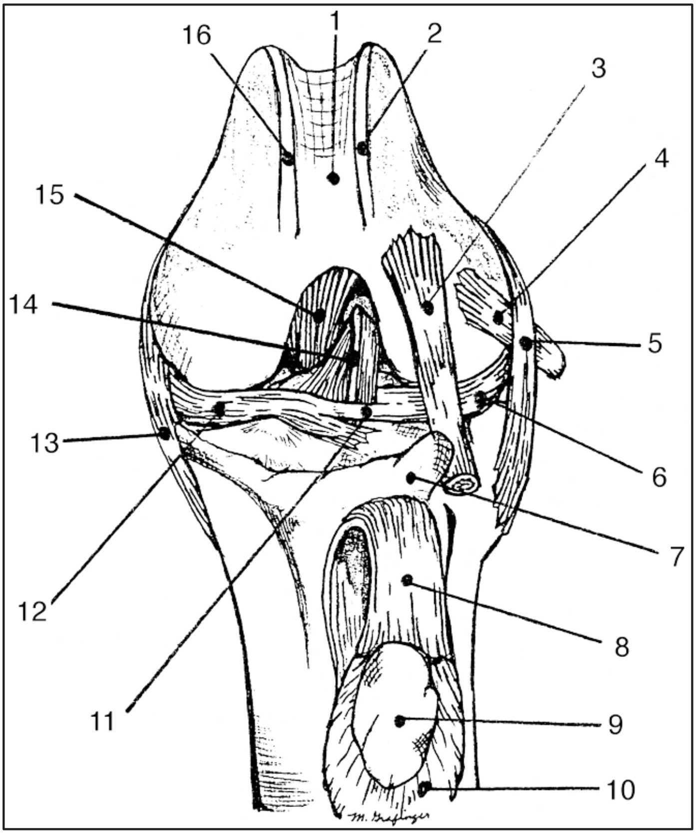


Fig. 1. Cranial view of the left stifle showing associated ligaments and structures. 1, femoral trochlea; 2, lateral ridge of femoral trochlea; 3, tendon of long digital extensor; 4, tendon of popliteus; 5, lateral collateral ligament; 6, lateral meniscus; 7, tibial tuberosity; 8, patellar ligament; 9, patella; 10, parapatellar fibrocartilage; 11, intermeniscal ligament; 12, medial meniscus; 13, medial collateral ligament; 14, cranial cruciate ligament; 15, caudal cruciate ligament; 16, medial ridge of the trochlea. Illustration and figure legend from Carpenter & Cooper (2000) with permission.

ligamentous support to the stifle: two collateral ligaments and two crossing cruciate ligaments termed cranial and caudal based on their tibial attachment (Arnoczky and Marshall, 1977). The cruciate ligaments are intra-articular but are covered by synovia and thus considered extra-synovial. They are composed of bundles of collagen fibres which are organised into fascicles and separated by connective tissue containing nerves and blood vessels (Arnoczky et al., 1979; Vasseur et al., 1985). The central core of the ligaments is relatively poorly vascularised (Vasseur et al., 1985).

While the cranial ligament is the smallest and shortest of the two cruciate ligaments in dogs (Arnoczky and Marshall, 1977), the opposite is true in cats where the cranial ligament is larger than its caudal counterpart (Umphlet, 1993). The cranial cruciate ligament (CrCL) attaches to the caudomedial aspect of the lateral femoral condyle and the caudolateral part of the intercondyloid fossa of the femur (figure 1) and runs diagonally in a cranial, medial and distal direction to insert in the cranial intercondyloid area of the tibia (Arnoczky and Marshall, 1977). It is most narrow in the mid region and fans out proximally and distally. The ligament is composed of two functional parts; the larger caudolateral band is taut in extension but loose in flexion, while the smaller craniomedial band remains under tension in both flexion and extension (Arnoczky and Marshall, 1977; Heffron and Campbell, 1978).

The main functions of the CrCL are to prevent hyperextension of the stifle joint and cranial displacement of the tibia relative to the femur (Arnoczky and Marshall, 1977; Korvick et al., 1994b). In collaboration with the caudal cruciate ligament (CdCL) and the collateral ligaments it also inhibits internal rotation of the tibia, but none of the ligaments limits external rotation (Arnoczky and Marshall, 1977). The major nerve supply to the stifle joint comes from the medial articular nerve, and joint motion is controlled by mechanoreceptors in the ligaments, which prevents extensive motion by a proprioceptive mechanical feedback (reviewed in de Rooster et al. (2006)). Both external ground forces and internal muscle generated forces affect the stifle joint during motion and result in a cranially oriented shear force during weight bearing, first described as "cranial tibial

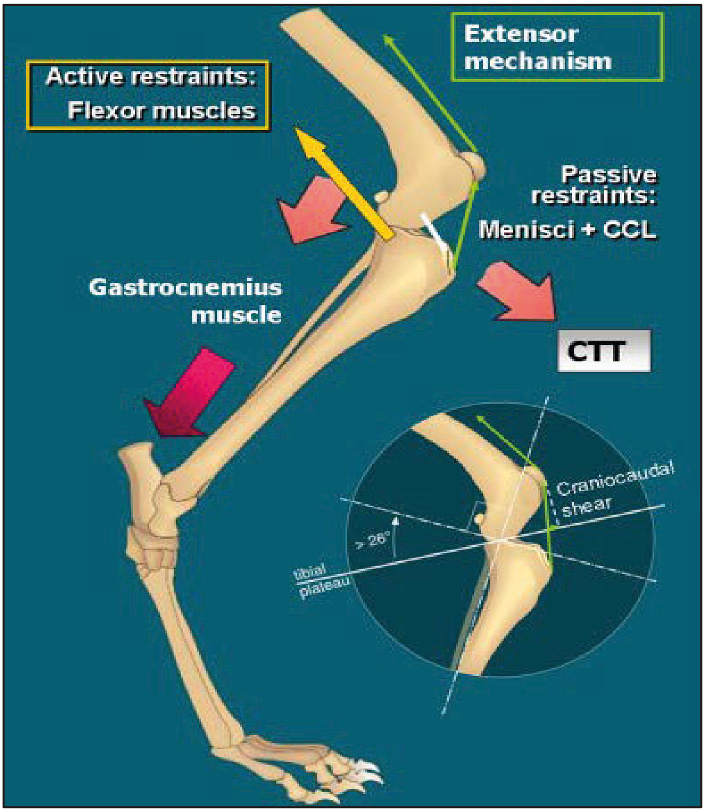


Fig. 2. Forces acting on the canine stifle joint. The cranial tibial thrust (CrCL) in the stance face of the gait is generated by contraction of the gastronemicus muscle and counteracted by active (flexor muscles) and passive (menisci and CrCL) components. From Griffon (2010) with permission.

thrust" in dogs by Slocum and Devine (1983). This shear force is generated because of the slope of the tibial plateau, which is oriented in a caudodistal direction (figure 2).

The extent of the shear force is dependent on the magnitude of the joint compressive force together with the slope of the tibial plateau (Slocum and Slocum, 1993). In the normal canine stifle joint, the CrCL passively resists the shear force, but rupture of the ligament allows cranial translation, increased internal rotation and adduction of the tibia when the joint is loaded. In vivo kinematic studies in dogs have shown that the stance phase of the gait cycle is more affected than the swing face after transection of the cranial cruciate ligament, and approximately 10 mm of increased cranial tibial translation during the stance phase has been observed (Korvick et al., 1994b; Tashman et al., 2004).

Meniscal injury

The menisci are two fibrocartilaginous semilunar disks located between the tibia and the femoral condyles (figure 3). The menisci have thick, convex peripheral borders and thin and concave central borders. They are wedge-shaped in cross-section, and the lateral meniscus is larger than the medial (Carpenter Jr and Cooper, 2000; Kowaleski et al., 2018). The medial meniscus attaches both to the medial collateral ligament, the joint capsule and the tibia, while the lateral meniscus is attached to the tibia and the femur. Since the lateral meniscus has a less firm attachment to the tibia than the medial meniscus, it is more mobile and moves with the femoral condyle during rotation. Consequently, it is less likely to be injured than the rather immobile medial meniscus (Kowaleski et al., 2018). While blood vessels originating in the synovium provides blood supply to the peripheral 15-25% of the menisci, the central core of the menisci is avascular with poor healing ability (Arnoczky and Warren, 1983). The menisci elongates and absorbs energy following loading of the joint, thus playing an important role in load transmission across the stifle (Kowaleski et al., 2018). By deepening the tibial articular surface, the menisci also provide better accommodation of the femoral condyles on the tibial plateau. This increases the stability of the stifle and relieves the incongruity between the femur and the tibia (Carpenter Jr and Cooper, 2000). In the CrCL-intact stifle, the caudal horn of the menisci elevates the caudal aspect of the tibial plateau, thereby functionally decreasing its slope. In the CrCL-deficient stifle, the caudal horn has been described to rather function as a wedge, preventing further tibial subluxation and thereby increasing the risk of a meniscal tear (Slocum and Slocum, 1993; Kowaleski et al., 2018). Due to the factors mentioned above, meniscal injuries are commonly observed in dogs with CCLD and is typically reported in 33-71% of CCLD cases (Dymond et al., 2010; Fitzpatrick and Solano, 2010; Christopher et al., 2013). The frequency of meniscal injury in cats with CCLD has been reported to be in the same range as for dogs (Ruthrauff et al., 2011). The medial meniscus is most often affected in both species and the injuries occur both in connection with the primary CCLD injury and as a postoperative complication (Fitzpatrick and Solano, 2010; Ruthrauff et al., 2011). Meniscal injuries are classified according to appearance, location, shape and extent with bucket handle tears being the most common (Kowaleski et al., 2018).

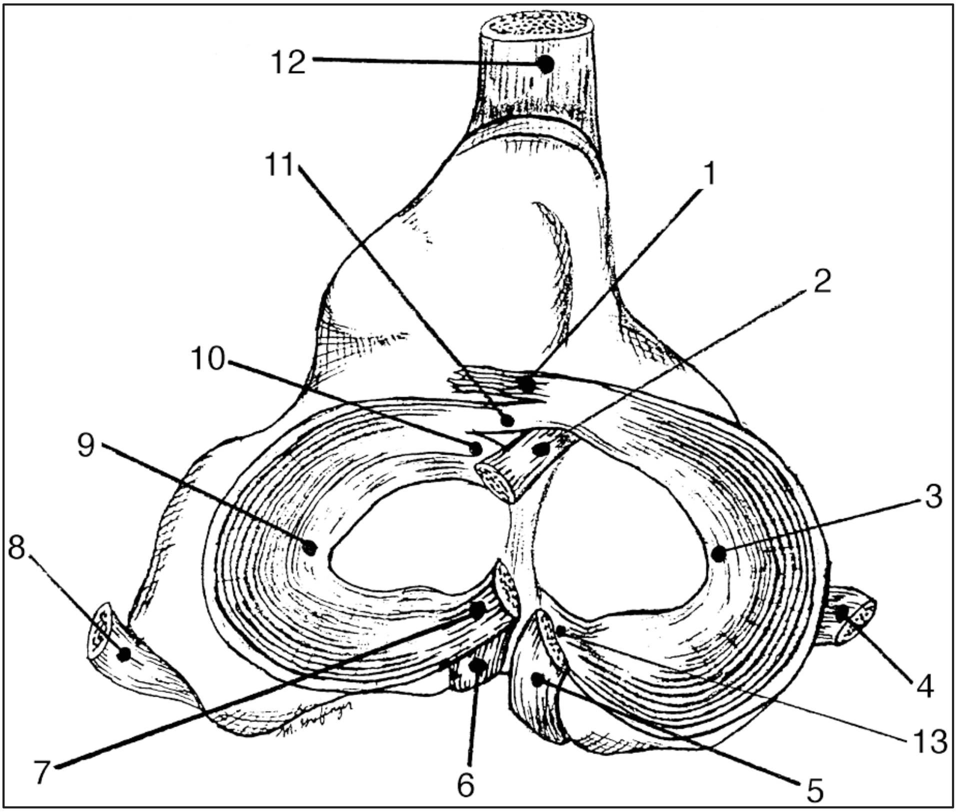


Fig. 3. Proximal view of the left tibial tableau showing associated ligaments and structures. 1, cranial meniscotibial ligament of the medial meniscus; 2, cranial cruciate ligament; 3, medial meniscus; 4, medial collateral ligament; 5, caudal cruciate ligament; 6, caudal meniscotibial ligament of the lateral meniscus; 7, meniscofemoral ligament; 8, lateral collateral ligament; 9, lateral meniscus; 10, cranial meniscotibial ligament of the lateral meniscus; 11, intermeniscal ligament; 12, patellar ligament; 13, caudal meniscotibial ligament of the medial meniscus. Illustration and figure legend from Carpenter & Cooper (2000) with permission.

Aetiopathogenesis and epidemiology

The term cranial cruciate ligament disease covers different disorders affecting this important anatomic structure, including traumatic avulsion of the femoral or tibial attachment and acute traumatic rupture secondary to excessive strain (Kowaleski et al., 2018). However, previous studies in dogs have suggested that the majority of CrCL ruptures are due to progressive degeneration resulting in partial or complete rupture of the ligament during normal activity (Bennett et al., 1988; Griffon, 2010), and the most common site of ligament rupture is the midsection where the ligament is most narrow (Vasseur et al., 1985). Histologic evaluation of the ligaments has revealed degenerative changes, evident at an earlier age in medium and large sized dogs (>15 kg) compared to small dogs (Vasseur et al., 1985). A decrease with aging in the elasticity and strain energy of the intact cruciate ligament has also been demonstrated (Vasseur et al., 1985; Doring et al., 2018). Moreover, changes in the composition of the extracellular matrix (ECM) of the ruptured CrCL have been confirmed and suggest that diseased CrCLs have an increased ECM turnover compared to intact CrCLs (Hayashi et al., 2003; Comerford et al., 2004). Despite years of clinical and basic scientific investigation, the aetiopathogenesis of the disease is still poorly understood. The progressive degeneration of the ligament has been attributed to a variety of factors that may be broadly classified as genetic, conformational, environmental, immune-mediated and inflammatory. These factors have been thoroughly reviewed by Griffon (2010) and are summarised in figure 4.

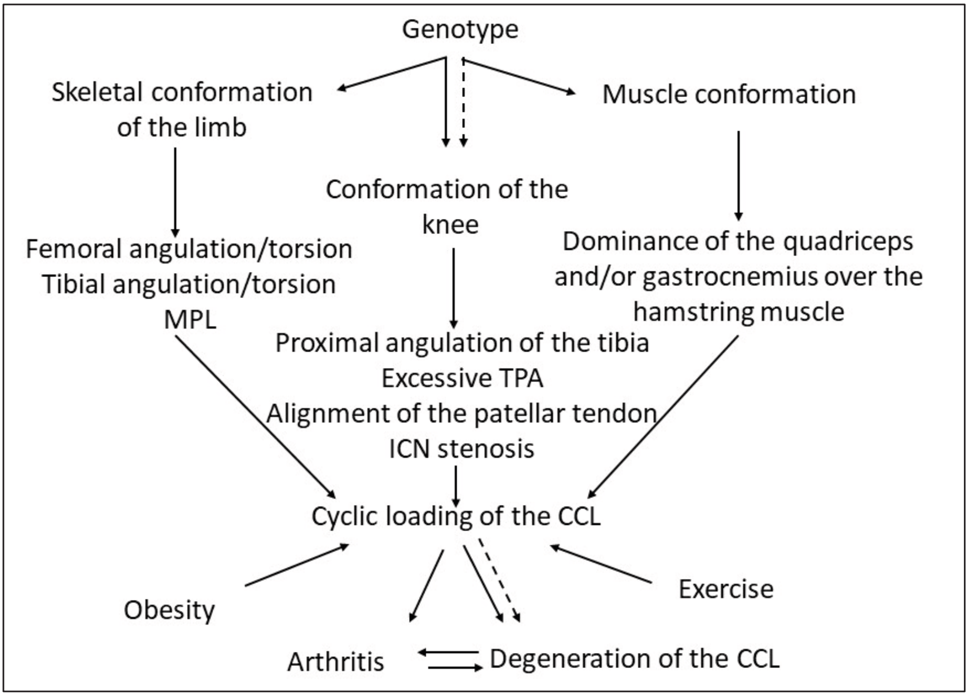


Fig. 4. The potential interrelationship between the different factors implicated in the pathogenesis of CCLD. TPA, tibial plateau angle; MPL, medial patellar luxation; ICN, intercondylar notch stenosis; CCLD, cranial cruciate ligament disease. Illustration adapted from Griffon (2010) with permission.

While CCLD in dogs is one of the most discussed and studied topics in veterinary orthopaedics, the condition in cats has achieved little attention and very few studies have been conducted. Trauma is likely to play an important role in cats (Scavelli and C., 1987; Harasen, 2005), and although Harasen (2005) suggested that two distinct populations of cats with CCLD exists, one traumatic and one degenerative, less is known about feline than canine CCLD (Ruthrauff et al., 2011).

In recent studies, the reported average age at diagnosis of CCLD in dogs is 4 to 8 years (Grierson et al., 2011; Guthrie et al., 2012; Taylor-Brown et al., 2015), and large dogs tend to present with the disease at a younger age (Bennett et al., 1988; Whitehair et al., 1993). In the currently largest study of cats with CCLD by Ruthrauff et al. (2011), the age of the 95 included cats ranged from 6 months to 14 years, with a median age of 7 years. The same study reported a median body weight of 5.7 kg. Relatively similar results have been found in the few additional reports which have been published (Scavelli and C., 1987; Harasen, 2005).

Although CCLD occurs in dogs of all sizes, the initial publications reported the disease to typically affect small and medium sized dogs (Singleton, 1969). The picture has changed over the years, and since the late 1980s, the condition has been more frequently encountered in medium and large sized dogs (Whitehair et al., 1993). Most studies report an average body weight at presentation between 25 and 38 kg (Bennett et al., 1988; Molsa et al., 2014; Taylor-Brown et al., 2015). Increased body weight has also been identified as a risk factor for disease development, particularly in younger dogs (Whitehair et al., 1993; Duval et al., 1999; Taylor-Brown et al., 2015). Several studies have examined the relationship between sex, neuter status and CCLD in dogs (Duval et al., 1999; Witsberger et al., 2008; Adams et al., 2011; Guthrie et al., 2012; Taylor-Brown et al., 2015). The results of these studies imply that neutered dogs of both sexes, and possibly entire females, could be at greater risk of CCLD than entire males. However, neutered dogs are more prone to weight gain than entire dogs (McGreevy et al., 2005), and Adams et al. (2011) found obese dogs to be four times more likely to be affected by CCLD than normal weight dogs. An approximately even sex distribution has been reported in feline cases of CCLD (Ruthrauff et al., 2011).

In dogs with CCLD, bilateral rupture is reported in approximately 20-60% of cases (Moore and Read, 1995; Buote et al., 2009; Grierson et al., 2011; Muir et al., 2011; Guthrie et al., 2012). While some dogs present with bilateral disease, most have unilateral CCLD at initial presentation and rupture of the contralateral ligament occurs later. The average time between rupture of the initial and contralateral CrCL is reported to be less than a year (Buote et al., 2009; Grierson et al., 2011). Radiographic OA in the contralateral stifle joint has been identified as a risk factor for contralateral rupture in dogs initially presenting with unilateral disease (Chuang et al., 2014). Dogs that sustain a consequent contralateral rupture have been stated to be younger than dogs with unilateral disease (Cabrera et al., 2008; Grierson et al., 2011). It has also been suggested that Rottweilers have a higher risk of bilateral disease than other breeds (Guthrie et al., 2012). No information regarding the occurrence of bilateral disease in cats is available.

Since CCLD is a disease with acknowledged breed predispositions, the influence of genetic factors in dogs has been studied. Wilke et al. (2006) investigated the prevalence, heritability and mode of inheritance for CCLD in Newfoundland dogs and found a moderate value for heritability with a possible recessive inheritance mode. In another study, microsatellite markers located in four chromosomes were significantly associated with the CrCL rupture trait in the same breed (Wilke et al., 2009), and it is suggested that neurological pathways could be involved (Baird et al., 2014a). In addition, a connection between CCLD susceptibility and key genes associated with ligament strength, stability and extracellular matrix formation has been reported in Newfoundland dogs, Labrador retrievers, Rottweilers and Staffordshire bull terriers (Baird et al., 2014b).

Medial patellar luxation and poor conformation of the pelvic limb such as genu varum and tibial deformities, may lead to misalignment of the stifle joint, which might predispose to CCLD. However, the presence of such conformational traits is inconsistent in dogs with CCLD and the initial reports were based on clinical observations (Griffon, 2010). Although an association between a steep tibial plateau angle (TPA) and CCLD has been reported (Morris and Lipowitz, 2001; Janovec et al., 2017), studies in Labrador retrievers have failed to confirm such a relationship (Wilke et al., 2002; Reif and Probst, 2003). The relationship between the TPA and development of CCLD is still controversial and may vary between breeds. Furthermore, a causal relationship between the disease and additional factors related to stifle conformation, such as an association between a narrow intercondylar notch on the distal femur and alignment of the patellar tendon, has been proposed, but not verified (Schwandt et al., 2006; Kyllar and Cizek, 2018).

Immune complexes have been detected in stifle synovial fluid and membranes of dogs with CCLD, which has led to a suggestion of an immunologic component as a piece in the aethiological puzzle (reviewed in Doom et al. (2008)). Lymphocytic-plasmocytic synovitis has been diagnosed in affected stifles with a reported prevalence as high as 67% (Galloway and Lester, 1995). However, inflammatory changes have also been detected in the synovium of the stable contralateral stifle joint of dogs with unilateral CCLD (Bleedorn et al., 2011). A recent study by Doring et al. (2018) found inflammatory changes, similar to the lymphoplasmacytic synovitis described in dogs with CCLD, in more than 40% of dogs with bilaterally intact CrCL at post-mortem examination. Moreover, positive correlations between the severity of degenerative CrCL lesions with age, body weight and synovial inflammation were identified. Whether the synovitis is a primary event which stimulates progressive fiber disruption of the CrCL or triggered by minor fiber damage caused by other factors, remains elusive (Doom et al., 2008).

Treatment

The complex and multifactorial origin of CCLD impairs the development of preventive strategies. As for other tendons and ligaments, the healing potential of the cruciate ligaments is poor, and ligament rupture alters the kinematic properties of the stifle and hind limb (Arnoczky and Marshall, 1977; Cabaud et al., 1979). Although restoration of normal stifle movement is a primary treatment goal, the multiplanar motion of the joint and the complex structure and function of the ligament further complicates development of optimal treatment strategies (Tonks et al., 2011). A ruptured CrCL can be treated either surgically or conservatively. Surgical treatment is frequently recommended to accomplish a more rapid stabilisation of the stifle joint and return to clinical function (Kowaleski et al., 2018). Over 60 variations of surgical procedures have been described to stabilise the joint either by bioscaffolds, stabilising sutures or tibial osteotomies (Bergh et al., 2014).

The purpose of intra-articular stabilisation (IS) is to utilise grafts for reconstruction of the ruptured CrCL. Intra-articular stabilisation with auto- or allo-grafts is routinely used in humans with anterior cruciate ligament rupture (ACLR), and procedures such as the over-the-top technique using fascia lata was earlier recommended for CCLD treatment in large dogs (Korvick et al., 1994a; Paschos and Howell, 2016). Although different biologic and prosthetic grafts have been explored as treatment options for dogs, there is a risk of premature graft failure and an ideal material for use as a ligament substitute in dogs is still to be invented (Kowaleski et al., 2018). Intra-articular procedures have been reported inferior to extra-articular stabilisation (ES) and tibial osteotomy techniques in restoring function in dogs and is minimally used in veterinary surgery today (Conzemius et al., 2005; Duerr et al., 2014). However, the techniques have a potential for regaining popularity in the future if further investigations can circumvent the insufficient postoperative viability of the grafts (Barnhart et al., 2016; Kowaleski et al., 2018).

A different approach for stifle stabilisation is using extra-articular techniques. These procedures depend on periarticular fibrosis for long-term stability since the initial stability created by the surgical procedure is only temporary (Kowaleski et al., 2018). In a review by Tonks et al. (2011), the extra-articular stabilisation methods were classified according to whether autogenous structures or synthetic materials were used as grafts. The techniques using synthetic materials can further be categorised to include capsular imbrication, circumfabellar prostheses, and anchor and bone tunnel techniques. Today, the most commonly used technique is the lateral fabellotibial suture (LFS) procedure (von Pfeil et al., 2018). In this technique, a suture is placed around the fabellae for femoral fixation and anchored to the tibia, as illustrated in figure 5. The method is intended to resolve cranial tibial thrust by maintaining the strain applied to the prosthesis at the time of implantation, and various types of suture materials and technique variations are available (Tonks et al., 2011). Biological ES procedures using transposition/transferring of local tissue to stabilise the joint include procedures such as fibular head transposition where the joint is stabilised by reorientation of the lateral collateral ligament (Smith and Torg, 1985). Although tibial osteotomy procedures have gained increased popularity over the last decades, the ES techniques are still the most commonly used surgical treatment of CCLD in small dogs, according to a recent large-scale US survey (Duerr et al., 2014). The ES procedures are described as relatively easy to perform and do not require advanced surgical equipment (Chauvet et al., 1996). However, they have the disadvantage that the applied sutures can break or stretch and elongate too early post-surgery. In most cases the tension of the suture is only conserved for six to eight weeks post-implantation (Stork et al., 2001).

Different theoretical biomechanical models of the stifle have been proposed as a basis for the tibial osteotomy procedures which have developed over the past three decades.

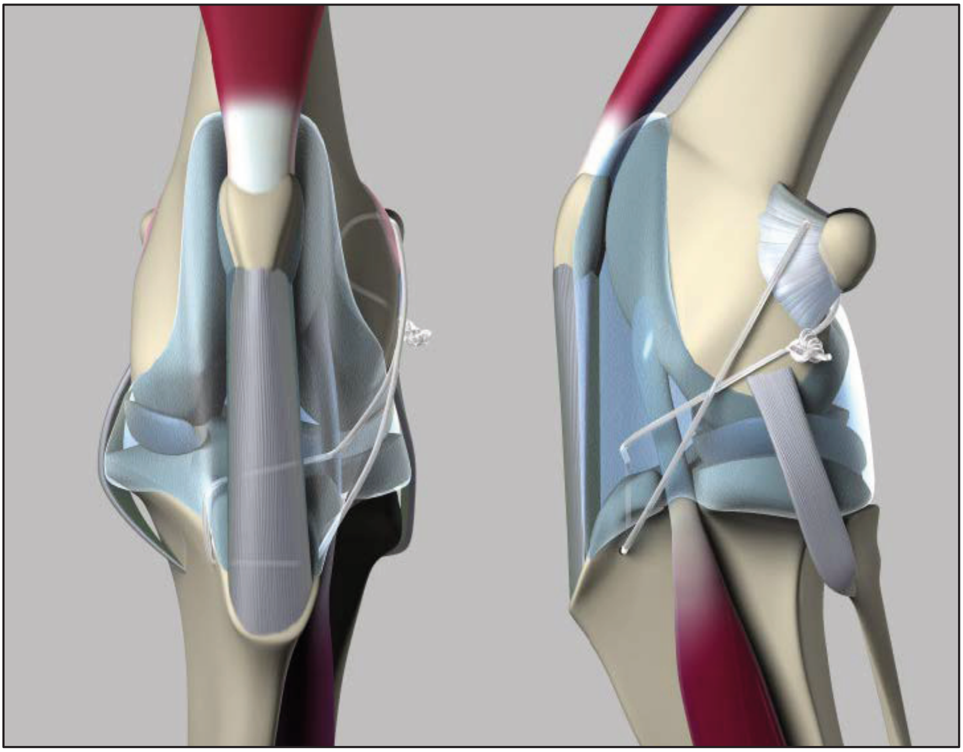


Fig. 5. Craniocaudal and lateral views of the lateral fabellotibial suture technique. Illustration from Tonks (2011) with permission.

By neutralising the cranial tibial share force, the osteotomies intend to functionally stabilise the stifle joint during weight bearing (Boudrieau, 2009). The two most commonly used and studied osteotomy techniques are the tibial plateau leveling osteotomy (TPLO) and the tibial tuberosity advancement (TTA) (Bergh et al., 2014).

The TPLO procedure intends to control the cranial tibial share forces by leveling the tibial plateau, which in turn enhances the effectiveness of the active forces of the stifle flexors. This is accomplished by reduction of the tibial plateau angle by a circular osteotomy in the proximal tibia and rotation of the loose, proximal fragment until a desired leveling of the tibial plateau is achieved (Slocum and Slocum, 1993). The osteotomy is then stabilised by a special TPLO plate as illustrated in figure 6a. The TPLO technique increases the loading on the caudal cruciate ligament and is therefore not suitable for patients with concurrent caudal cruciate ligament injuries. According to the initial report by Slocum and Slocum (1993), the cranial drawer movement and the cranial tibial thrust is neutralised in approximately 50% of the treated animals after surgery.

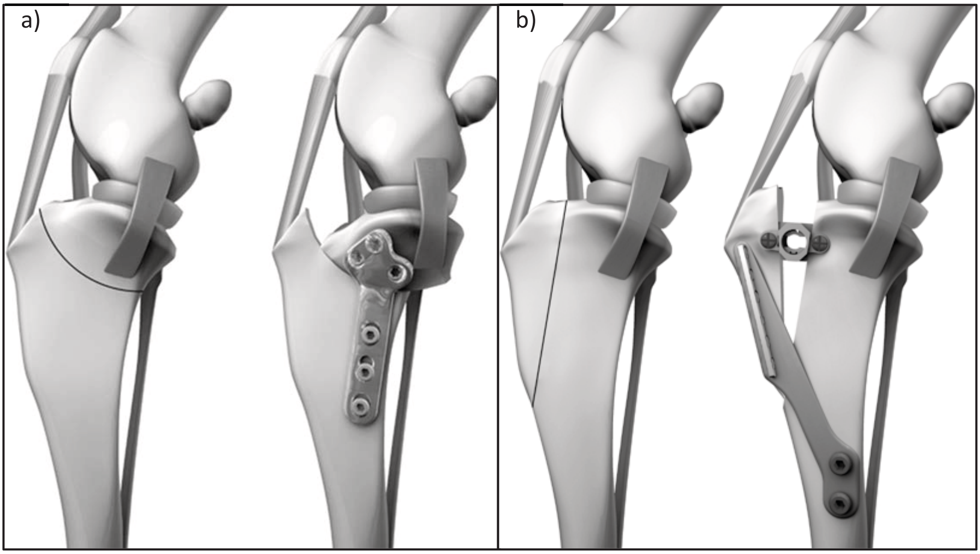


Fig. 6. Lateral osteotomy and postoperative illustration of tibial plateau leveling osteotomy (a) and tibial tuberosity advancement (b), from Kim (2011) with permission.

The procedure has been described in combination with a closing wedge osteotomy to address an excessive steep tibial plateau angle and proximal tibial varus/valgus/tibial torsion (Talaat et al., 2006; Weh et al., 2011).

While the TPLO technique has been in use since the early nineties, the TTA was first introduced in 2002 (Montavon et al., 2002). It is described as technically easier to perform than the more advanced TPLO (Boudrieau, 2009). As for TPLO, the TTA procedure aims at neutralising the shear force by dynamically stabilise the stifle, but instead of leveling the tibial plateau, the shear component of the total joint force is neutralised by a reduction of the angle between the patellar tendon and the tibial plateau from approximately 105 to 90 degrees (Kim et al., 2008; Boudrieau, 2009). As illustrated in figure 6b, this is accomplished by an osteotomy of the tibial tuberosity in the frontal plane and moving this bone fragment forward, locking it in a cranially advanced position using a winged metal cage positioned in the proximal osteotomy in combination with a forked bone plate (Montavon et al., 2002; Boudrieau, 2009). Several revised TTA techniques have been developed. One such technique is the modified Maquet procedure (MMP). The main differences from a standard TTA is that the MMP uses different implants and the osteotomy is left incomplete so that the tibial tuberosity retains its distal attachment to the tibial diaphysis (Etchepareborde et al., 2011; Ramirez et al., 2015).

Due to the high percentage of concurrent meniscal tears in dogs with CCLD, joint exploration with meniscal inspection is recommended to identify and treat meniscal injuries and has been performed in most studies of surgically treated CCLD in dogs (e.g. Christopher et al. (2013), Conzemius et al. (2005) and Stauffer et al. (2006)). The integrity of the menisci is assessed by arthrotomy or arthroscopy during the surgical procedure. Both methods are reported with a questionable efficacy in detecting meniscal injuries and a certain degree of morbidity (Hoelzler et al., 2004; Ertelt and Fehr, 2009). Meniscal injury is usually treated with a partial, segmental or total meniscectomy, aiming at removing the damaged parts of the menisci and preserve as much functional tissue as possible (Kowaleski et al., 2018).

Non-surgical management of dogs with CCLD is generally accepted as a tolerable treatment option in small patients and in cases where surgical treatment is contraindicated due to medical reasons (Pond and Campbell, 1972; McKee and Cook, 2006). Though generally regarded as inferior to surgical treatment, conservative management is a widely used treatment option for dogs weighing less than 15 kg (Comerford et al., 2013). One of the few studies of conservative CCLD treatment in dogs found lameness in small dogs to decrease after the injury with help of anti-inflammatory drugs and activity restriction (Vasseur, 1984). Although the stifle remained unstable and secondary osteoarthritis developed over time, this study reported a good clinical outcome in most dogs <15 kg.

Whereas restricted activity and house confinement used to be the core recommendations following CCLD surgery, structured physiotherapy is considered an important part of modern day CCLD treatment (Korvick et al., 1994a; Comerford et al., 2013). The focus of physiotherapy is functional restoration of the patient, and several different rehabilitation schemes have been proposed for dogs with CCLD (Marsolais et al., 2002; Monk et al., 2006; Jerre, 2009). Physiotherapy has been shown to be superior to exercise-restriction and advantageous for both conservative and surgically treated dogs (Marsolais et al., 2002; Monk et al., 2006; Wucherer et al., 2013; Baltzer et al., 2018).

The basics of the surgical treatment options in cats are the same as for dogs and both conservative management and different surgical methods have been deemed successful (Scavelli and C., 1987; de Sousa et al., 2015; Mindner et al., 2016; Kneifel et al., 2018). However, the recommendations are based on a very limited number of studies. Extra-articular stabilisation techniques are presumably most commonly used, although case reports describing osteotomy procedures such as TPLO and TTA have been published and gained attention in recent years (Harasen, 2005; Hoots and Petersen, 2005; Perry and Fitzpatrick, 2010; Mindner et al., 2016). Moreover, TPLO and TTA have recently been evaluated in feline ex vivo biomechanical models, and neither techniques accomplished stabilisation of the CrCL deficient stifle (Retournard et al., 2016; Bilmont et al., 2018). Consequently, a simple transposition of the techniques from the dog to the cat is likely not appropriate.

Clinical outcome

In the initial description of the TPLO procedure, Slocum and Slocum (1993) stated that "The tibial plateau levelling osteotomy has been a joy to use and a blessing for the patients. […] Full return to function should occur by the third to forth postoperative month. This means that the hunting dog returns to hunting, the field trial dog returns to trialing, the show dog returns to a winning form in the show ring, the obedience dog returns to competition, the police dog returns to active police work, the seeing eye dog returns to guiding the blind, and the companion dog returns to hiking and chasing sticks for hours on end". Although nothing would have been better than for this description to mirror the reality, the existing research provide evidence for a way more pixelated truth than this initial perfect picture.

Numerous studies have reported complications after surgical treatment of CCLD in dogs. The definitions of postoperative complications as minor, major and catastrophic differ between studies and consequently, direct comparisons cannot be made. One of the largest studies of postoperative complications available evaluated 1000 dogs surgically treated with TPLO by highly experienced surgeons (Fitzpatrick and Solano, 2010). Complications occurred in 14.8% of the cases, of which 6.6% were defined as major. In recent years, many studies have assessed complications after osteotomy procedures, while complication reports after other techniques such as LFS are less commonly published. Both follow-up times, number of included cases, clinics and surgeons differ greatly between studies, and the reported complication frequency spans from less than 10 to over 60% (Pacchiana et al., 2003; Stauffer et al., 2006; Gatineau et al., 2011).

Surgical site infection (SSI) is one of the most commonly reported complications after surgical treatment of CCLD in dogs. In the TPLO study by Fitzpatrick and Solano (2010) referred to above, SSI occurred in 6.6% of the cases, whereas a recent report by Hans et al. (2017) found an incidence of 25.9% for the same procedure. Postoperative meniscal tears have been reported to occur in 1.9-21.7% of surgically treated canine CCLD cases (Metelman et al., 1995; Casale and McCarthy, 2009; Gatineau et al., 2011; Kalff et al., 2011). A high frequency of postoperative meniscal tears may be due to the surgical techniques failing to provide enough joint stability to protect the meniscus from damage. Release of the intact medial meniscus has therefore been recommended by some authors as part of the initial surgical CCLD treatment to prevent development of consequent meniscal injuries, but are now generally avoided (Lafaver et al., 2007; Duerr et al., 2014). Although SSIs and meniscal injuries are relatively common following all the different stifle stabilisation methods, other complications, such as implant failures, are more procedure specific. Implant-related complications include tibial tuberosity fractures (with or without implant failure) for the osteotomy techniques and reaction/ruptures of the suture material for the LFS-procedures (Dymond et al., 2010).

Surgical stifle stabilisations are highly operator dependent procedures, and the surgeon's familiarity with a particular procedure can be as important as his or her general experience level. Although the literature provides conflicting results regarding the impact of surgeon experience level on complications after CCLD surgery (Pacchiana et al., 2003; Christopher et al., 2013; Gordon-Evans et al., 2013), it should be noted that as for the complications, a uniform, standardised classification is lacking. Thus, the grading of experience differ between studies and the results are not directly comparable. Orthopaedic surgical procedures are generally regarded as technically advanced and it is therefore not surprising that postoperative complications are frequent.

Very few studies have reported complications after surgical treatment of CCLD in cats. In a case report by Mindner et al. (2016), intraoperative complications occurred in 5/11 and minor postoperative complications in 3/11 cats treated by TPLO. Moreover, long term follow-up assessments are lacking in cats and only a single follow-up study has been published (Scavelli and C., 1987). In that study, 16 conservatively treated cats were followed for an average of 20.5 months. Although persistent cranial drawer movement, medial stifle capsular thickening and radiographically evident OA were reported in more than 80% of the cats, all cats had a clinically normal gait without apparent muscle atrophy at follow-up.

Most studies assessing treatment outcome in dogs have a follow-up time of less than six months and/or focus on risk factors for postoperative complications (Bergh et al., 2014). In addition to complication reports, outcomes have been evaluated by clinical examination, radiographic judgement of osteoarthritis, owner assessments and gait analysis. Many studies have reported that OA of the stifle joint progresses following CCLD, independent of the treatment method used (Chauvet et al., 1996; Hurley et al., 2007; Au et al., 2010). Information obtained from owner questionnaires/interviews and visual gait observations are commonly used for assessment of long-term outcome, while objective measurements such as force plate gait evaluation and thigh circumference are less often reported (Bergh et al., 2014).

Although good limb function has been reported after intra- and extra-articular procedures, these methods are generally considered to yield sub-optimal long-term outcomes, particularly in large dogs (Chauvet et al., 1996; Jerre, 2009; Gordon-Evans et al., 2013; Barnhart et al., 2016). In one randomised blinded controlled clinical trial of 80 dogs by Gordon-Evans et al. (2013), 1-year outcome after LFS and TPLO surgery, including gait analysis and owner evaluation, were reported. The results indicated that both groups improved after surgery and 93% of owners were very satisfied after TPLO and 75% after LFS. Vasseur (1984) evaluated outcomes of 85 conservatively treated dogs. The treatment included activity restriction and weight loss and analgesic medication if deemed necessary. After an average follow-up time of 3-4 years, 85.6% of dogs <15 kg and 19.3% of dogs >15 kg were considered clinically normal or improved. A newer study reporting 1-year outcome in 40 overweight dogs >20 kg after conservative treatment with physiotherapy, weight loss and NSAIDs treatment compared to TPLO surgery with the same postoperative protocol, has been conducted (Wucherer et al., 2013). This randomised prospective study reported improvement in both groups assessed by gait analysis and owner evaluation, but dogs in the TPLO group had a greater improvement than the dogs treated conservatively.

In general, direct comparison of outcomes between studies is difficult due to large variations in study design, follow-up times and method chosen for outcome assessment. Moreover, only a few canine studies reporting long-term outcomes following more than two treatment methods have been published (Chauvet et al., 1996; Conzemius et al., 2005; Christopher et al., 2013; Molsa et al., 2014). Although there is some evidence in favour of TPLO as the preferred treatment option in dogs, no general agreement exists on which surgical method yields the best outcome (Bergh et al., 2014). Consequently, selection of surgical technique has largely been based on the preference of the surgeon rather than definitive evidence that one technique is better than another in the treatment of CCLD in dogs (Korvick et al., 1994a).

Functional outcome assessment tools

Outcome after treatment for orthopaedic conditions in dogs and cats can be evaluated by the use of kinetic and kinematic gait analyses, such as force plates and pressure walkways, and force plate gait analysis (FPGA) is often viewed as the gold standard for lameness evaluation in dogs (Quinn et al., 2007). Although such systems can provide important information regarding postoperative locomotion and function, gait analysis systems are expensive and considerable training is necessary for their use. Therefore, they are generally limited to specialised referral centers and research facilities. Moreover, the measurements are conducted at a single occasion with the animal outside of its home environment and the results are dependent upon factors such as animal size and gait velocity. The gait analysis systems are consequently better suited for monitoring lameness in an individual animal over time than to compare results across individuals (Lascelles et al., 2006). In addition, the use of such objective measurement tools requires a certain degree of animal cooperation, which can be challenging, particularly in cats. Due to these factors, subjective scales (numeric rating scales or visual analogue scales) are the commonly used lameness assessments tools in clinical practice and have also been applied in many studies reporting lameness in dogs (e.g. Dymond et al. (2010), Wucherer et al. (2013)).

In addition to clinical lameness evaluations, owner assessment of the animal's locomotion, posture and behaviour provide valuable, complementary information. Owner surveys are therefore commonly used for outcome assessments, both in veterinary orthopaedic research and in clinical practice. Traditionally, such owner assessments consisted of simple questions regarding the surgical outcome and owner satisfaction with the treatment (as in Chauvet et al. (1996), Lafaver et al. (2007) and Moore and Read (1995)). In recent years more sophisticated owner-assessment tools have been developed, and several standardised quality of life (QoL) questionnaires for evaluation of chronic pain in dogs and cats are currently available (Brown et al., 2007; Hercock et al., 2009; Hielm-Bjorkman et al., 2009; Benito et al., 2013a). Although these questionnaires rely on the owners' subjective assessment of their pet, they provide an opportunity for a uniform assessment of long-term outcome. Walton et al. (2013) compared results from three such clinical metrology instruments, the Liverpool Osteoarthritis in Dogs (LOAD), the Canine Brief Pain Inventory (CBPI) and the Helsinki Chronic Pain Index (HCPI) with FPGA measurements in 222 dogs with OA and found moderate correlations between the three instruments and a weak, but significant correlation between the former two and FPGA measurements. Brown et al. (2013) also evaluated the relationship between the CBPI and FPGA in dogs with OA. Although no correlation between the CBPI and FPGA measurements was identified in that study, both methods detected improvement in lameness, and the study concluded that the choice of outcome assessment should be based on the purpose of the study in question. One QoL questionnaire, the Feline Musculoskeletal Pain Index (FMPI), was developed by Benito et al. (2013a) and designed to assess chronic pain caused by degenerative joint disease in cats. This questionnaire has been validated and undergone reliability testing and is available in a Swedish version (Benito et al., 2013b; Gruen et al., 2015; Stadig, 2017).

Study design

One of the most important questions for veterinary surgeons and pet owners is deciding which surgical procedure provides the best chance of clinical recovery for the animal. During the past decades there has been a move towards the use of evidence-based medicine to assist in the clinical decision-making, first in human medicine and later adapted by the veterinary society (Vandeweerd et al., 2012). Evidence-based medicine depend on critical evaluation of scientific evidence to enable selection of high-quality, well designed studies, and applying the results to individual patients (Aragon and Budsberg, 2005). A basic understanding of the concepts of association and causality, and knowledge of different study designs are some key aspects to enable critical appraisal of scientific literature and is thus crucial to practice evidence-based medicine.

Dohoo et al. (2014) explains associations between exposures (e.g. inherent risk factors and treatment methods) and outcomes (e.g. limb function after surgery) as “a complex web of relationships involving animals and all aspects of their environment” and emphasises that it is only by “studying these associations under field conditions that we can begin to understand this web of relationships”. Scientific studies can be divided into to two groups; experimental and observational studies, approaching this complex “web” from different angles. A summary of the different study designs based on the definitions from Dohoo et al. (2014) and Caswell et al. (2018) is presented in figure 7.

The key feature of experimental studies is that the exposure/intervention is controlled by the researcher. Experimental studies are classified according to whether they are experiments conducted under artificial conditions or carried out as clinical trials in “real-life” clinical/field settings, where randomised controlled trials (RCTs) are considered to yield the highest level of evidence in evidence-based medicine (Vandeweerd et al., 2012). Random allocation of the study subjects is used to prevent systematic errors, facilitate objective evaluation of the outcome (blinding) and ensure comparability of the exposure groups (Sargeant et al., 2014). While experimental studies decrease variation at the design stage, observational studies rather embrace its presence (Dohoo et al., 2014). In observational study designs, the allocation of study subjects to exposure groups is not controlled by the researcher but relate naturally occurring exposures to disease occurrence (Sargeant et al., 2014). Although observational studies are generally better suited for establishing associations than for proving causal relationships, they can be used to estimate the prevalence or incidence of a condition, to investigate the distribution of conditions over time and to explore risk factors and compare treatment options (Stroup et al., 2000; Sargeant et al., 2014; Sargeant et al., 2016). Observational studies are often easier and less expensive to carry out than RCTs, and conducting RCTs is consequently often out of reach for researchers in veterinary medicine (Vandeweerd et al., 2012). As illustrated by the systematic reviews by Aragon and Budsberg (2005) and Bergh et al. (2014), the majority of CCLD research publications are observational studies.

Blinding of research participants is often used to ensure objective evaluation of the outcome in RCTs. However, blinding in surgical trials are more challenging compared to other fields of clinical research, such as drug trials. Blinding of the participating surgeons is often impossible due to the nature of surgical procedures. Sham incisions are required for patient/animal owner blinding to compare conservative and surgical treatments; however, this raises ethical questions. Moreover, it must be ensured that the surgeons have gained

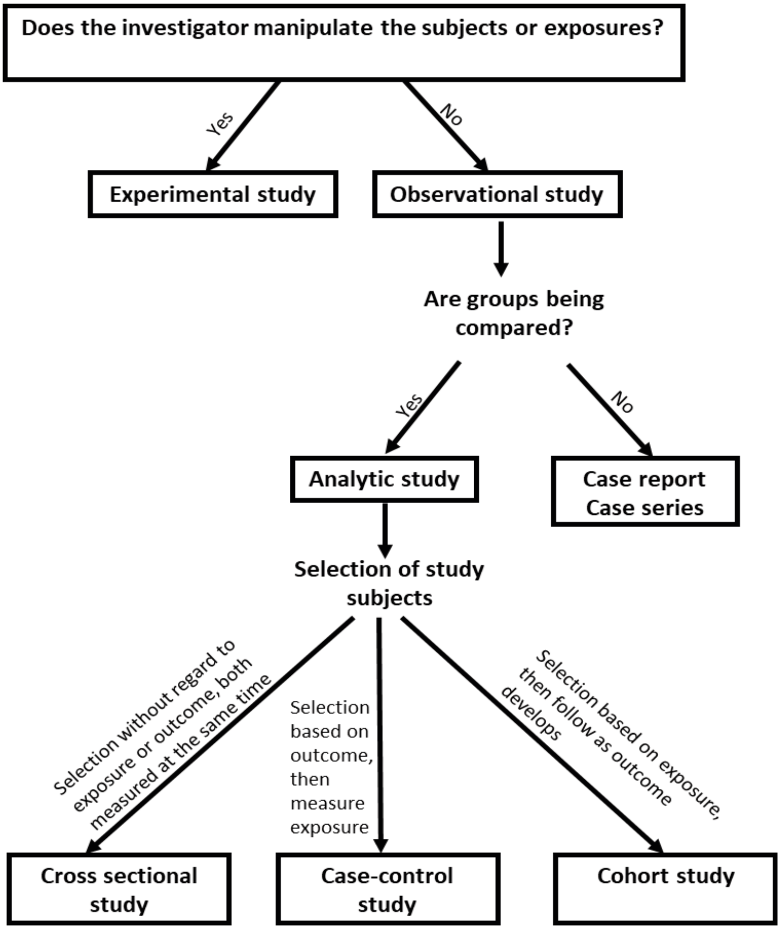


Fig. 7. Schematic illustration of different type of study designs. The selection of subjects defines the three classic analytical study types. Illustration based on Dohoo et al. (2014) and Caswell et al. (2018).

equal familiarity with all surgical techniques if different surgical procedures are being compared (Bono and Tornetta, 2006).

Observational studies are useful when an experimental design is impossible or undesirable due to practical or ethical restraints (Dohoo et al., 2014). Randomisation can rarely be used in risk factor studies as these factors often are related to inherent animal characteristics. Moreover, if risk factors are considered harmful, a forced application would be unethical (Sargeant et al., 2014). By enabling use of medical records, observational studies allow for investigation of "real-life" data; the actual patients that comprise the veterinarians' everyday caseload, thus making the results relevant to clinical practice (Caswell et al., 2018). Altogether, some research questions (e.g. identification of prognostic factors associated with good or poor treatment outcome) are best answered using an observational study design.

Observational studies can be either retrospective or prospective depending on how the cases are recruited. Retrospective enrolment utilises existing data, and thereby simplifies and speeds up the data collection process compared to prospective enrolment. Studies in veterinary orthopaedic research are often based on retrospective clinical data, such as medical records, with its inherent limitations regarding quality, completeness and representability. This is illustrated by the detection of mostly lower-class evidence in the two systematic reviews of CCLD literature by Aragon and Budsberg (2005) and Bergh et al. (2014), mentioned above. When cases are prospectively enrolled, it is possible to standardise the sampling and analysis since the data is collected with a predefined aim. Therefore, prospective enrolment of cases may prevent systematic errors and reduce variability of the cases. The main drawback of prospective designs is that these studies require planning in advance and are often more expensive and time-consuming than retrospective studies (Caswell et al., 2018).

Bias and validity

Dohoo et al. (2014) define source population as the population from which the study subjects are drawn. A study is said to be internally valid if one can make unbiased inferences about the associations of interest in the source population, and externally valid if one can make correct inferences to populations beyond the source population (Dohoo et al., 2014). The term bias is used to describe systematic error in the design, conduct or analysis that renders results invalid (Thrusfield and Christley, 2018). Bias is often divided into three major types: selection bias which results from the manner in which the study subjects are selected, bias due to confounding as a result of mixing the effect of the study factor with the effect of extraneous variables, and information bias due to misclassification or inaccurate measurements of either exposure or outcome (Kleinbaum et al., 1982).

The within-breed genetic variation is not constant for a given breed. It is dependent on breeding strategies causing genetic drift over time and varies between different geographical areas. Thus, disease prevalence for a given breed reported from one country, may lack validity in another (Collins et al., 2011). When breed-specific prevalence estimates are published, it is common for both the cases and controls to be sampled from veterinary hospital populations, most commonly at referral or university clinics in the UK or US. Since the late 1980s, several large databases containing clinical information (such as diagnosis and animal characteristics) have served as basis for different observational studies reporting prevalence of orthopaedic conditions and their risk factors in dogs, including breed predisposition (e.g. LaFond et al. (2002), O'Neill et al. (2016), Whitehair et al. (1993)). Although different approaches have been used (insurance claims in the case of the Agria insurance database, referral practice records in the Veterinary Medical Data Base and primary-care practice records in the VetCompass system, reviewed in O'Neill et al. (2014)), all these larger databases are based on non-standardised case recordings from veterinary practices. Even when data from several hospitals are combined, a lack of knowledge about the population at risk will likely introduce a selection bias, since both cases and controls are sampled from the hospital populations. As the purpose of controls is to provide valid information regarding the background frequency of an exposure (i.e. a particular dog breed) within the population at risk of becoming a case (i.e. individuals who are free of the disease in question), correct control selection is crucial for the validity of case-control studies (Dohoo et al., 2014). Hospital populations, in particular referral populations, are mostly composed of sick dogs and cats. Since sick animals can develop other conditions, disease beside the condition of interest does not inherently make animals unsuitable as controls. However, many diseases in dogs are breed-related and some breeds are therefore likely to be overrepresented in a control population composed of sick dogs, introducing a risk of selection bias. How the use of clinical record data can answer important questions regarding risk factors in the field of veterinary orthopaedics while avoiding the common pitfalls mentioned above, should gain further attention.

Knowledge gaps

Although orthopaedic diseases such as CCLD were among the most common reasons for animal insurance payments in Sweden when this project was initiated, the impact of such diseases was unknown. There was a paucity of Scandinavian studies reporting breed predisposition for orthopaedic disease and epidemiological studies were lacking.

A variety of studies had evaluated the pathophysiology, epidemiology and treatment outcome of CCLD in dogs, but little was known regarding inherent risk factors for development of the disease. Neutering had been implied as a potential risk factor for CCLD, but newer studies evaluating CCLD in a population of primarily entire dogs were absent. In addition, only a few studies had evaluated long-term outcome after more than two different treatment options of CCLD. Although most studies were retrospective and conducted at referral hospitals with procedures performed by a few, often highly experienced, surgeons, the influence of selection bias on case selection and treatment outcomes had not been thoroughly addressed. Moreover, studies including lifestyle of the dog as a factor in outcome evaluations were lacking. Since no studies evaluating the impact of CCLD on the risk of euthanasia had been published, information regarding the influence of CCLD on life expectancy was not available. Few studies reporting outcome of CCLD-treatment in small dogs had been conducted in recent years and evidence-based literature comparing outcome of conservative treatment with appropriate physiotherapy to surgery in normal weight and small dogs were lacking. In cats, the knowledge about CCLD was profoundly limited; very few studies had been conducted and minimal information regarding treatment, complications, prognosis and long-term outcome existed.

Aims and objectives

By addressing central aspects of the knowledge gaps presented above, the overall aim of this project was to expand the understanding of orthopaedic diseases in dogs and cats. With an emphasis on breed susceptibility and factors that may influence the prognosis of cranial cruciate ligament disease, this was implemented through the specific objectives of the three papers included in this thesis:

- To estimate breed susceptibility for common orthopaedic conditions in popular dog breeds in Norway and Sweden (Paper I).
- To describe the characteristics and long-term outcome of surgically and conservatively treated cats with CCLD and evaluate whether treatment method affected the quality of life of cats with the disease (Paper II).
- To estimate the importance of treatment method and preoperative risk factors for long-term outcome after CCLD-treatment in dogs (Paper III).

Material and Methods

General (paper I-III)

The studies included in this thesis originated as an extension of a project initiated as two master theses at the Swedish University of Agricultural Sciences (SLU). A summary of the methods is provided here. A more detailed description of the applied material and methods are to be found in the individual papers.

Electronical medical records search

The electronical medical records of cats and dogs presented at two Veterinary University Hospitals (University Animal Hospital, Norwegian University of Life Sciences (NMBU) and University Animal Hospital, SLU) between January 2011 and December 2016 were evaluated. Both hospitals see a mix of referral and primary cases. The medical record system at NMBU was Profvet Clinic (Sanimalis Norge A/S) and at SLU Trofast (Trofast AB). In Trofast, a clinical diagnosis is mandatory and searchable. Although Profvet Clinic has a comparable setup, the use of the diagnosis field is arbitrary. Consequently, all medical records of patients admitted to the surgical department at NMBU during the study period had to be screened manually to avoid missing records. The patients at SLU were identified by searching through patient files according to their clinical orthopaedic diagnosis. All medical record evaluations were carried out between September 2017 and September 2018.

Database description

During the initial screening, all dogs and cats that were surgically treated for orthopaedic diseases during the study period were registered in Excel databases. For cases with a diagnosis of CCLD, both conservatively and surgically treated cases were included. The initial information recorded was case number, species, breed, age, weight, sex and orthopaedic diagnosis. Bilaterally affected animals were initially recorded at two separate cases, but only the first incidence has been included in the analyses. Additional clinical information (comorbidities, treatment, surgeon, peri- and postoperative factors such as anaesthesia length, body temperature, complications, antibiotic and NSAIDs use) was registered for the eligible cases in study II and III. As illustrated in figure 8, the combined databases consisted of approximately 1500 cases, with 35 different orthopaedic diagnoses. All statistical analyses were conducted in Stata 14 and 15 (StataCorp, 2017).

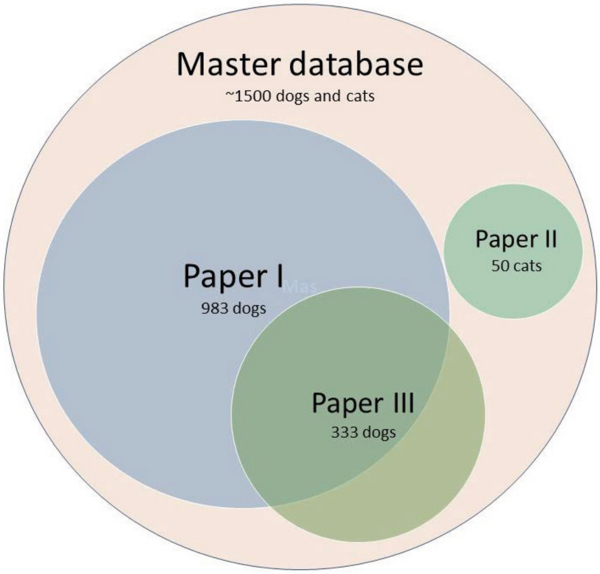


Fig. 8. Venn diagram illustrating the relationship between the study samples in paper I, II and III.

Paper I

Breed susceptibility for common surgically treated orthopaedic diseases in 12 dog breeds

The database described above constituted the basis for the cases in this retrospective case-control study. County of residence at the time of surgery was registered for all included dogs. The four most common diagnoses in the database were included; elbow dysplasia (medial compartment disease (MCD), humeral trochlear osteochondrosis (OC) and ununited anconeal process (UAP)), fractures of the radius and/or ulna, medial patellar luxation and cranial cruciate ligament disease. The geographical distribution of the dogs was calculated separately for the Norwegian and Swedish cases and the number of dogs from each county was divided by the total number of eligible dogs.

A comparable control group was generated from demographic and geographic data extracted from the national ID-registries. The control group was restricted to breeds present in all the counties represented in the clinical database. In addition to mixed breed dogs, this included the Border Collie, the Cavalier King Charles spaniel, the Chihuahua, the English cocker spaniel, the Flat-coated retriever, the German shepherd dog, the Golden retriever, the Jack Russell terrier, the Labrador retriever, the Rottweiler, the Shetland sheepdog, and the Staffordshire bull terrier. The numbers of these breeds in the control group were further adjusted in accordance with their county-wise contribution to reflect the breed distribution in the source population, as illustrated by the following example: 55% of the eligible cases at SLU came from the county of Uppsala, 25% from Stockholm, but only 1% from Västerbotten. In the national ID-registry, 755 Labrador retrievers were registered in Uppsala, 3331 in Stockholm and 452 in Västerbotten. These numbers where then multiplied (755*0.55=415, 3331*0.25=833 and 452*0.01=5) and repeated for the other counties. Summed together the adjusted number of Labrador retrievers comprising the control population was 1277, which is closer to the raw registration numbers in Uppsala than in Stockholm. Similar calculations were carried out for all breeds.

As the outcome was binary, logistic regression was used to obtain estimates for the effect of breed on the risk of acquiring the included orthopaedic diagnoses, with mixed breed dogs as the reference. Separate univariable analyses using simple logistic regression was performed for each county, followed by a multivariable logistic regression model, including a fixed effect for country, for the combined Norwegian and Swedish population. Results were presented as odds ratios with 95 % confidence intervals and p-values.

Paper II

Cranial cruciate ligament disease in cats – an epidemiological retrospective study of 50 cats (2011-2016)

Routine clinical and available follow-up information (including complications and date and cause of death) of cats with ruptured CrCL was registered for inclusion in this retrospective cohort study. Owners and referring veterinarians were contacted for additional information, and cases without complete follow-up information were excluded. The cases were divided in two groups; one conservatively managed and one surgically treated with LFS. The “Feline Musculoskeletal Pain Index” questionnaire was distributed to the owners of cats alive at follow-up for assessment of chronic pain as a long-term outcome. The FMPI contained 18 questions about the cats’ ability to perform different activities, pain and overall quality of life. The results were scored from −1 (above normal ability to perform the activity) to 4 (not at all able to perform the activity) as described by Benito et al. (2013a), and a low score indicated less chronic pain. Additional questions regarding treatment and NSAID use were included in the questionnaire.

Associations between categorical and continuous variables were explored by two-sample t-tests and Wilcoxon rank sum test for normally and non-normally distributed variables, respectively. Associations between categorical variables were tested using the $\chi 2$ test or the Fisher exact test.

Paper III

The effect of treatment strategy on long-term outcome in dogs with cranial cruciate ligament disease, an epidemiological study of 333 dogs

In this retrospective cohort study, routine clinical data including available follow-up information was retrieved from the medical records. Additional information was obtained via telephone interviews with owners and referring veterinarians and standardised questions about additional complications, subsequent CCLD, and date and reason for death/euthanasia were asked. Reason for death/euthanasia was retrospectively classified as related to CCLD or not and was the end-point of the study. Euthanasia related to CCLD was defined as all deaths where lameness from the affected hind-limb(s) was contributing to the decision of euthanasia. Treatment method was defined as the main exposure variable. All dogs without surgical correction of the CCLD were defined as conservatively treated. Surgically treated dogs were categorised into two groups; LFS and osteotomy (treated by TPLO, TTA or MMP). All postsurgical related variables (such as postoperative complications and bilateral disease) were regarded as intervening variables, and thus not considered for inclusion in the statistical analyses.

Appropriate parametric and non-parametric univariable statistical methods were used to examine differences in descriptive variables between the groups and Kaplan-Meier survival curves to describe differences in time-to-event for the treatment groups. Maximum follow-up time was set to 6 years (72 months). A Cox proportional hazards model was applied to estimate the effect of possible risk factors on time to CCLD-related euthanasia. Dogs that were alive at the end of the study period, lost to follow-up or dead due to causes unrelated to CCLD were censored. A hazard ratio (HR), 95% confidence interval and p-value were calculated for each variable. Manual stepwise backward elimination was applied for selection of variables and the variable for hospital was forced into in the final model. Biologically plausible interactions were considered for inclusion. Model validation was checked according to Dohoo et al. (2014).

Results

Paper I

In total, 983 surgically treated dogs (495 at SLU and 488 at NMBU) were eligible for inclusion and 636 (64.6%) were treated for either ED, MPL, CCLD or fractures of the radius and/or ulna. Surgically treated ED, MPL and fractures of the radius and/or ulna occurred most frequently in young dogs, while dogs with CCLD had a median age of 5.8 years. Elbow dysplasia and CCLD were most common in medium and large sized dogs, while the median weight for dogs with MPL and fractures of the radius and/or ulna was below five kg. The breeds found at-risk for ED were the Labrador retriever (OR = 5.73, CI 3.04-10.81, p <0.001), the Rottweiler (OR = 5.63, CI 2.62-12.07, p <0.001), the German shepherd dog (OR = 3.31, CI 1.56-7.02, p = 0.002) and the Staffordshire bull terrier (OR = 3.08, CI 1.25-7.59, p = 0.014). The Chihuahua was the only breed where an increased risk of surgically treatment for MPL was identified (OR = 2.80, CI 1.47-5.32, p = 0.002). The results regarding risk of CCLD in the Labrador retriever were conflicting. While an OR lower than in mixed breed dogs were found in Sweden (OR = 0.44, CI 0.18-1.04, p = 0.062), it was higher than mixed breeds dogs in Norway (OR = 2.85, CI 1.13-7.17, p = 0.026). Moreover, no increased risk was identified in the combined analysis (OR equal to mixed breed dogs). The Rottweiler was the only breed where an increased risk of CCLD was identified (OR = 3.96, CI 2.39-6.56, P <0.001). The German shepherd dog (OR = 0.10, CI 0.01-0.70, p = 0.021) and the Chihuahua (OR = 0.16, CI 0.04-0.66, p = 0.011) were found to have a decreased risk of CCLD. In addition to mixed breed dogs, only three of the breeds (the Cavalier King Charles spaniel, the Chihuahua and the Shetland sheepdog) had cases of fractures of the radius and/or ulna, but no difference in risk could be identified. Compared to the size of the adjusted control populations, the risk for being surgically treated for ED, MPL, CCLD and fractures of the radius and/or ulna were generally lower at NMBU compared to SLU (OR between 0.50 and 0.67).

Paper II

During the 6-year period, 60/493 (12.2%) of the patients diagnosed with CCLD at SLU and NMBU were cats, of which 50 had complete follow-up information and were included in the study. The median follow-up time were 41 months after diagnosis of CCLD. Median age at time of diagnosis was 9.0 years (range 0.4-15.3), median weight 4.9 kg (range 2.0-8.3) and 20 cats (40%) were registered as overweight. Thirty-nine cats (78.0%) were mixed breed and 11 (12%) purebred. The most common clinical presentation was acute onset of lameness with duration less than a week prior to diagnosis. Seven cats (14%) developed bilateral CCLD with a median interval between the bilateral injuries of 18.8 months (range 4.4-37.7). Twenty-eight cats (56%) were treated conservatively and 22 (44%) surgically with LFS. None of the initially conservatively treated cats needed surgical intervention later. All surgically treated cats where arthrotomy was performed (19/22, 86%) had a total CrCL rupture and 9/19 (47%) had meniscal injuries. Multi-ligament stifle injuries (defined as concurrent injury to collateral ligaments and/or CdCL) were diagnosed in five surgically treated cats. Postoperative surgical complications were recorded in 6/22 (27%) cases. Of the initial 50 cats, 29 (58%) were still alive at follow-up. Owners of 24/29 (83%) completed the FMPI questionnaire and the median total score for all cats was 3 (range −6 to 15). The median total score of the surgically treated cats was 5 (range 0−15) vs. 0.5 (range −6 to 7) for the conservatively treated cats ($p = 0.02$). The difference between the groups was still significant when the two cats with multi-ligament stifle injuries were excluded ($p = 0.05$).

Paper III

A total of 333 dogs fulfilled the inclusion criteria. Of these, 65 (19.5%) were conservatively treated, 125 (37.6%) treated with LFS and 143 (42.9%) with osteotomy procedures (71 TPLOs, 54 TTAs, 18 MMPs). Mixed breed dogs were most common, followed by Rottweilers and Labrador retrievers. The median age of dogs treated conservatively and with LFS were significantly higher than of dogs treated with osteotomy procedures (7.6 and 7.7 years vs. 4.2 years, $p < 0.001$). The median weight in the osteotomy group was higher than in the other groups (35.0 kg vs. 11.3 kg (LFS) and 17.9 kg (conservative), $p < 0.001$). There were significantly more female than male dogs ($p = 0.030$). One hundred and thirty-four (40.2%) dogs had a comorbidity recorded at treatment initiation and non-orthopaedic comorbidities were significantly more common among conservatively than LFS treated dogs ($p = 0.012$). At follow-up, 164 (49.3 %) dogs were still alive, 108 (32.4%) were dead/euthanised due to reasons unrelated to CCLD. The reason for euthanasia was CCLD-related in 61 dogs (18.3%); 19 (29.2%) in the conservatively treated group, 19 (15.2%) in the LFS group and 23 (16.1%) in the osteotomy group. The final multivariable Cox proportional hazard model included variables for hospital, treatment method, orthopaedic comorbidities, age and weight. Age and weight were found to be confounders for treatment method. The overall effect of treatment had a p-value of 0.035. The hazard of CCLD-related euthanasia for dogs treated by osteotomy was significantly lower than for the conservatively treated dogs (HR = 0.40, CI 0.19-0.81, p = 0.012). It was also lower for the dogs treated by LFS (HR = 0.56, CI 0.28-1.14, p = 0.109). No difference was found between the two surgical techniques (p = 0.370). The hazard of CCLD-related euthanasia increased with other orthopaedic comorbidities (HR = 3.09, CI 1.59-6.00, p = 0.001), age (HR = 1.12, CI 1.01-1.25, p = 0.040) and weight (HR = 1.03, 1.01-1.05, p = 0.001). The model validation did not reveal violations of the model assumptions.

Discussion

Importance of orthopaedic diseases in dogs and cats

Information regarding breed susceptibility for orthopaedic disorders in dogs may aid in the development of preventive measures, such as specific breeding strategies aimed at reducing disease prevalence and thereby improve animal welfare, as well as act as a guide for potential pet owners and a motivational measure for dog breeders.

A recent study reported musculoskeletal disorders as the most common reason for retirement due to health issues in working guide dogs (Caron-Lormier et al., 2016) and illustrates the particular importance of such diseases in dogs with an active life style. Three of the four breeds identified in paper I as having an increased risk of surgery for ED were the same as in several other studies. These breeds, the Labrador retriever, the Rottweiler and the German shepherd dog are commonly used as working dogs. Considering the time and resources required to educate a dog for important jobs in the society such as guide dogs and police dogs, lameness leading to withdrawal from working dog service has an impact beyond the welfare of the individual affected. The result of reducing the frequency of diseases such as ED in working dog populations is therefore important in a wider perspective and development of preventive measures should have a broader interest. An interesting finding from paper I was that the Staffordshire bull terrier had a high OR for ED. There is only one other study available reporting this breed among breeds predisposed for ED (Kirberger and Stander, 2007). As mentioned in the introduction, the Staffordshire bull terrier has gained great popularity in Norway and Sweden over recent years and has become one of the most common breeds in both countries. This may help explain why there is only one other study to date concerning this breeds' predisposition to ED.

Medial patellar luxation is far more common than lateral luxation in dogs (Bosio et al., 2017). Although several of the breeds included in paper I, such as the Chihuahua, the Cavalier King Charles spaniel and the Jack Russel terrier, are reported to have a high prevalence of patellar luxation (LaFond et al., 2002; Alam et al., 2007; O'Neill et al., 2016; Bosio et al., 2017), the Chihuahua was the only breed where an increased risk of MPL was identified. An increased risk of surgically treated MPL in this breed in Norway and Sweden is not surprising given the results from a recent Swedish study which reported the prevalence of patellar luxation in Swedish Chihuahuas to be as high as 23% (Nilsson et al., 2018). Some other studies have reported the Labrador retriever to have an increased prevalence of MPL (Gibbons et al., 2006; Alam et al., 2007; Bound et al., 2009). However, the Labrador retriever is the most common dog breed in the UK where many of these studies were conducted (Farrell et al., 2015). In the large-scale epidemiologic study by O'Neill et al. (2016) which investigated breed susceptibility for patellar luxation in dogs attending primary-care veterinary practices in the UK, no increased risk was identified in Labradors. The study thus concluded that earlier studies may have suffered referral bias due to the generally high level of Labrador retriever ownership. Although the Labrador retriever is one of the most popular breeds in Norway and Sweden as well, no Labrador retrievers presented with MPL in our material. According to the results from O'Neill and our study, it may seem more likely for Norwegian and Swedish Labradors to have a decreased rather than increased risk of the disease.

Fractures of long bones are the most common fracture types in both dogs and cats (Ness et al., 1996). Radius and ulna fractures are mostly encountered in small and miniature dogs, typically in toy breeds such as the Italian greyhound, the Pomeranian, the Chihuahua and the Yorkshire terrier and are often due to minor trauma (Piras et al., 2011). The absence of fractures of the radius and ulna in larger breeds in our material could therefore be expected. Considering the low body weight of the dogs with fractures of the radius and ulna in paper I, it is not surprising that the Chihuahua, the Cavalier King Charles spaniel and the Shetland sheepdog were the only studied breeds with the diagnosis.

Cranial cruciate ligament disease in dogs and cats

Aethiopathogenesis and epidemiology

As could be expected given the high prevalence of CCLD in dogs reported in other canine studies, the disease was among the most prevalent surgically treated orthopaedic conditions at SLU and NMBU during the study period. However, cruciate ligament ruptures are considered uncommon in cats. Knowing that the population of cats is almost the double of dogs in both Norway and Sweden, the low percentage (12.2%) of feline versus canine patients in paper II supports the assumption that CCLD is more common in dogs than in cats.

Although no reports of breed susceptibility to CCLD in cats have been published, mixed breed cats were more common than purebreds both in paper II and in the study by Ruthrauff et al. (2011). Since mixed breed domestic short- and longhaired cats also predominates the general cat population, there is currently no suspicion of any particular breed predisposition for the disease in cats. It should, however, be noticed that the available results only contain information on a small number of cats. Consequently, studies including more cats and appropriate control groups are needed for any conclusions to be drawn. In contrast to the situation in cats, purebred dogs outnumber mixed breeds in the Norwegian and Swedish dog population. In paper I, an increased risk of CCLD was detected in the Rottweiler, and a decreased risk in the German shepherd dog and the Chihuahua, which is consistent with earlier reports. However, in contrast to the findings from most other studies and despite the Labrador retriever being one of the most common breeds presenting with CCLD, the combined OR for CCLD was identical to mixed breed dogs. The country specific OR for CCLD in the Labrador retriever was lower than for mixed breed dogs in Sweden, but higher in Norway. As for several other breeds originally bred for hunting, and the retriever breeds in particular, two quite different types of Labradors exist; a slim, lighter working type and a heavier built show type. It is not known whether the likelihood of orthopaedic diseases is the same for both types. Moreover, the relative frequencies of show and field bred Labradors in Norway and Sweden are unknown. This could be a contributing factor to the deviating results observed in the two countries. Further investigations are needed to identify if there is a difference in risk of CCLD between the two strains of Labradors. Moreover, studies using other sample frames for case and control selection in Norway and Sweden (e.g. Agria insurance data) is needed for comparison before any further inference regarding the validity of the deviating results identified in paper I can be drawn.

In concordance with the results from Ruthrauff et al. (2011), an even sex distribution was identified for the cats suffering CCLD in paper II. In paper III, more female than male dogs were diagnosed with the disease, which is also in concordance with the current literature. Both Whitehair et al. (1993), Duval et al. (1999) and Taylor-Brown et al. (2015) reported a higher CCLD prevalence in female than in male dogs and an increased risk of CCLD in neutered compared to entire female dogs. The two latter studies found neutering to be the important risk factor, and no isolated effect of sex was identified. In the epidemiologic study by Adams et al. (2011), obesity was reported as an independent risk factor for CCLD, and in contrast to the studies mentioned above, no association between neutering and CCLD was identified. Moreover, neither body weight nor body condition differed significantly between entire and neutered dogs, although this could be expected given the greater risk of obesity in neutered compared to entire dogs reported in other studies (McGreevy et al., 2005). Since obesity neither was included in our study nor the other studies mentioned above, it is still unclear whether obesity is a confounder for neutering. An underlying association between obesity and neutering could possibly contribute to the reported higher risk of CCLD among neutered females and should therefore be addressed in future studies. Since neuter practices differ considerably between countries, the relationship between age at neutering, obesity and CCLD should also be explored. Although exact percentages of entire and neutered dogs unfortunately could not be retrieved from the medical records in paper III, the clear majority of dogs in Norway and Sweden are entire, as mentioned in the introduction. The high female-to-male ratio in paper III could therefore indicate that sex is a risk factor for CCLD in dogs, independent of neutering status.

Although the median age of the dogs in paper III was in the same range as in most other studies of CCLD treatment in dogs, it is worth noticing that the median age of dogs treated conservatively and by LFS were more than 3 years higher than the median age of the dogs treated by the osteotomy procedures. While the median age of the dogs treated by LFS were in the upper range of what has been reported in comparable studies, the opposite holds for the osteotomy procedures (Stauffer et al., 2006; Casale and McCarthy, 2009; Fitzpatrick and Solano, 2010; Christopher et al., 2013). Taken together, this illustrates that a selection bias was evident at the two hospitals in our study and might be more pronounced than in other comparable studies. It is, however, interesting that the average age reported in the studies mentioned above were generally 1-2 years lower than in the epidemiological study of CCLD in primary-care practices by Taylor-Brown et al. (2015). The median age of the dogs in the latter study was 7.4 years, which is approximately equal to the median age of the dogs treated conservatively and by LFS in our study. As earlier mentioned, most studies of CCLD treatment in dogs are conducted at university hospitals and referral practices. The discrepancy between the age of the dogs diagnosed in the primary-care setting and the age reported in conjunction with surgical treatment, imply that a considerable referral bias is likely evident in most studies of CCLD treatment in dogs. The case load at SLU and NMBU is composed of a mix of primary and referred patients, which could explain the somewhat older age of the dogs treated conservatively and by LFS in our study compared to most others.

The age of the cats in paper II was comparable to the few other published studies on CCLD in cats (Harasen, 2005; Ruthrauff et al., 2011; Mindner et al., 2016). Since a degenerative pathogenesis is suspected in most cases of CCLD in dogs, it is perhaps not surprising that the disease is most commonly observed in middle-aged to older dogs. However, considering that the aetiology is considered primarily traumatic in cats, it is interesting that the cats both in our material and in earlier studies were, on average, older than the reported age of dogs with the diagnosis.

While the median body weight of the cats in paper II was similar to that of randomly selected healthy controls in two earlier studies of CCLD in cats (Harasen, 2005; Wessely et al., 2017), and also in the same range as in the study by Ruthrauff et al. (2011), the median weight (23.6 kg) of the dogs in paper III was in the lower range of what has been reported in comparable studies. In the same manner as the median age was higher, the median weight was lower in both the conservatively treated and the LFS group than in the group treated by osteotomy procedures. This illustrates that the choice of CCLD treatment is likely to be influenced by the signalment of the dog, and the former two treatment options were more commonly used in smaller, older dogs. While the average body weight of dogs in the few other epidemiological studies where conservatively treated dogs have been included, such as the study by Taylor-Brown et al. (2015) mentioned above, has been in the same range as for the dogs in paper III, the reported body weight of surgically treated dogs are typically higher, ranging between 30 and 40 kg (Moore and Read, 1995; Stauffer et al., 2006; Casale and McCarthy, 2009; Christopher et al., 2013; Molsa et al., 2014). As mentioned in the introduction, although CCLD was originally described to mostly affect small and medium sized, middle-aged dogs, it is now generally considered a problem in larger dog breeds, peaking at a somewhat lower age. A change in disease predisposition over time can be explained by variations in the canine population due to factors such as modified breeding strategies and shifting breed popularity. Another potentially important and rarely addressed issue is the impact of the rapid development of small animal veterinary practices since the first larger CCLD studies were published in the sixties (i.e. Singleton (1969)). Orthopaedic surgery is now an important part of the everyday caseload in many primary small animal practices, a very unlikely scenario in the early days of small animal surgery. Consequently, an overrepresentation of surgically challenging cases for referral as could be expected today, was presumably less likely in the early reports. These older studies were therefore probably less influenced by a referral bias than newer studies conducted at university hospitals and referral practices. This reasoning is further supported by the results reported from primary-care practices in Taylor-Brown et al. (2015) and also paper III, as discussed above. Taken together with the findings from a recent UK surgeon survey of the current management of CCLD rupture in small dogs Comerford et al. (2013), which found conservative management to be a widely used treatment choice for this patient group, it seems likely for the discrepancy between the early and later reports of CCLD in dogs to, at least to a certain extent, to be a consequence of referral bias.

Considering the factors mentioned in the above paragraphs, it occurs that both the body weight and age of dogs reported in non-randomised studies where no conservatively treated dogs are included, are likely to be biased upwards. As such, the results of studies reporting outcome of one, or comparing several surgical techniques, might only be valid for dogs of similar body size and weight as the included cases. A corresponding logic can be applied for other variables related to inherent animal characteristics where a selection bias can be expected, such as concurrent comorbidities and severity of symptoms at presentation. When facing the multitude of rapidly expanding literature and conflicting evidence within the field of veterinary orthopaedic research, clinical decision-making and application of an ideal treatment might be difficult. Careful consideration of how different studies define "normal" and how different outcome measures are used is thus of particular importance when results are being interpreted and studies compared (Tonks et al., 2011). Given the relative lack of prospective randomised controlled trials available within veterinary orthopaedic research, the external validity of the results should always be carefully assessed when the treatment success of a particular surgical technique is reported or when one treatment option is deemed superior to another.

Bilateral disease was less than half as common in the cats in paper II as in the dogs in paper III even if the follow-up times were approximately similar. Although no feline studies are available for comparison, the occurrence of subsequent contralateral ruptures in cats in paper II was substantially lower than the 20–50% typically reported in canine studies. Moreover, several cats had CdCL ruptures and collateral ligament injuries, which are rare in dogs with CCLD (Pacchiana et al., 2003). The most common presentation for the cats in paper II was lameness of less than one-week duration. Although not included in the study due to inconsistent reporting in the records, a traumatic event was suspected in most of these cases.

There is an ongoing discussion about the aetiology of CCLD in cats. Although the study by Harasen (2005) supported both a traumatic and a degenerative aetiology of the disease, no histological evidence of a degenerative process in feline CrCL was identified in a recent study by Wessely et al. (2017). However, while 19 CrCLs were histologically examined in the latter study, only a single CrCL was included in the former. Since short-lasting, suspected trauma-induced, lameness was the most frequent presentation of the cats in our study and multi-ligament injuries were fairly common, a traumatic aetiology of CCLD in cats could be supported. On the other hand, as CCLD is a relatively rare disease in cats, 14% bilateral cases is a considerable number for a solely traumatic condition. Furthermore, the occurrence of a higher median age in cats than in dogs, where a degenerative pathogenesis *is* known, is another factor which could indicate that other, still unknown aspects play a role in the development of CCLD in cats.

Meniscal injury

The percentage of meniscal injury (47%) in the surgically treated cats in paper II was somewhat lower than an earlier report of 67% (Ruthrauff et al., 2011), but equals the number typically reported in canine studies. However, it is worth noticing that the percentage of meniscal injury in the cats were substantially higher than the 20-23% we observed in the dogs treated by LFS and osteotomy procedures in study III, despite comparable rates of joint inspections. The FMPI scores indicated that surgically treated cats experienced more chronic pain than the cats that were conservatively managed at long-term follow-up. Although the degree of meniscal injury was unknown among conservatively treated cats, these findings do not support meniscal injury as an argument for surgical treatment is cases of feline CCLD.

In most studies, including paper II and III in this thesis, concurrent meniscal injuries are treated in conjunction with the surgical stifle stabilisation. Thus, it is difficult to isolate the clinical effect due to meniscectomies from that of the stifle joint stabilisation procedure. It should be noted that an increasing number of surgeons have questioned the need for a routine meniscal examination (Jandi and Schulman, 2007; McCready and Ness, 2016). Although the results from a prospective cohort study by Ritzo et al. (2014) indicated that the type of meniscal treatment may have a greater impact on the postoperative outcome than the surgical CCLD technique itself, a recent study evaluating long-term outcome after TPLO surgery without joint exploration reported a low incidence of persistent lameness (Bureau, 2017). The systematic review of management of meniscal injuries in dogs by McCready and Ness (2016) concluded that the quality of evidence regarding treatment of meniscal injuries is generally low. Questions regarding the optimal treatment and impact of meniscal injuries on the prognosis of dogs and cats with CCLD remains to be answered.

Treatment and clinical outcome

Postoperative complications were relatively common for surgically treated dogs and cats that were included in paper II and III. Although none of the papers focused on postoperative complications, assessment of their impact is important in outcome evaluations and require attention. While the complication percentage for the LFS procedures in dogs (25.6%) was comparable to the cats (27%), the osteotomy procedures had a somewhat higher complication frequency at 36.4%. Classification of the complications was not performed, and consequently, the numbers can only be compared to other studies reporting overall complication levels. Although no comparable complication reports after LFS treatment in cats are available, the complication level in paper II was comparable with the TPLO treated cats in the study by Mindner et al. (2016). The percentage of complications among the dogs included in paper III was in the higher range of earlier studies, such as Casale and McCarthy (2009), Gatineau et al. (2011), Pacchiana et al. (2003) and Wolf et al. (2012), particularly for the osteotomy procedures. The reason for this will remain elusive, but it is worth noticing that in contrast to most other studies, where the procedures typically are performed by one or a few surgeons, more than a dozen surgeons with different levels of experience and familiarity with the procedures conducted the surgeries.

Although the results of the quality of life assessment of the cats in paper II indicated that the conservatively treated cats experienced less chronic pain at long-term follow-up than the surgically treated, the FMPI scores were suggestive of chronic pain for a number of cats in both groups. Previous studies have reported a normal locomotion pattern one year after experimental CrCL transection in cats, and good functional recovery after conservative treatment of CCLD (Scavelli and C., 1987; Suter et al., 1998). During the past two decades, single case reports with a low number of cats have described translation of the osteotomy techniques from dogs to cats, and although the preliminary results have been considered promising, such as the use of TPLO by Mindner et al. (2016), no long-term evaluations have been conducted. Since concurrent meniscal injuries was common among the cats with CCLD in the study by Ruthrauff et al. (2011), the authors suggested that surgical stabilisation with stifle exploration should be considered to limit the progression of degenerative joint disease as a result of meniscal injury in cases of feline CCLD. However, too few publications regarding outcome after CCLD in relation to treatment method in cats have been published to allow any conclusions regarding an optimal treatment strategy to be drawn.

The shortage of evidence-based literature within veterinary orthopaedic research is further illustrated by the results from the available literature reviews of surgical treatments for CCLD in dogs. In the review by Aragon and Budsberg (2005), manuscripts reporting outcome of one or more surgical CCLD techniques with some measure of patient follow-up were included. Only 28 studies with low-class evidence were identified, and the review concluded that there was insufficient evidence for favouring one surgical technique over another. A more recent review was conducted by Bergh et al. (2014) and a minimum of 6 months follow-up time was required for inclusion. Of the 444 peer-reviewed manuscripts identified, only 34 met the inclusion criteria, of which 7 were prospective studies. The rest were either case series or retrospective comparative studies. This latter review concluded that although the evidence is inconclusive, and too sparse for comparing the efficacy of different treatment interventions, there is some evidence in favour of TPLO as the preferred treatment method. This conclusion seems to be in concordance with the views of veterinary practitioners and surgeons as well; a 2016 survey of American veterinary orthopaedic surgeons suggested that TPLO was the preferred method for CCLD treatment of dogs >15 kg (von Pfeil et al., 2018). Although the findings from paper III provide further support for osteotomy procedures as the better treatment choice for CCLD in most dogs, issues relating to the external validity of the results should be kept in mind and generalisation avoided due to the biases discussed in the sections above. In particular, too little evidence is available for any conclusions to be drawn regarding the optimal treatment of CCLD in small dogs, and information related to treatment outcome for dogs managed in primary-care veterinary practices are lacking. Results from the multivariable Cox model in paper III showed that surgically treated dogs had a lower risk of CCLD-related euthanasia than the conservatively treated. This implies that, at least in this particular population of dogs, there is a risk of treatment failure resulting in euthanasia following conservative treatment of CCLD. Surgical treatment resulted in longer survival, and osteotomies had the lowest hazard of CCLD-related euthanasia. In the previously described study by Wucherer et al. (2013) of overweight dogs >20 kg, conservative treatment resulted in a less favorable outcome than TPLO, which is in concordance with our findings. It should, however, be noticed that two-thirds of the dogs in the conservative treatment group in that study had a successful outcome at the 52-week evaluation. Knowing that conservatively treated cats are doing well at long-term follow-up and that the hazard of CCLD-related euthanasia in the dogs in paper III was lower for lighter dogs, it seems reasonable to assume that conservative management might be a viable alternative for smaller dogs. Although the literature in general recommends surgical treatment unless there are clear contraindications (McKee and Cook, 2006), the arguments above can explain why conservative treatment is still widely used for small dogs, as shown by the results of the survey by Comerford et al. (2013). Moreover, the inclusion or exclusion of postoperative rehabilitation/physiotherapy has been documented to affect the clinical outcome (Marsolais et al., 2002), and prospective studies evaluating the impact of different rehabilitation programs as part of CCLD treatment are lacking. Further prospective randomised studies are warranted to get closer to the optimal treatment strategy of CCLD, in particular for small dogs.

Functional outcome assessment tools

Objective tools for gait analysis such as force plates and pressure walkways provide an opportunity for standardised, repeatable analysis of lameness in companion animals and have been included in most recent studies designed to test the efficacy of treatment interventions in dogs with CCLD. In some studies, FPGA has been performed in conjunction with other measurement tools such as thigh circumference and stifle joint goniometry values (Gordon-Evans et al., 2013; Molsa et al., 2014). Objective measurements are undoubtedly important tools for outcome assessment of diseases causing lameness in dogs and cats, but, ultimately, it will always be the owners’ perception of their pets’ function which determines their satisfaction with the treatment. Without the possibility to ask our pets about their function or degree of pain, owners observing them on a daily basis is the closest one can get in veterinary medicine to a measure of an animal’s overall function and wellbeing. Using quality of life questionnaires for assessment of pets’ behaviour and ability to perform various activities in the home environment is therefore important. This is particularly advantageous for cats, which are more prone to stress in a clinical setting than dogs. A proper validation of such clinical metrology instruments is crucial for ensuring that the questionnaires measure what was intended and that the included questions are understood in a similar way by all respondents; they should have sound discriminatory capacity and reliability. It is also important that the questionnaires are validated in the language they are to be used, since the perception of a question can change in the translation from the original language. The FMPI questionnaire has been compared to several other QoL instruments and evaluated to be a sound tool for owner assessment in cats (Stadig et al., 2017). Since it also was available in a Swedish translated version (Stadig, 2017), it was chosen as the instrument for outcome assessments of the cats in paper II.

Thus far, only results from individual outcome measurement methods have been used to evaluate the stifle functionality of dogs and cats with CCLD. In a recent study by Hyytiainen et al. (2018), commonly used objective evaluation methods were combined and presented as a numerical index, the Finnish Canine Stifle Index. This instrument does not require advanced equipment, and results are given on a scale. The use of such a testing battery has the potential of simplifying and providing a more uniform evaluation of the overall functional performance level of animals over time compared to single objective measurements. As such, it could be a useful supplement to QoL assessments in studies comparing outcomes of different treatment interventions in future CCLD research, in particular for studies conducted in primary practices where advanced gait analysers are unavailable.

All of the outcome measurement tools discussed above have in common that they evaluate the function of dogs still alive. Consequently, dogs being dead at the time of assessment will not be included, and paper III was the first published study to evaluate disease-related euthanasia in relation to treatment method in dogs with CCLD. Chronic clinical dysfunction due to a persistent lameness which results in a decision of euthanasia is the most serious outcome of CCLD and our results showed that a high percentage of the dogs with CCLD included in paper III were dead at the time of owner contact. It is also worth emphasising that already at one-year follow-up, 12.9% of the dogs had died or been euthanised. These findings suggest that exclusion of euthanised dogs has the potential to bias the results in long-term studies evaluating clinical function of dogs with CCLD. However, it is important to acknowledge that time to CCLD-related euthanasia only measure the most disastrous outcome and provide no information regarding the function of the dogs still alive. Inclusion of functional outcome assessment tools are therefore crucial to be able to answer the core question – given the individual animal's history, signalment and clinical findings; which treatment option is likely to provide the best outcome? Moreover, it is important to acknowledge that "best outcome" is no solid definition but will vary from case to case. For the owner of a middle-aged inactive, smaller sized dog, a 90% chance of return to 80% function with a simple, or no, surgical procedure and a minimal risk of severe complications, could be considered a very good prognosis. In contrast, a 50% chance of full functional recovery, but a 50% chance of severe complications following a complicated surgical procedure with hospitalisation and intensive rehabilitation, could make the owner mentioned above decide on euthanasia instead. For an owner of a young working dog, the conclusions could be the other way around; the latter scenario would be the only viable option, and a return to 80% function would be disastrous and result in a decision of euthanasia. With no clear-cut treatment recommendations available, similar considerations should be attempted from the first time a dog or a cat presents at its primary-care veterinarian and kept in mind throughout the whole process of diagnostics, treatment and follow-up.

Methodological considerations

Study design

All three studies included in this thesis are retrospective, observational studies. Since the raw data were not originally recorded for research purposes, assessing data quality and representativity is particularly important to be able to correctly describe and understand the intricate web of relationships between exposures and outcomes in the datasets.

Paper I was designed as a case-control study and paper II and III as historical cohorts. In general, cohorts are considered to provide stronger evidence than case-control studies since they measure development of new cases rather than existing ones and confirm that the proposed cause preceded development of the outcome (Caswell et al., 2018). The retrospective design of the included cohort studies in this thesis is typical for veterinary orthopaedic research, but possesses inherent weaknesses compared to the more time consuming, but structured data collection possible in a prospective design. In human orthopaedic research, several large-scale standardised databases, such as the Scandinavian ACL registries holding detailed surgical treatment data and follow-up information of an extensive number of patients, have been established during the past decades (e.g. Granan et al. (2008)). Such databases have served as the basis for numerous large-scale prospective cohort studies and are a valuable source of epidemiological orthopaedic data. Due to the paucity of RCTs in veterinary orthopaedic research, one could argue for a particular value of similar structured databases in this field of research. However, the establishment and maintenance of such large databases require extensive planning and large-scale funding over many years (Granan et al., 2008), resources seldom available to companion animal researchers. It is therefore not surprising that comparable large, prospective cohorts are yet to be established within the field of veterinary orthopaedics.

Different breed profiles among the orthopaedic cases at SLU and NMBU drew attention to the importance of appropriate control group selection for the validity of studies reporting breed susceptibility, and ultimately resulted in the geographically adjusted control group used in paper I. Some studies have a well-defined source population, but in studies based on hospital populations this is often not the case (Wacholder et al., 1992). In the present work some animals came from afar while others lived nearby, thus the actual source population from which the cases originated was unknown. As mentioned in the introduction of this thesis, regional variations in breed distribution were more pronounced than overall differences between Norway and Sweden. The Swedish University of Agricultural Sciences is situated in a middle-sized Swedish town, Uppsala, while NMBU is located in the city centre of Oslo, the capital of Norway. Both are referral hospitals receiving cases from a wide geographical range, thus basing the controls on raw ID-registry population data from Uppsala and Oslo, or the total registration numbers for Sweden and Norway, would introduce selection bias as they do not represent the actual source population. To minimise this potential bias, the ID-registry numbers from each county were adjusted by their relative contribution to the database of eligible cases. Nevertheless, we acknowledge that the representability of using such ID-register data for the control group calculations is difficult to assess and a limitation to the study design. While ID-marking is mandatory for all Swedish dogs and for pure-breed Norwegian dogs to be registered in the national kennel club, it is voluntary for mixed breed dogs in Norway. This discrepancy is another potential source of selection bias.

Many canine orthopaedic epidemiological studies report breed predisposition as raw prevalence without comparison to a control group (as in Guthrie et al. (2012) and Bosio et al. (2017)) or have sampled both cases and controls from hospital populations. The latter is typically the case for studies originating from large clinical databases such as the VetCompass system in the UK and the Banfield and Veterinary Medical Databases in the USA (Whitehair et al., 1993; O'Neill et al., 2014). Although containing data on thousands of animals, the information is restricted to dogs admitted to veterinary care, and not the actual source population. Even when such large clinical databases are used, the reported risk of disease can appear too high if the breed under investigation is less frequently represented in the database than in the source population (i.e. has a lower than average disposition for other diseases). Since the late 1990s, a Swedish database of dogs insured in the Agria insurance company has been used to compare breed predisposition of different diseases (Egenvall et al., 2000; Bergstrom et al., 2006; Egenvall et al., 2009; Heske et al., 2014). A limitation of using insured dogs as the reference is that uninsured dogs are not included. There is a possibility that owners of dogs belonging to breeds known to be susceptible to breed-specific health problems are more than average likely to insure their dogs. Whether this is counteracted by breed-specific restrictions on insurance payments for particular treatments, such as caesarean sections in breeds prone to dystocia, is unclear. Another limitation with insurance data is that the diagnosis is only recorded if the cost of the veterinary visit exceeds the deducible of the insurance. This likely leads to an underrepresentation of conservatively treated CCLD cases and other orthopaedic diseases where the diagnosis is based solely on clinical findings without the need of a more advanced diagnostic work-up.

If the controls fail to provide an unbiased sample of the population at risk of a disease, it may cause an incorrect impression that some breeds are predisposed to a particular condition. Hence, it is not surprising that the reported breed predispositions differ between studies. Although most studies do acknowledge the lack of a representative control group as a limitation, this important source of bias has rarely been problematised. However, the issue has come to light during the past 10 years, owing in particular to the work by Egenvall and O'Neill with colleagues, which have addressed the problem in relation to insurance and primary-care epidemiological data, respectively (Egenvall et al., 2009; O'Neill et al., 2014).

The findings from paper I illustrates that breed susceptibility reported from single-centre studies and/or studies with limited caseloads, including our study, should be interpreted with caution. It also highlights the importance of using large caseloads from different geographical regions and appropriate control groups when breed susceptibility for disease is reported. In general, small differences in breed susceptibilities should not be overstressed. Although some important sources of bias have been discussed in earlier sections, additional limitations to the studies included in this thesis should addressed. Firstly, only NMBU and SLU cases were included, and the unbalanced number of cases at the two hospitals resulted in different group sizes. Secondly, information regarding animals referred to other veterinary hospitals in the areas were lost, and conservatively treated dogs were not included in paper I. Moreover, it is not unlikely that the treatment and referral patterns of dogs with the same orthopaedic disease might differ between breeds due to factors such as size and temperament of the dog and differences in limb conformation affecting the surgical complexity. Consequently, this might contribute to the referral caseloads being biased towards more complicated cases, an issue briefly discussed earlier. Finally, the information in the databases could not be retrospectively confirmed or rejected; all results therefore rely on correct reporting of data. Information regarding the severity of lameness at initial presentation was not available for the cats and dogs in paper II and III, and radiographic OA assessments were lacking. An association between lameness severity, radiographic findings and treatment choice could bias the results in paper II and III.

While exposures such as two surgical treatment methods can be assigned to the study subjects by a formal randomisation process in RCTs, and further controlled by using block randomisation to ensure that important covariates (e.g. weight, age or radiographic OA-score) are equally distributed between the exposed and non-exposed animals when the study sample is small, these factors are normally uncontrolled in observational studies. It is therefore not uncommon for exposed subjects in observational studies to differ systematically from the unexposed, thereby making it inherently difficult to prove causality (Sargeant et al., 2014). Multivariable regression models, such as the logistic and cox regression analyses used in the studies included in this thesis, are commonly applied to adjust for such systematic differences in observational studies. However, other methods, such as the use of propensity scores, have been described. The propensity score is the likelihood of treatment assignment conditioned on the observed baseline characteristics, and it can be used to balance exposure groups and thereby reduce the effects of confounding in observational data (Austin, 2011). Although discussing propensity scores is beyond the scope of this thesis, by allowing estimation of average effects on the population level (marginal effects), the propensity score methods mimics controlled clinical trials (Austin, 2011). Since many observational studies in veterinary orthopaedic research is comparing treatments, thereby aiming at answering the same questions as in RCTs, propensity scores provide an interesting, but seldom used addition to the traditional regression methods.

The troublesome bias of the surgeon

The surgeon is a core element of all orthopaedic procedures. While the outcome of a certain medical treatment protocol initiated by a board-certified internist or a newly graduated veterinarian can be assumed to be identical, the individual surgeon’s experience with the procedure in question is likely to influence the treatment success. As mentioned, several surgeons with variable levels of experience performed the procedures included in the present work, and more than one surgeon were often involved in a particular case. We could not reliably determine the primary surgeon's level of experience or degree of familiarity with the procedure, and consequently were not able to evaluate if any association between experience and the outcome were present. Intuitively, more experience should entail less complications and more favourable outcomes. However, studies including several surgeons reduce the risk of a "single surgeon bias", and thus more accurately reflect the true complication frequency. It is possible to adjust for "the surgeon effect" analytically by the use of a multilevel approach. If experience level is classified, it can be assessed by including it as a fixed effect in the multivariable model. However, an underlying assumption is that experience equals skills. Although this might be reasonable, the relationship between experience and competence is unlikely linear as a high number of outliers can be expected (e.g. very talented young, less experienced surgeons and highly experienced surgeons with bad results). The influence of factors related to individual surgeons is consequently not possible to determine exactly. Furthermore, this important source of bias is rarely addressed in veterinary orthopaedic studies. The confounding bias of the surgeon is likely to influence the external validity of the studies. Therefore, extrapolation of results from studies of procedures performed by "experts" at a certain surgical technique (e.g. TPLO) to outcome expectations in common clinical practice should be avoided.

Statistical models

Survival analysis such as Cox proportional hazard models have an advantage compared to other multivariable regression models in the handling of incomplete data (Dohoo et al., 2014). All cases are included until their last recorded data alive or until they experience the event of interest. The event of interest is not restricted to death but can be used in assessment of other outcome types (e.g. postoperative complications). Patients being lost to follow-up is commonly encountered in all longitudinal studies and constitutes a problem in retrospective cohort studies based on incomplete clinical data, such as paper II and III included in this thesis. Since cases with incomplete follow-up can be included when survival models are applied, it is possible to gain more information from the same number of patient records compared to the more commonly used linear and logistic regression models. Due to this obvious advantage, survival analysis has gained wide acceptance in the human orthopaedic literature (Khan, 2017). However, they are still seldom used in small animal orthopaedic research publications.

The expected outcome of a given treatment of an individual animal with CCLD is, as mentioned, likely dependent on contributions from many different factors related to the characteristics of the individual, treatment (including surgeon and surgical technique) and the postoperative management. Common for all multivariable regression models such as linear, logistic and cox proportional hazard models is that there is a single outcome variable and all the remaining variables are explanatory variables. The intricacy of such factors and their interrelationship cannot be completely resolved within the frame of these traditional regression models, and even less so when applied to a retrospective data set with its inherent problems regarding data quality. Modern graphical multivariate modelling tools such as Additive Bayesian Network models provide a different framework for analysis of composite systems by focusing on structure discovery (Ward and Lewis, 2013). It allows for all variables to possibly be both outcome and explanatory and can therefore provide insight into associations in the complicated and correlated datasets which are often encountered in retrospective clinical research.

Future perspectives

The research conducted in this PhD-project has provided some answers, but further issues remain to be addressed.

Although the results from paper I provide important answers regarding breed predispositions for common orthopaedic diseases in Norwegian and Swedish dogs, the implications of using different control groups (i.e. hospital controls, insurance data, adjusted and unadjusted ID-registry data) in relation to breed susceptibility for disease should be addressed. More work is needed to collect prevalence data for inherited diseases in all breeds; to determine the impact of such diseases on animal welfare, develop preventive measures and perform better welfare risk assessments.

Further knowledge is required to understand the multifactorial and intricate causes of cranial cruciate ligament disease in dogs and cats. The results from paper II and III elucidate important aspects of the disease in both species but are accompanied by ambiguity typical for retrospective studies. Thus, causality cannot be inferred with complete certainty which illustrates the need for well-designed prospective studies within the field of veterinary orthopaedic research. The results from our studies only constitute a small piece of the complex CCLD puzzle.

As previously discussed, there is a need to enhance the understanding of the association between bodyweight, obesity and neutering as risk factors for development of CCLD. To gain further insight into the aethiopathogenesis, it is necessary to include dogs presenting at primary care practices, as referral populations are likely to suffer from selection bias. Since lifestyle and signalment of the dog (for instance body size and obesity) can influence treatment choice and also pet owners' perception of treatment success, such factors should be accounted for in future outcome evaluations of different treatment options. Moreover, better knowledge about the relative importance of the different components of treatment interventions (e.g. meniscectomy, stifle stabilisation technique, postoperative rehabilitation) would allow informed choices among veterinary surgeons on CCLD treatment. In particular, to objectively evaluate conservative treatment as an option for small dogs, prospective studies comparing non-surgical and surgical treatment options are needed. Although the results from paper II enhanced the current understanding of CCLD treatment in cats, more studies, preferably with a prospective, randomised design, are required to enable assessment of the different treatment options in cats. There is also a general need for exploration of the association between surgeon experience level and outcome after surgery. Furthermore, paper III demonstrates that survival analysis is often more appropriate than the logistic regression models typically used in retrospective studies reporting treatment outcome after CCLD surgery. Survival analysis provides a useful methodological framework with a potential for better utilisation of clinical data in companion animal orthopaedic research in the future.

Concluding remarks

- When a clinical case population was compared to a geographically adjusted control population for reporting breed susceptibility for orthopaedic diseases in dogs in Norway and Sweden, most results, such as an increased risk of CCLD in the Rottweiler and MPL in the Chihuahua, were in concordance with the current literature.
- Although commonly regarded as a predisposed breed, an increased risk of CCLD was not identified in the Labrador retriever. The Staffordshire bull terrier was found to have increased risk of ED.
- Breed predispositions are not necessarily consistent between countries; thus it is important to use large caseloads from different geographic regions and appropriate control groups when reporting breed susceptibility for a given disease.
- Conservatively treated cats with CCLD experienced less chronic pain at long-term follow-up compared to surgically treated cats, according to a QoL assessment.
- Multi-ligament stifle injuries were fairly common in cats with surgically treated CCLD.
- Although trauma is considered important for development of CCLD in cats, subsequent rupture of the contralateral CrCL was not uncommon.
- Meniscal disease and postoperative complications were frequently observed in surgically treated cats and dogs with CCLD.
- Euthanasia related to CCLD in dogs was not uncommon, indicating that the disease can result in such severe lameness that it affects life expectancy.
- Treatment strategy, age, body weight and other orthopaedic comorbidities were identified as risk factors for CCLD-related euthanasia. A lower hazard was associated with osteotomy techniques compared to conservative management.
- Information regarding life expectancy in relation to risk factors and treatment intervention is valuable for a dog owner facing a decision about treatment of CCLD.
- Unanswered questions still remain regarding the epidemiology of orthopaedic diseases in Norwegian and Swedish dogs and cats. In general, the evidence-based

literature comparing outcomes after the various treatment options of CCLD in dogs and cats is sparse.

Reference list

ACAC, 2010. Contribution of the pet care industry to the Australian economy (Report). Australian Companion Animal Council. Available at: https://www.paws4play.com.au/pdfs/2010-Bis-Shrapnel-EconomPet-Benefits.pdf.

Adams, P., Bolus, R., Middleton, S., Moores, A.P., Grierson, J., 2011. Influence of signalment on developing cranial cruciate rupture in dogs in the UK. J. Small Anim. Pract. 52, 347-352. http://dx.doi.org/10.1111/j.1748-5827.2011.01073.x

Agria Pet Insurance, 2019. The economical impact of CCLD in Agria insurance claims (Personal communication).

Alam, M.R., Lee, J.I., Kang, H.S., Kim, I.S., Park, S.Y., Lee, K.C., Kim, N.S., 2007. Frequency and distribution of patellar luxation in dogs. 134 cases (2000 to 2005). Vet. Comp. Orthop. Traumatol. 20, 59-64. http://dx.doi.org/10.1055/s-0037-1616589

AMA, 2016. Pet ownership in Australia (Report). Animal Medicines Australia Pty Ltd. Available at: https://animalmedicinesaustralia.org.au/wp-content/uploads/2016/11/AMA_Pet-Ownership-in-Australia-2016-Report_sml.pdf.

Aragon, C.L., Budsberg, S.C., 2005. Applications of evidence-based medicine: cranial cruciate ligament injury repair in the dog. Vet. Surg. 34, 93-98. http://dx.doi.org/10.1111/j.1532-950X.2005.00016.x

Arnoczky, S., Marshall, J., 1977. The cruciate ligaments of the canine stifle: an anatomical and functional analysis. Am. J. Vet. Res. 38, 1807-1814.

Arnoczky, S.P., Rubin, R.M., Marshall, J.L., 1979. Microvasculature of the cruciate ligaments and its response to injury. An experimental study in dogs. J. Bone Joint Surg. Am. 61, 1221-1229.

Arnoczky, S.P., Warren, R.F., 1983. The microvasculature of the meniscus and its response to injury. An experimental study in the dog. Am. J. Sports Med. 11, 131-141. http://dx.doi.org/10.1177/036354658301100305

Asher, L., Buckland, E.L., Phylactopoulos, C.I., Whiting, M.C., Abeyesinghe, S.M., Wathes, C.M., 2011. Estimation of the number and demographics of companion dogs in the UK. BMC Vet. Res. 7, 74. http://dx.doi.org/10.1186/1746-6148-7-74

Au, K.K., Gordon-Evans, W.J., Dunning, D., O'Dell-Anderson, K.J., Knap, K.E., Griffon, D., Johnson, A.L., 2010. Comparison of short- and long-term function and radiographic osteoarthrosis in dogs after postoperative physical rehabilitation and tibial plateau leveling osteotomy or lateral fabellar suture stabilization. Vet. Surg. 39, 173-180. http://dx.doi.org/10.1111/j.1532-950X.2009.00628.x

Austin, P.C., 2011. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivariate Behav. Res. 46, 399-424. http://dx.doi.org/10.1080/00273171.2011.568786

AVMA, 2012. US pet ownership & demographics sourcebook. American Veterinary Medical Association.

Baird, A.E., Carter, S.D., Innes, J.F., Ollier, W., Short, A., 2014a. Genome-wide association study identifies genomic regions of association for cruciate ligament rupture in Newfoundland dogs. Anim. Genet. 45, 542-549. http://dx.doi.org/10.1111/age.12162

Baird, A.E., Carter, S.D., Innes, J.F., Ollier, W.E., Short, A.D., 2014b. Genetic basis of cranial cruciate ligament rupture (CCLR) in dogs. Connect. Tissue Res. 55, 275-281. http://dx.doi.org/10.3109/03008207.2014.910199

Baltzer, W.I., Smith-Ostrin, S., Warnock, J.J., Ruaux, C.G., 2018. Evaluation of the clinical effects of diet and physical rehabilitation in dogs following tibial plateau leveling osteotomy. J. Am. Vet. Med. Assoc. 252, 686-700. http://dx.doi.org/10.2460/javma.252.6.686

Barnhart, M.D., Maritato, K., Schankereli, K., Wotton, H., Naber, S., 2016. Evaluation of an intra-articular synthetic ligament for treatment of cranial cruciate ligament disease in dogs: a six-

month prospective clinical trial. Vet. Comp. Orthop. Traumatol. 29, 491-498. http://dx.doi.org/10.3415/VCOT-15-12-0206
Bellumori, T.P., Famula, T.R., Bannasch, D.L., Belanger, J.M., Oberbauer, A.M., 2013. Prevalence of inherited disorders among mixed-breed and purebred dogs: 27,254 cases (1995-2010). J. Am. Vet. Med. Assoc. 242, 1549-1555. http://dx.doi.org/10.2460/javma.242.11.1549
Benito, J., Depuy, V., Hardie, E., Zamprogno, H., Thomson, A., Simpson, W., Roe, S., Hansen, B., Lascelles, B.D., 2013a. Reliability and discriminatory testing of a client-based metrology instrument, feline musculoskeletal pain index (FMPI) for the evaluation of degenerative joint disease-associated pain in cats. Vet. J. 196, 368-373. http://dx.doi.org/10.1016/j.tvjl.2012.12.015
Benito, J., Hansen, B., Depuy, V., Davidson, G.S., Thomson, A., Simpson, W., Roe, S., Hardie, E., Lascelles, B.D., 2013b. Feline musculoskeletal pain index: responsiveness and testing of criterion validity. J. Vet. Intern. Med. 27, 474-482. http://dx.doi.org/10.1111/jvim.12077
Bennett, D., Tennant, B., Lewis, D.G., Baughan, J., May, C., Carter, S., 1988. A reappraisal of anterior cruciate ligament disease in the dog. J. Small Anim. Pract. 29, 275-297.
Bergh, M.S., Sullivan, C., Ferrell, C.L., Troy, J., Budsberg, S.C., 2014. Systematic review of surgical treatments for cranial cruciate ligament disease in dogs. J. Am. Anim. Hosp. Assoc. 50, 315-321. http://dx.doi.org/10.5326/JAAHA-MS-6356
Bergstrom, A., Nodtvedt, A., Lagerstedt, A.S., Egenvall, A., 2006. Incidence and breed predilection for dystocia and risk factors for cesarean section in a Swedish population of insured dogs. Vet. Surg. 35, 786-791. http://dx.doi.org/10.1111/j.1532-950X.2006.00223.x
Bilmont, A., Retournard, M., Asimus, E., Palierne, S., Autefage, A., 2018. Effect of tibial plateau levelling osteotomy on cranial tibial subluxation in the feline cranial cruciate deficient stifle joint: an ex vivo experimental study. Vet. Comp. Orthop. Traumatol. 31, 273-278. http://dx.doi.org/10.1055/s-0038-1653960
Bleedorn, J.A., Greuel, E.N., Manley, P.A., Schaefer, S.L., Markel, M.D., Holzman, G., Muir, P., 2011. Synovitis in dogs with stable stifle joints and incipient cranial cruciate ligament rupture: a cross-sectional study. Vet. Surg. 40, 531-543. http://dx.doi.org/10.1111/j.1532-950X.2011.00841.x
Bono, C.M., Tornetta, P., 2006. Common errors in the design of orthopaedic studies. Injury. 37, 355-360. http://dx.doi.org/10.1016/j.injury.2006.01.028
Bosio, F., Bufalari, A., Peirone, B., Petazzoni, M., Vezzoni, A., 2017. Prevalence, treatment and outcome of patellar luxation in dogs in Italy. A retrospective multicentric study (2009-2014). Vet. Comp. Orthop. Traumatol. 30, 364-370. http://dx.doi.org/10.3415/VCOT-16-05-0073
Boudrieau, R.J., 2009. Tibial plateau leveling osteotomy or tibial tuberosity advancement? Vet. Surg. 38, 1-22. http://dx.doi.org/10.1111/j.1532-950X.2008.00439.x
Bound, N., Zakai, D., Butterworth, S.J., Pead, M., 2009. The prevalence of canine patellar luxation in three centres. Clinical features and radiographic evidence of limb deviation. Vet. Comp. Orthop. Traumatol. 22, 32-37.
Brown, D.C., Boston, R.C., Coyne, J.C., Farrar, J.T., 2007. Development and psychometric testing of an instrument designed to measure chronic pain in dogs with osteoarthritis. Am. J. Vet. Res. 68, 631-637. http://dx.doi.org/10.2460/ajvr.68.6.631
Brown, D.C., Boston, R.C., Farrar, J.T., 2013. Comparison of force plate gait analysis and owner assessment of pain using the Canine Brief Pain Inventory in dogs with osteoarthritis. J. Vet. Intern. Med. 27, 22-30. http://dx.doi.org/10.1111/jvim.12004
Buote, N., Fusco, J., Radasch, R., 2009. Age, tibial plateau angle, sex, and weight as risk factors for contralateral rupture of the cranial cruciate ligament in Labradors. Vet. Surg. 38, 481-489. http://dx.doi.org/10.1111/j.1532-950X.2009.00532.x
Bureau, S., 2017. Owner assessment of the outcome of tibial plateau levelling osteotomy without meniscal evaluation for treatment of naturally occurring cranial cruciate ligament rupture:

130 cases (2009 to 2013). J. Small Anim. Pract. 58, 468-475. http://dx.doi.org/10.1111/jsap.12691
Burton, N., Owen, M., 2008. Canine elbow dysplasia 2. Treatment and prognosis. In Pract. 30, 552-557. http://dx.doi.org/http://dx.doi.org/10.1136/inpract.30.10.552
Cabaud, H.E., Rodkey, W.G., Feagin, J.A., 1979. Experimental studies of acute anterior cruciate ligament injury and repair. Am. J. Sports Med. 7, 18-22. http://dx.doi.org/10.1177/036354657900700105
Cabrera, S.Y., Owen, T.J., Mueller, M.G., Kass, P.H., 2008. Comparison of tibial plateau angles in dogs with unilateral versus bilateral cranial cruciate ligament rupture: 150 cases (2000-2006). J. Am. Vet. Med. Assoc. 232, 889-892. http://dx.doi.org/10.2460/javma.232.6.889
Caron-Lormier, G., England, G.C.W., Green, M.J., Asher, L., 2016. Using the incidence and impact of health conditions in guide dogs to investigate healthy ageing in working dogs. Vet. J. 207, 124-130. http://dx.doi.org/10.1016/j.tvjl.2015.10.046
Carpenter Jr, D.H., Cooper, R.C., 2000. Mini review of canine stifle joint anatomy. Anat. Histol. Embryol. 29, 321-329.
Casale, S.A., McCarthy, R.J., 2009. Complications associated with lateral fabellotibial suture surgery for cranial cruciate ligament injury in dogs: 363 cases (1997-2005). J. Am. Vet. Med. Assoc. 234, 229-235. http://dx.doi.org/10.2460/javma.234.2.229
Caswell, J.L., Bassel, L.L., Rothenburger, J.L., Grone, A., Sargeant, J.M., Beck, A.P., Ekman, S., Gibson-Corley, K.N., Kuiken, T., LaDouceur, E.E.B., Meyerholz, D.K., Origgi, F.C., Posthaus, H., Priestnall, S.L., Ressel, L., Sharkey, L., Teixeira, L.B.C., Uchida, K., Ward, J.M., Webster, J.D., Yamate, J., 2018. Observational study design in veterinary pathology, part 1: Study design. Vet. Pathol. 55, 607-621. http://dx.doi.org/10.1177/0300985818785705
Chauvet, A.E., Johnson, A.L., Pijanowski, G.J., Homco, L., Smith, R.D., 1996. Evaluation of fibular head transposition, lateral fabellar suture, and conservative treatment of cranial cruciate ligament rupture in large dogs: a retrospective study. J. Am. Anim. Hosp. Assoc. 32, 247-255. http://dx.doi.org/10.5326/15473317-32-3-247
Christopher, S.A., Beetem, J., Cook, J.L., 2013. Comparison of long-term outcomes associated with three surgical techniques for treatment of cranial cruciate ligament disease in dogs. Vet. Surg. 42, 329-334. http://dx.doi.org/10.1111/j.1532-950X.2013.12001.x
Chuang, C., Ramaker, M.A., Kaur, S., Csomos, R.A., Kroner, K.T., Bleedorn, J.A., Schaefer, S.L., Muir, P., 2014. Radiographic risk factors for contralateral rupture in dogs with unilateral cranial cruciate ligament rupture. PLoS One. 9, e106389. http://dx.doi.org/10.1371/journal.pone.0106389
Collins, L.M., Asher, L., Summers, J., McGreevy, P., 2011. Getting priorities straight: risk assessment and decision-making in the improvement of inherited disorders in pedigree dogs. Vet. J. 189, 147-154. http://dx.doi.org/10.1016/j.tvjl.2011.06.012
Comerford, E., Forster, K., Gorton, K., Maddox, T., 2013. Management of cranial cruciate ligament rupture in small dogs: a questionnaire study. Vet. Comp. Orthop. Traumatol. 26, 493-497. http://dx.doi.org/10.3415/VCOT-12-06-0070
Comerford, E.J., Innes, J.F., Tarlton, J.F., Bailey, A.J., 2004. Investigation of the composition, turnover, and thermal properties of ruptured cranial cruciate ligaments of dogs. Am. J. Vet. Res. 65, 1136-1141.
Conzemius, M.G., Evans, R.B., Besancon, M.F., Gordon, W.J., Horstman, C.L., Hoefle, W.D., Nieves, M.A., Wagner, S.D., 2005. Effect of surgical technique on limb function after surgery for rupture of the cranial cruciate ligament in dogs. J. Am. Vet. Med. Assoc. 226, 232-236.
de Rooster, H., de Bruin, T., van Bree, H., 2006. Morphologic and functional features of the canine cruciate ligaments. Vet. Surg. 35, 769-780. http://dx.doi.org/10.1111/j.1532-950X.2006.00221.x
de Sousa, R., Sutcliffe, M., Rousset, N., Holmes, M., Langley-Hobbs, S.J., 2015. Treatment of cranial cruciate ligament rupture in the feline stifle. Biomechanical comparison of a standard

fabella-tibial suture and lateral sutures placed between quasi-isometric points. Vet. Comp. Orthop. Traumatol. 28, 401-408. http://dx.doi.org/10.3415/VCOT-14-05-0078
Dohoo, I.R., Martin, S.W., Stryhn, H., 2014. Veterinary epidemiologic research. VER, Inc. Charlotte, P.E.I.
Doom, M., de Bruin, T., de Rooster, H., van Bree, H., Cox, E., 2008. Immunopathological mechanisms in dogs with rupture of the cranial cruciate ligament. Vet. Immunol. Immunopathol. 125, 143-161. http://dx.doi.org/10.1016/j.vetimm.2008.05.023
Doring, A.K., Junginger, J., Hewicker-Trautwein, M., 2018. Cruciate ligament degeneration and stifle joint synovitis in 56 dogs with intact cranial cruciate ligaments: Correlation of histological findings and numbers and phenotypes of inflammatory cells with age, body weight and breed. Vet. Immunol. Immunopathol. 196, 5-13. http://dx.doi.org/10.1016/j.vetimm.2017.12.006
Duerr, F.M., Martin, K.W., Rishniw, M., Palmer, R.H., Selmic, L.E., 2014. Treatment of canine cranial cruciate ligament disease. A survey of ACVS Diplomates and primary care veterinarians. Vet. Comp. Orthop. Traumatol. 27, 478-483. http://dx.doi.org/10.3415/VCOT-14-03-0047
Duval, J.M., Budsberg, S.C., Flo, G.L., Sammarco, J.L., 1999. Breed, sex, and body weight as risk factors for rupture of the cranial cruciate ligament in young dogs. J. Am. Vet. Med. Assoc. 215, 811-814.
Dymond, N.L., Goldsmid, S.E., Simpson, D.J., 2010. Tibial tuberosity advancement in 92 canine stifles: initial results, clinical outcome and owner evaluation. Aust. Vet. J. 88, 381-385. http://dx.doi.org/10.1111/j.1751-0813.2010.00627.x
DyreID, 2018. Populasjon hund og katt (Personal communication).
Egenvall, A., Bonnett, B.N., Olson, P., Hedhammar, A., 2000. Gender, age, breed and distribution of morbidity and mortality in insured dogs in Sweden during 1995 and 1996. Vet. Rec. 146, 519-525. http://dx.doi.org/10.1136/vr.146.18.519
Egenvall, A., Nodtvedt, A., Penell, J., Gunnarsson, L., Bonnett, B.N., 2009. Insurance data for research in companion animals: benefits and limitations. Acta Vet. Scand. 51, 42. http://dx.doi.org/10.1186/1751-0147-51-42
Ertelt, J., Fehr, M., 2009. Cranial cruciate ligament repair in dogs with and without meniscal lesions treated by different minimally invasive methods. Vet. Comp. Orthop. Traumatol. 22, 21-26. http://dx.doi.org/10.3415/VCOT-07-06-0063
Etchepareborde, S., Brunel, L., Bollen, G., Balligand, M., 2011. Preliminary experience of a modified Maquet technique for repair of cranial cruciate ligament rupture in dogs. Vet. Comp. Orthop. Traumatol. 24, 223-227. http://dx.doi.org/10.3415/VCOT-10-01-0012
Farrell, L.L., Schoenebeck, J.J., Wiener, P., Clements, D.N., Summers, K.M., 2015. The challenges of pedigree dog health: approaches to combating inherited disease. Canine Genet. Epidemiol. 2, 3. http://dx.doi.org/10.1186/s40575-015-0014-9
FEDIAF, 2017. European Facts & Figures (Report). The European Pet Food Industry. Available at: http://www.fediaf.org/component/attachments/attachments.html?task=attachment&id=2019.
Fitzpatrick, N., Solano, M.A., 2010. Predictive variables for complications after TPLO with stifle inspection by arthrotomy in 1000 consecutive dogs. Vet. Surg. 39, 460-474. http://dx.doi.org/10.1111/j.1532-950X.2010.00663.x
Galloway, R.H., Lester, S.J., 1995. Histopathological evaluation of canine stifle joint synovial membrane collected at the time of repair of cranial cruciate ligament rupture. J. Am. Anim. Hosp. Assoc. 31, 289-294. http://dx.doi.org/10.5326/15473317-31-4-289
Gatineau, M., Dupuis, J., Plante, J., Moreau, M., 2011. Retrospective study of 476 tibial plateau levelling osteotomy procedures. Rate of subsequent 'pivot shift', meniscal tear and other complications. Vet. Comp. Orthop. Traumatol. 24, 333-341. http://dx.doi.org/10.3415/VCOT-10-07-0109

Ghirlanda, S., Acerbi, A., Herzog, H., Serpell, J.A., 2013. Fashion vs. function in cultural evolution: the case of dog breed popularity. PLoS One. 8, e74770. http://dx.doi.org/10.1371/journal.pone.0074770

Gibbons, S.E., Macias, C., Tonzing, M.A., Pinchbeck, G.L., McKee, W.M., 2006. Patellar luxation in 70 large breed dogs. J. Small Anim. Pract. 47, 3-9. http://dx.doi.org/10.1111/j.1748-5827.2006.00004.x

Gordon-Evans, W.J., Griffon, D.J., Bubb, C., Knap, K.M., Sullivan, M., Evans, R.B., 2013. Comparison of lateral fabellar suture and tibial plateau leveling osteotomy techniques for treatment of dogs with cranial cruciate ligament disease. J. Am. Vet. Med. Assoc. 243, 675-680. http://dx.doi.org/10.2460/javma.243.5.675

Granan, L.P., Bahr, R., Steindal, K., Furnes, O., Engebretsen, L., 2008. Development of a national cruciate ligament surgery registry: the Norwegian National Knee Ligament Registry. Am. J. Sports Med. 36, 308-315. http://dx.doi.org/10.1177/0363546507308939

Grierson, J., Asher, L., Grainger, K., 2011. An investigation into risk factors for bilateral canine cruciate ligament rupture. Vet. Comp. Orthop. Traumatol. 24, 192-196. http://dx.doi.org/10.3415/VCOT-10-03-0030

Griffon, D.J., 2010. A review of the pathogenesis of canine cranial cruciate ligament disease as a basis for future preventive strategies. Vet. Surg. 39, 399-409. http://dx.doi.org/10.1111/j.1532-950X.2010.00654.x

Gruen, M.E., Griffith, E.H., Thomson, A.E., Simpson, W., Lascelles, B.D., 2015. Criterion validation testing of clinical metrology instruments for measuring degenerative joint disease associated mobility impairment in cats. PLoS One. 10, e0131839. http://dx.doi.org/10.1371/journal.pone.0131839

Guthrie, J.W., Keeley, B.J., Maddock, E., Bright, S.R., May, C., 2012. Effect of signalment on the presentation of canine patients suffering from cranial cruciate ligament disease. J. Small Anim. Pract. 53, 273-277. http://dx.doi.org/10.1111/j.1748-5827.2011.01202.x

Hans, E.C., Barnhart, M.D., Kennedy, S.C., Naber, S.J., 2017. Comparison of complications following tibial tuberosity advancement and tibial plateau levelling osteotomy in very large and giant dogs 50 kg or more in body weight. Vet. Comp. Orthop. Traumatol. 30, 299-305. http://dx.doi.org/10.3415/VCOT-16-07-0106

Harasen, G.L., 2005. Feline cranial cruciate rupture: 17 cases and a review of the literature. Vet. Comp. Orthop. Traumatol. 18, 254-257. http://dx.doi.org/10.1055/s-0038-1632963

Hayashi, K., Frank, J.D., Dubinsky, C., Zhengling, H., Markel, M.D., Manley, P.A., Muir, P., 2003. Histologic changes in ruptured canine cranial cruciate ligament. Vet. Surg. 32, 269-277. http://dx.doi.org/10.1053/jvet.2003.50023

Heffron, L.E., Campbell, J.R., 1978. Morphology, histology and functional anatomy of the canine cranial cruciate ligament. Vet. Rec. 102, 280-283. http://dx.doi.org/10.1136/vr.102.13.280

Hercock, C.A., Pinchbeck, G., Giejda, A., Clegg, P.D., Innes, J.F., 2009. Validation of a client-based clinical metrology instrument for the evaluation of canine elbow osteoarthritis. J. Small Anim. Pract. 50, 266-271. http://dx.doi.org/10.1111/j.1748-5827.2009.00765.x

Heske, L., Nodtvedt, A., Jaderlund, K.H., Berendt, M., Egenvall, A., 2014. A cohort study of epilepsy among 665,000 insured dogs: incidence, mortality and survival after diagnosis. Vet. J. 202, 471-476. http://dx.doi.org/10.1016/j.tvjl.2014.09.023

Hielm-Bjorkman, A.K., Rita, H., Tulamo, R.M., 2009. Psychometric testing of the Helsinki chronic pain index by completion of a questionnaire in Finnish by owners of dogs with chronic signs of pain caused by osteoarthritis. Am. J. Vet. Res. 70, 727-734. http://dx.doi.org/10.2460/ajvr.70.6.727

Hodgman, S.F.J., 1963. Abnormalities and defects in pedigree dogs–I. An investigation into the existence of abnormalities in pedigree dogs in the British Isles. J. Small Anim. Pract. 4, 447-456. http://dx.doi.org/10.1111/j.1748-5827.1963.tb01301.x

Hoelzler, M.G., Millis, D.L., Francis, D.A., Weigel, J.P., 2004. Results of arthroscopic versus open arthrotomy for surgical management of cranial cruciate ligament deficiency in dogs. Vet. Surg. 33, 146-153. http://dx.doi.org/10.1111/j.1532-950X.2004.04022.x
Hoots, E.A., Petersen, S.W., 2005. Tibial plateau leveling osteotomy and cranial closing wedge ostectomy in a cat with cranial cruciate ligament rupture. J. Am. Anim. Hosp. Assoc. 41, 395-399. http://dx.doi.org/10.5326/0410395
Hurley, C.R., Hammer, D.L., Shott, S., 2007. Progression of radiographic evidence of osteoarthritis following tibial plateau leveling osteotomy in dogs with cranial cruciate ligament rupture: 295 cases (2001-2005). J. Am. Vet. Med. Assoc. 230, 1674-1679. http://dx.doi.org/10.2460/javma.230.11.1674
Hyytiainen, H.K., Molsa, S.H., Junnila, J.J.T., Laitinen-Vapaavuori, O.M., Hielm-Bjorkman, A.K., 2018. Developing a testing battery for measuring dogs' stifle functionality: the Finnish Canine Stifle Index (FCSI). Vet. Rec. 183, 324. http://dx.doi.org/10.1136/vr.104588
Jandi, A.S., Schulman, A.J., 2007. Incidence of motion loss of the stifle joint in dogs with naturally occurring cranial cruciate ligament rupture surgically treated with tibial plateau leveling osteotomy: longitudinal clinical study of 412 cases. Vet. Surg. 36, 114-121. http://dx.doi.org/10.1111/j.1532-950X.2006.00226.x
Janovec, J., Kyllar, M., Midgley, D., Owen, M., 2017. Conformation of the proximal tibia and cranial cruciate ligament disease in small breed dogs. Vet. Comp. Orthop. Traumatol. 30, 178-183. http://dx.doi.org/10.3415/VCOT-16-07-0115
Jerre, S., 2009. Rehabilitation after extra-articular stabilisation of cranial cruciate ligament rupture in dogs. Vet. Comp. Orthop. Traumatol. 22, 148-152.
[dataset] Jordbruksverket, 2018. Statistik ur hundregistret. Jordbruksverket. Available at: http://www.jordbruksverket.se/download/18.63ce7af168237994fb96d04/1546964651472/Antal%20hundar%20per%20län%20och%20kommun%202018.pdf
Kalff, S., Meachem, S., Preston, C., 2011. Incidence of medial meniscal tears after arthroscopic assisted tibial plateau leveling osteotomy. Vet. Surg. 40, 952-956. http://dx.doi.org/10.1111/j.1532-950X.2011.00910.x
Keijser, S.F.A., Meijndert, L.E., Fieten, H., Carriere, B.J., van Steenbeek, F.G., Leegwater, P.A.J., Rothuizen, J., Nielen, M., 2017. Disease burden in four populations of dog and cat breeds compared to mixed-breed dogs and European shorthair cats. Prev. Vet. Med. 140, 38-44. http://dx.doi.org/10.1016/j.prevetmed.2017.02.016
Khan, T., 2017. Survival analysis of time-to-event data in orthopaedic surgery: Current concepts. Bone & Joint 360 6, 37-39.
Kim, S.E., Pozzi, A., Kowaleski, M.P., Lewis, D.D., 2008. Tibial osteotomies for cranial cruciate ligament insufficiency in dogs. Vet. Surg. 37, 111-125. http://dx.doi.org/10.1111/j.1532-950X.2007.00361.x
King, M.D., 2017. Etiopathogenesis of canine hip dysplasia, prevalence, and genetics. Vet. Clin. North Am. Small Anim. Pract. 47, 753-767. http://dx.doi.org/10.1016/j.cvsm.2017.03.001
Kirberger, R.M., Stander, N., 2007. Incidence of canine elbow dysplasia in South Africa. J. S. Afr. Vet. Assoc. 78, 59-62. http://dx.doi.org/10.4102/jsava.v78i2.290
Kleinbaum, D.G., Kupper, L.L., Morgenstern, H., 1982. Epidemiologic research: Principles and quantitative methods. John Wiley & Sons Inc. New York, United States.
Kneifel, W., Borak, D., Bockstahler, B., Schnabl-Feichter, E., 2018. Use of a custom-made limb-press model to assess intra- and extracapsular techniques for treating cranial cruciate ligament rupture in cats. J. Feline Med. Surg. 20, 271-279. http://dx.doi.org/10.1177/1098612X17704562
Korvick, D.L., Johnson, A.L., Schaeffer, D.J., 1994a. Surgeons' preferences in treating cranial cruciate ligament ruptures in dogs. J. Am. Vet. Med. Assoc. 205, 1318-1324.
Korvick, D.L., Pijanowski, G.J., Schaeffer, D.J., 1994b. Three-dimensional kinematics of the intact and cranial cruciate ligament-deficient stifle of dogs. J. Biomech. 27, 77-87.

Kowaleski, M.P., Boudrieau, R.J., Pozzi, A., 2018. Stifle joint. In: Johnston, S.A., Tobias, K.M. (Eds.), Veterinary Surgery : Small Animal. Elsevier, St.Louis, Missouri.
Kyllar, M., Cizek, P., 2018. Cranial cruciate ligament structure in relation to the tibial plateau slope and intercondylar notch width in dogs. J. Vet. Sci. 19, 699-707. http://dx.doi.org/10.4142/jvs.2018.19.5.699
Lafaver, S., Miller, N.A., Stubbs, W.P., Taylor, R.A., Boudrieau, R.J., 2007. Tibial tuberosity advancement for stabilization of the canine cranial cruciate ligament-deficient stifle joint: surgical technique, early results, and complications in 101 dogs. Vet. Surg. 36, 573-586. http://dx.doi.org/10.1111/j.1532-950X.2007.00307.x
LaFond, E., Breur, G.J., Austin, C.C., 2002. Breed susceptibility for developmental orthopedic diseases in dogs. J. Am. Anim. Hosp. Assoc. 38, 467-477. http://dx.doi.org/10.5326/0380467
Lascelles, B.D., Henry, J.B., 3rd, Brown, J., Robertson, I., Sumrell, A.T., Simpson, W., Wheeler, S., Hansen, B.D., Zamprogno, H., Freire, M., Pease, A., 2010. Cross-sectional study of the prevalence of radiographic degenerative joint disease in domesticated cats. Vet. Surg. 39, 535-544. http://dx.doi.org/10.1111/j.1532-950X.2010.00708.x
Lascelles, B.D., Roe, S.C., Smith, E., Reynolds, L., Markham, J., Marcellin-Little, D., Bergh, M.S., Budsberg, S.C., 2006. Evaluation of a pressure walkway system for measurement of vertical limb forces in clinically normal dogs. Am. J. Vet. Res. 67, 277-282. http://dx.doi.org/10.2460/ajvr.67.2.277
Leroy, G., 2011. Genetic diversity, inbreeding and breeding practices in dogs: results from pedigree analyses. Vet. J. 189, 177-182. http://dx.doi.org/10.1016/j.tvjl.2011.06.016
Marsolais, G.S., Dvorak, G., Conzemius, M.G., 2002. Effects of postoperative rehabilitation on limb function after cranial cruciate ligament repair in dogs. J. Am. Vet. Med. Assoc. 220, 1325-1330.
McCready, D.J., Ness, M.G., 2016. Systematic review of the prevalence, risk factors, diagnosis and management of meniscal injury in dogs: Part 2. J. Small Anim. Pract. 57, 194-204. http://dx.doi.org/10.1111/jsap.12462
McGreevy, P.D., Thomson, P.C., Pride, C., Fawcett, A., Grassi, T., Jones, B., 2005. Prevalence of obesity in dogs examined by Australian veterinary practices and the risk factors involved. Vet. Rec. 156, 695-702. http://dx.doi.org/10.1136/vr.156.22.695
McKee, M.W., Cook, J.L., 2006. The stifle. In: Houlton, J., Cook, J.L., Innes, J.F., Langley-Hobbs, S.J. (Eds.), BSAVA Manual of Canine and Feline Musculoskeletal Disorders Blackwell Professional Publishing.
Metelman, A.L., Schwarz, P.D., Salman, M., Alvis, M.R., 1995. An evaluation of three different cranial cruciate ligament surgical stabilization procedures as they relate to postoperative meniscal injuries. Vet. Comp. Orthop. Traumatol. 8, 118-123. http://dx.doi.org/10.1055/s-0038-1632440
Michelsen, J., 2013. Canine elbow dysplasia: aetiopathogenesis and current treatment recommendations. Vet. J. 196, 12-19. http://dx.doi.org/10.1016/j.tvjl.2012.11.009
Mindner, J.K., Bielecki, M.J., Scharvogel, S., Meiler, D., 2016. Tibial plateau levelling osteotomy in eleven cats with cranial cruciate ligament rupture. Vet. Comp. Orthop. Traumatol. 29, 528-535. http://dx.doi.org/10.3415/VCOT-15-11-0184
Molsa, S.H., Hyytiainen, H.K., Hielm-Bjorkman, A.K., Laitinen-Vapaavuori, O.M., 2014. Long-term functional outcome after surgical repair of cranial cruciate ligament disease in dogs. BMC Vet. Res. 10, 266. http://dx.doi.org/10.1186/s12917-014-0266-8
Monk, M.L., Preston, C.A., McGowan, C.M., 2006. Effects of early intensive postoperative physiotherapy on limb function after tibial plateau leveling osteotomy in dogs with deficiency of the cranial cruciate ligament. Am. J. Vet. Res. 67, 529-536. http://dx.doi.org/10.2460/ajvr.67.3.529

Montavon, P.M., Damur, D.M., Tepic, S., 2002. Advancement of the tibial tuberosity for the treatment of cranial cruciate ligament deficient canine stifle. In, 1st World Orth Vet Congress 2002, Munich, Germany.
Moore, K.W., Read, R.A., 1995. Cranial cruciate ligament rupture in the dog--a retrospective study comparing surgical techniques. Aust. Vet. J. 72, 281-285. http://dx.doi.org/10.1111/j.1751-0813.1995.tb03555.x
Morris, E., Lipowitz, A.J., 2001. Comparison of tibial plateau angles in dogs with and without cranial cruciate ligament injuries. J. Am. Vet. Med. Assoc. 218, 363-366. http://dx.doi.org/10.2460/javma.2001.218.363
Muir, P., Schwartz, Z., Malek, S., Kreines, A., Cabrera, S.Y., Buote, N.J., Bleedorn, J.A., Schaefer, S.L., Holzman, G., Hao, Z., 2011. Contralateral cruciate survival in dogs with unilateral non-contact cranial cruciate ligament rupture. PLoS One. 6, e25331. http://dx.doi.org/10.1371/journal.pone.0025331
Ness, M.G., Abercromby, R.H., May, C., Turner, B.M., Carmichael, S., 1996. A survey of orthopaedic conditions in small animal veterinary practice in Britain. Vet. Comp. Orthop. Traumatol. 9, 43-52. http://dx.doi.org/10.1055/s-0038-1632502
Nilsson, K., Zanders, S., Malm, S., 2018. Heritability of patellar luxation in the Chihuahua and Bichon Frise breeds of dogs and effectiveness of a Swedish screening programme. Vet. J. 234, 136-141. http://dx.doi.org/10.1016/j.tvjl.2018.01.010
[dataset] NKK, 2017. Registreringstall alle raser. The Norwegian Kennel Club. Available at: https://www.nkk.no/getfile.php/131972992-1517566047/Dokumenter/Om%20NKK/Organisasjonen/Statistikk/2017%20-%20Registreringstall%20alle%20raser%2C%20inkludert%20de%20siste%2025%20%C3%A5rene.xlsx
[dataset] NKK, 2018. Antall hunder registrert pr fylke. The Norwegian Kennel Club. Available at: https://www.nkk.no/getfile.php/132102894-1548924154/Dokumenter/Om%20NKK/Organisasjonen/Statistikk/2018%20Antall%20hunder%20registrert%20pr%20fylke%20%28delt%20ned%20til%20kommune%2C%20rasegr%2C%20rase%29.xlsx
NKK, 2019. Brachycephalic Obstructive Airway Syndrome (BOAS) The Norwegian Kennel Club Available at: https://www.nkk.no/boas/category1341.html. (accessed 20.08.2019).
Animal Welfare Act (LOV-2009-06-19-97). 2009. Norwegian Ministry of Agriculture and Food. Available at: https://lovdata.no/dokument/NL/lov/2009-06-19-97. (accessed 15.05.2019).
Djurskyddslag (SFS 2018:1192). 2018. Näringsdepartementet. Available at: https://www.riksdagen.se/sv/dokument-lagar/dokument/svensk-forfattningssamling/djurskyddslag-20181192_sfs-2018-1192. (accessed 14.05.2019).
O'Neill, D.G., Church, D.B., McGreevy, P.D., Thomson, P.C., Brodbelt, D.C., 2014. Approaches to canine health surveillance. Canine Genet. Epidemiol. 1, 2. http://dx.doi.org/10.1186/2052-6687-1-2
O'Neill, D.G., Meeson, R.L., Sheridan, A., Church, D.B., Brodbelt, D.C., 2016. The epidemiology of patellar luxation in dogs attending primary-care veterinary practices in England. Canine Genet. Epidemiol. 3, 4. http://dx.doi.org/10.1186/s40575-016-0034-0
Olsson, S.O., Baekbo, P., Hansson, S.O., Rautala, H., Osteras, O., 2001. Disease recording systems and herd health schemes for production diseases. Acta Vet. Scand. Suppl. 94, 51-60. http://dx.doi.org/10.1186/1751-0147-42-S1-S51
Pacchiana, P.D., Morris, E., Gillings, S.L., Jessen, C.R., Lipowitz, A.J., 2003. Surgical and postoperative complications associated with tibial plateau leveling osteotomy in dogs with cranial cruciate ligament rupture: 397 cases (1998-2001). J. Am. Vet. Med. Assoc. 222, 184-193. http://dx.doi.org/10.2460/javma.2003.222.184
Paschos, N.K., Howell, S.M., 2016. Anterior cruciate ligament reconstruction: principles of treatment. EFORT Open Rev 1, 398-408. http://dx.doi.org/10.1302/2058-5241.1.160032

PDSA, 2013. Animal Wellbeing Report 2013: The state of our pet nation (Report). People's Dispensary for Sick Animals. Available at: https://www.pdsa.org.uk/media/2579/paw_report_2013.pdf.
Perry, K., Fitzpatrick, N., 2010. Tibial tuberosity advancement in two cats with cranial cruciate ligament deficiency. Vet. Comp. Orthop. Traumatol. 23, 196-202. http://dx.doi.org/10.3415/VCOT-09-02-0014
Piras, L., Cappellari, F., Peirone, B., Ferretti, A., 2011. Treatment of fractures of the distal radius and ulna in toy breed dogs with circular external skeletal fixation: a retrospective study. Vet. Comp. Orthop. Traumatol. 24, 228-235. http://dx.doi.org/10.3415/VCOT-10-06-0089
Pond, M., Campbell, J., 1972. The canine stifle joint I. Rupture of the anterior cruciate ligament: an assessment of conservative and surgical treatment. J. Small Anim. Pract. 13, 1-10.
Prestrud, K.W., 2019. Registration numbers of the three pilot breeds in the Nordic countries (Personal communication).
Quinn, M.M., Keuler, N.S., Lu, Y., Faria, M.L., Muir, P., Markel, M.D., 2007. Evaluation of agreement between numerical rating scales, visual analogue scoring scales, and force plate gait analysis in dogs. Vet. Surg. 36, 360-367. http://dx.doi.org/10.1111/j.1532-950X.2007.00276.x
Ramirez, J., Barthelemy, N., Noel, S., Claeys, S., Etchepareborde, S., Farnir, F., Balligand, M., 2015. Complications and outcome of a new modified Maquet technique for treatment of cranial cruciate ligament rupture in 82 dogs. Vet. Comp. Orthop. Traumatol. 28, 339-346. http://dx.doi.org/10.3415/VCOT-14-10-0153
Reif, U., Probst, C.W., 2003. Comparison of tibial plateau angles in normal and cranial cruciate deficient stifles of Labrador retrievers. Vet. Surg. 32, 385-389. http://dx.doi.org/10.1053/jvet.2003.50047
Retournard, M., Bilmont, A., Asimus, E., Palierne, S., Autefage, A., 2016. Effect of tibial tuberosity advancement on cranial tibial subluxation in the feline cranial cruciate deficient stifle joint: An ex vivo experimental study. Res. Vet. Sci. 107, 240-245. http://dx.doi.org/10.1016/j.rvsc.2016.06.005
Ritzo, M.E., Ritzo, B.A., Siddens, A.D., Summerlott, S., Cook, J.L., 2014. Incidence and type of meniscal injury and associated long-term clinical outcomes in dogs treated surgically for cranial cruciate ligament disease. Vet. Surg. 43, 952-958. http://dx.doi.org/10.1111/j.1532-950X.2014.12220.x
Ruthrauff, C.M., Glerum, L.E., Gottfried, S.D., 2011. Incidence of meniscal injury in cats with cranial cruciate ligament ruptures. Can. Vet. J. 52, 1106-1110.
Sallander, M., Hedhammar, A., Rundgren, M., Lindberg, J.E., 2001. Demographic data of a population of insured Swedish dogs measured in a questionnaire study. Acta Vet. Scand. 42, 71-80.
Sargeant, J.M., Kelton, D.F., O'Connor, A.M., 2014. Study designs and systematic reviews of interventions: building evidence across study designs. Zoonoses Public Health 61 Suppl 1, 10-17. http://dx.doi.org/10.1111/zph.12127
Sargeant, J.M., O'Connor, A.M., Dohoo, I.R., Erb, H.N., Cevallos, M., Egger, M., Ersboll, A.K., Martin, S.W., Nielsen, L.R., Pearl, D.L., Pfeiffer, D.U., Sanchez, J., Torrence, M.E., Vigre, H., Waldner, C., Ward, M.P., 2016. Methods and processes of developing the strengthening the reporting of observational studies in epidemiology - veterinary (STROBE-Vet) statement. J. Vet. Intern. Med. 30, 1887-1895. http://dx.doi.org/10.1111/jvim.14574
Scavelli, T.D., C., S.S., 1987. Nonsurgical management of rupture of the cranial cruciate ligament in 18 cats. J. Am. Anim. Hosp. Assoc. 23, 337–340.
SCB, 2012. Hundar, katter och andra sällskapsdjur (Report). Available at: https://www.skk.se/globalassets/dokument/om-skk/scb-undersokning-hundar-katter-och-andra-sallskapsdjur-2012.pdf.

Schwandt, C.S., Bohorquez-Vanelli, A., Tepic, S., Hassig, M., Dennler, R., Vezzoni, A., Montavon, P.M., 2006. Angle between the patellar ligament and tibial plateau in dogs with partial rupture of the cranial cruciate ligament. Am. J. Vet. Res. 67, 1855-1860. http://dx.doi.org/10.2460/ajvr.67.11.1855

Singleton, W.B., 1969. Observations based upon the surgical repair of 106 cases of anterior cruciate ligament rupture. J. Small Anim. Pract. 10, 269-278. http://dx.doi.org/10.1111/j.1748-5827.1969.tb04657.x

[dataset] SKK, 2015. SKK verksamhet. The Swedish Kennel Club. Available at: https://www.skk.se/globalassets/dokument/om-skk/verksamhetssiffror-skk-2015.pdf

[dataset] SKK, 2018. Registreringsstatistik. The Swedish Kennel Club. Available at: https://www.skk.se/globalassets/...skk/registreringsstatistik-2018

Slocum, B., Devine, T., 1983. Cranial tibial thrust: a primary force in the canine stifle. J. Am. Vet. Med. Assoc. 183, 456-459.

Slocum, B., Slocum, T.D., 1993. Tibial plateau leveling osteotomy for repair of cranial cruciate ligament rupture in the canine. Vet. Clin. North Am. Small Anim. Pract. 23, 777-795.

Smith, G.K., Torg, J.S., 1985. Fibular head transposition for repair of cruciate-deficient stifle in the dog. J. Am. Vet. Med. Assoc. 187, 375-383.

Stadig, S., 2017. Evaluation of physical dysfunction in cats with naturally occurring osteoarthritis. Department of Clinical Science. Swedish University of Agricultural Sciences, Uppsala (PhD-thesis).

Stadig, S., Lascelles, B.D., Bergh, A., 2017. Preliminary validity testing of four clinical metrology instruments in osteoarthritic cats. In, BSAVA Congress Proceedings 2017, 494-495.

StataCorp, 2017. Stata Statistical Software: Release 15. StataCorp LLC, College Station, TX.

Stauffer, K.D., Tuttle, T.A., Elkins, A.D., Wehrenberg, A.P., Character, B.J., 2006. Complications associated with 696 tibial plateau leveling osteotomies (2001-2003). J. Am. Anim. Hosp. Assoc. 42, 44-50. http://dx.doi.org/10.5326/0420044

Stork, C.K., Gibson, N.R., Owen, M.R., Li, A., Schwarz, T., Bennett, D., Carmichael, S., 2001. Radiographic features of a lateral extracapsular wire suture in the canine cranial cruciate deficient stifle. J. Small Anim. Pract. 42, 487-490.

Stroup, D.F., Berlin, J.A., Morton, S.C., Olkin, I., Williamson, G.D., Rennie, D., Moher, D., Becker, B.J., Sipe, T.A., Thacker, S.B., 2000. Meta-analysis of observational studies in epidemiology: a proposal for reporting. JAMA 283, 2008-2012. http://dx.doi.org/10.1001/jama.283.15.2008

Suter, E., Herzog, W., Leonard, T.R., Nguyen, H., 1998. One-year changes in hind limb kinematics, ground reaction forces and knee stability in an experimental model of osteoarthritis. J. Biomech. 31, 511-517.

Talaat, M.B., Kowaleski, M.P., Boudrieau, R.J., 2006. Combination tibial plateau leveling osteotomy and cranial closing wedge osteotomy of the tibia for the treatment of cranial cruciate ligament-deficient stifles with excessive tibial plateau angle. Vet. Surg. 35, 729-739. http://dx.doi.org/10.1111/j.1532-950X.2006.00217.x

Tashman, S., Anderst, W., Kolowich, P., Havstad, S., Arnoczky, S., 2004. Kinematics of the ACL-deficient canine knee during gait: serial changes over two years. J. Orthop. Res. 22, 931-941. http://dx.doi.org/10.1016/j.orthres.2004.01.008

Taylor-Brown, F.E., Meeson, R.L., Brodbelt, D.C., Church, D.B., McGreevy, P.D., Thomson, P.C., O'Neill, D.G., 2015. Epidemiology of cranial cruciate ligament disease diagnosis in dogs attending primary-care veterinary practices in England. Vet. Surg. 44, 777-783. http://dx.doi.org/10.1111/vsu.12349

Thrusfield, M., Christley, R., 2018. Veterinary Epidemiology. Wiley Blackwell Hoboken N.J., USA.

Tonks, C.A., Lewis, D.D., Pozzi, A., 2011. A review of extra-articular prosthetic stabilization of the cranial cruciate ligament-deficient stifle. Vet. Comp. Orthop. Traumatol. 24, 167-177. http://dx.doi.org/10.3415/VCOT-10-06-0084

Umphlet, R.C., 1993. Feline stifle disease. Vet. Clin. North Am. Small Anim. Pract. 23, 897-913. http://dx.doi.org/10.1016/S0195-5616(93)50090-6

Vandeweerd, J.M., Kirschvink, N., Clegg, P., Vandenput, S., Gustin, P., Saegerman, C., 2012. Is evidence-based medicine so evident in veterinary research and practice? History, obstacles and perspectives. Vet. J. 191, 28-34. http://dx.doi.org/10.1016/j.tvjl.2011.04.013

Vannini, R., 2015. Treatment strategies in growing dogs and adult dogs with elbow disease. In, World Small Animal Veterinary Association World Congress.

Vasseur, P.B., 1984. Clinical results following nonoperative management for rupture of the cranial cruciate ligament in dogs. Vet. Surg. 13, 243-246. http://dx.doi.org/10.1111/j.1532-950X.1984.tb00801.x

Vasseur, P.B., Pool, R.R., Arnoczky, S.P., Lau, R.E., 1985. Correlative biomechanical and histologic study of the cranial cruciate ligament in dogs. Am. J. Vet. Res. 46, 1842-1854.

VDH, 2012. Geschäftsbericht zum Jahr 2012 (Report). Verband für das Deutsche Hundewesen. Available at: http://www.vdh.de/tl_files/media/pdf/VDH_Geschaeftsbericht_2012.pdf.

Veissier, I., Butterworth, A., Bock, B., Roe, E., 2008. European approaches to ensure good animal welfare. Appl. Anim. Behav. Sci. 113, 279-297. http://dx.doi.org/10.1016/j.applanim.2008.01.008

von Pfeil, D.J.F., Kowaleski, M.P., Glassman, M., Dejardin, L.M., 2018. Results of a survey of Veterinary Orthopedic Society members on the preferred method for treating cranial cruciate ligament rupture in dogs weighing more than 15 kilograms (33 pounds). J. Am. Vet. Med. Assoc. 253, 586-597. http://dx.doi.org/10.2460/javma.253.5.586

Wacholder, S., McLaughlin, J.K., Silverman, D.T., Mandel, J.S., 1992. Selection of controls in case-control studies. I. Principles. Am. J. Epidemiol. 135, 1019-1028. http://dx.doi.org/10.1093/oxfordjournals.aje.a116396

Walton, M.B., Cowderoy, E., Lascelles, D., Innes, J.F., 2013. Evaluation of construct and criterion validity for the 'Liverpool Osteoarthritis in Dogs' (LOAD) clinical metrology instrument and comparison to two other instruments. PLoS One. 8, e58125. http://dx.doi.org/10.1371/journal.pone.0058125

Ward, M.P., Lewis, F.I., 2013. Bayesian Graphical modelling: applications in veterinary epidemiology. Prev. Vet. Med. 110, 1-3. http://dx.doi.org/10.1016/j.prevetmed.2013.02.007

Wayne, R.K., Ostrander, E.A., 2007. Lessons learned from the dog genome. Trends Genet. 23, 557-567. http://dx.doi.org/10.1016/j.tig.2007.08.013

Weh, J.L., Kowaleski, M.P., Boudrieau, R.J., 2011. Combination tibial plateau leveling osteotomy and transverse corrective osteotomy of the proximal tibia for the treatment of complex tibial deformities in 12 dogs. Vet. Surg. 40, 670-686. http://dx.doi.org/10.1111/j.1532-950X.2011.00826.x

Wessely, M., Reese, S., Schnabl-Feichter, E., 2017. Aetiology and pathogenesis of cranial cruciate ligament rupture in cats by histological examination. J. Feline Med. Surg. 19, 631-637. http://dx.doi.org/10.1177/1098612X16645142

Whitehair, J.G., Vasseur, P.B., Willits, N.H., 1993. Epidemiology of cranial cruciate ligament rupture in dogs. J. Am. Vet. Med. Assoc. 203, 1016-1019.

Wiles, B.M., Llewellyn-Zaidi, A.M., Evans, K.M., O'Neill, D.G., Lewis, T.W., 2017. Large-scale survey to estimate the prevalence of disorders for 192 Kennel Club registered breeds. Canine Genet. Epidemiol. 4, 8. http://dx.doi.org/10.1186/s40575-017-0047-3

Wilke, V.L., Conzemius, M.G., Besancon, M.E., Evans, R.B., Ritter, M., 2002. Comparison of tibial plateau angle between clinically normal Greyhounds and Labrador Retrievers with and without rupture of the cranial cruciate ligament. J. Am. Vet. Med. Assoc. 221, 1426-1429. http://dx.doi.org/DOI 10.2460/javma.2002.221.1426

Wilke, V.L., Conzemius, M.G., Kinghorn, B.P., Macrossan, P.E., Cai, W., Rothschild, M.F., 2006. Inheritance of rupture of the cranial cruciate ligament in Newfoundlands. J. Am. Vet. Med. Assoc. 228, 61-64. http://dx.doi.org/10.2460/javma.228.1.61
Wilke, V.L., Robinson, D.A., Evans, R.B., Rothschild, M.F., Conzemius, M.G., 2005. Estimate of the annual economic impact of treatment of cranial cruciate ligament injury in dogs in the United States. J. Am. Vet. Med. Assoc. 227, 1604-1607.
Wilke, V.L., Zhang, S., Evans, R.B., Conzemius, M.G., Rothschild, M.F., 2009. Identification of chromosomal regions associated with cranial cruciate ligament rupture in a population of Newfoundlands. Am. J. Vet. Res. 70, 1013-1017. http://dx.doi.org/10.2460/ajvr.70.8.1013
Witsberger, T.H., Villamil, J.A., Schultz, L.G., Hahn, A.W., Cook, J.L., 2008. Prevalence of and risk factors for hip dysplasia and cranial cruciate ligament deficiency in dogs. J. Am. Vet. Med. Assoc. 232, 1818-1824. http://dx.doi.org/10.2460/javma.232.12.1818
Wolf, R.E., Scavelli, T.D., Hoelzler, M.G., Fulcher, R.P., Bastian, R.P., 2012. Surgical and postoperative complications associated with tibial tuberosity advancement for cranial cruciate ligament rupture in dogs: 458 cases (2007-2009). J. Am. Vet. Med. Assoc. 240, 1481-1487. http://dx.doi.org/10.2460/javma.240.12.1481
Wucherer, K.L., Conzemius, M.G., Evans, R., Wilke, V.L., 2013. Short-term and long-term outcomes for overweight dogs with cranial cruciate ligament rupture treated surgically or nonsurgically. J. Am. Vet. Med. Assoc. 242, 1364-1372. http://dx.doi.org/10.2460/javma.242.10.1364

Paper I

Boge *et al. Acta Vet Scand (2019) 61:19*
https://doi.org/10.1186/s13028-019-0454-4

Acta Veterinaria Scandinavica

RESEARCH

Open Access

Breed susceptibility for common surgically treated orthopaedic diseases in 12 dog breeds

Gudrun Seeberg Boge[1*], Elena Regine Moldal[1], Maria Dimopoulou[2], Eystein Skjerve[3] and Annika Bergström[2]

Abstract

Background: A retrospective case–control study was conducted to estimate breed predisposition for common orthopaedic conditions in 12 popular dog breeds in Norway and Sweden. Orthopaedic conditions investigated were elbow dysplasia (ED); cranial cruciate ligament disease (CCLD); medial patellar luxation (MPL); and fractures of the radius and ulna. Dogs surgically treated for the conditions above at the Swedish and Norwegian University Animal Hospitals between the years 2011 and 2015 were compared with a geographically adjusted control group calculated from the national ID-registries. Logistic regression analyses (stratified for clinic and combined) were used to calculate odds ratios (OR) and 95% confidence intervals. Mixed breed dogs were used as reference.

Results: Breeds found at-risk for ED were the Labrador retriever (OR = 5.73), the Rottweiler (OR = 5.63), the German shepherd dog (OR = 3.31) and the Staffordshire bull terrier (OR = 3.08). The Chihuahua was the only breed where an increased risk for MPL (OR = 2.80) was identified. While the Rottweiler was the only breed predisposed for CCLD (OR = 3.96), the results were conflicting for the Labrador retriever (OR = 0.44 in Sweden, 2.85 in Norway); the overall risk was identical to mixed-breed dogs.

Conclusions: Most results are in concordance with earlier studies. However, an increased risk of CCLD was not identified for the Labrador retriever, the Staffordshire bull terrier was found to have an increased risk of ED and some country-specific differences were noted. These results highlight the importance of utilising large caseloads and appropriate control groups when breed susceptibility is reported.

Keywords: Canine, Cruciate ligament, Elbow dysplasia, Fractures, Patellar luxation, Radius, Ulna

Background

Surgical correction of orthopaedic disease implies pain and sometimes an uncertain prognosis for the animal, in addition to emotional stress for both the dog and its owner. Moreover, the time and money spent on veterinary consultations and an often extensive postoperative rehabilitation process should not be neglected. Information regarding breed susceptibility in different orthopaedic disorders in dogs may aid in the development of preventive measures, as well as act as a guide for potential pet owners and a motivational measure for dog breeders.

*Correspondence: gudrun.seeberg.boge@nmbu.no
[1] Department of Companion Animal Clinical Sciences, Faculty of Veterinary Medicine, Norwegian University of Life Sciences, P.O. Box 369 sentrum, N-0102 Oslo, Norway
Full list of author information is available at the end of the article

Most of the common orthopaedic diseases seen in small animal practice today are considered multifactorial in origin, with physical conformation and genetics being predisposing factors. Several epidemiological studies have reported the prevalence of different orthopaedic conditions and their risk factors in dogs, including breed predisposition. Most of these studies have sampled the study subjects, both cases and controls, from hospital populations, often at larger referral and university hospitals, and have not taken the breed distribution of the background population into account [1, 2].

The purpose of controls is to provide valid information regarding the background frequency of an exposure (i.e. a particular dog breed) within the population at risk of becoming a case (i.e. individuals who are free of the disease in question) [3–5]. Correct control selection is crucial to the internal validity of case–control studies [6]. When both cases and controls are collected from hospital populations in defined geographic areas, the controls may fail to provide an unbiased sample of the population at risk, and results in respect to exposure status might be unreliable [3, 5]. In the context of breed susceptibility this may lead to an incorrect impression that some popular breeds are predisposed to conditions when in fact they are not. Hence, it is not surprising that the reported breed predispositions differ between studies [1, 2].

Unaffected individuals from the population of animals in the same geographic region as the hospitals where the cases are collected, can be used as controls to enhance the probability that cases and controls come from the same source population [7]. In Norway and Sweden, comprehensive national ID-registries containing searchable information of all ID-marked dogs (DyreID and DjurID, respectively) are available. ID-marking (microchipping) is mandatory for all dogs holding a passport in Europe,[1] all dogs in Sweden,[2] as well as for pure-breed dogs registered in the Norwegian Kennel Club.[3] Even though ID-marking is not mandatory for mixed-breed dogs in Norway, it is estimated that approximately 85% of all Norwegian dogs are marked (Vatn G, personal communication 2018). The numbers are likely higher in Sweden. The ID-databases provide an opportunity for selection of control animals from the same geographical areas as the hospital populations, and thereby increase the likelihood of sampling controls from the same source population as the cases.

The objective of this study was to estimate breed susceptibility for common orthopaedic conditions in popular dog breeds in Norway and Sweden.

Methods

Study design

A retrospective case–control study was performed, utilising clinical, demographic and geographic data from two Veterinary Teaching Hospitals in Norway and Sweden and demographic and geographic data from the Norwegian and Swedish national ID-registries, DyreID and DjurID.

Data extraction and study population

The study population consisted of all canine patients treated at two Veterinary Teaching Hospitals (VTH); University Animal Hospital, Swedish University of Agricultural Sciences (SLU) and University Animal Hospital, Norwegian University of Life Sciences (NMBU), between January 1, 2011 through December 31, 2015. Cases were purposively sampled from the study population to ensure inclusion of the most common surgically treated orthopaedic diseases and common dog breeds in the source population. Medical records of all dogs that were surgically treated for orthopaedic diseases were reviewed retrospectively and registered in a database. Diagnosis, demographic (breed, age, sex, body weight) and geographic (VTH and dog owners' county of residence at the time of surgery) data were recorded and each record was screened for completeness. Only initial surgery was recorded for animals with bilateral disease. Dogs were eligible for inclusion if they had a confirmed primary orthopaedic diagnosis in the medical records. For example, a diagnosis of medial patellar luxation (MPL) secondary to trauma with multiple injuries was excluded.

The national ID-databases in Norway and Sweden were chosen for generation of an appropriate control group. For the control group to be comparable to the study population in respect to demographic factors, the search was limited to dogs born between 2006 and 2015. To ensure inclusion of the most abundant breeds in the geographical areas where the study population originated, only dogs belonging to the 50 most common breeds in each of the Norwegian and Swedish counties were collected from the national ID-databases. The Fédération Cynologique Internationale (FCI) classification was used for breed classification.

Data handling

Substantial data cleaning steps were undertaken to ensure selection of the most commonly represented breeds in the source population, and that the eligibility criteria were met in such a way that the case and control populations were comparable.

First, the geographical distribution of dogs surgically treated for orthopaedic diseases in the study population was calculated separately for each country to estimate the geographical distribution of the source population. The dogs eligible for inclusion came from 17/21 Swedish and 16/18 Norwegian counties. The number of dogs from each county was divided by the total number of eligible dogs and reported as a percentage. The numbers from counties with less than 1% of the cases in the database (<5 cases) were excluded to avoid overemphasising the importance of counties with a marginal contribution to the study population. Seven Swedish and nine Norwegian

[1] Regulation (EU) No 576/2013 of the European Parliament and of the Council of 12 June 2013 on the non-commercial movement of pet animals and repealing Regulation (EC) No 998/2003. https://eur-lex.europa.eu/eli/reg/2013/576/oj. (Accessed 30 November 2018).

[2] Lag (2007:1150) om tillsyn över hundar och Katter. https://www.riksdagen.se/sv/dokument-lagar/dokument/svensk-forfattningssamling/lag-20071150-om-tillsyn-over-hundar-och_sfs-2007-1150. (Accessed 30 November 2018).

[3] https://www.nkk.no/dyreid/category1232.html. (Accessed 30 November 2018).

Table 1 Geographical distribution of dogs surgically treated for orthopaedic diseases at two Veterinary Teaching Hospitals

Swedish county	N (%)	Norwegian county	N (%)
Gävleborg	68 (14.47)	Akershus	107 (23.11)
Norrbotten	5 (1.06)	Buskerud	40 (8.64)
Stockholm	118 (25.11)	Hedmark	37 (7.99)
Uppsala	257 (54.68)	Oppland	16 (3.46)
Västerbotten	5 (1.06)	Oslo	208 (44.92)
Västernorrland	6 (1.28)	Telemark	28 (6.05)
Västmanland	11 (2.34)	Trøndelag	6 (1.30)
		Vestfold	15 (3.24)
		Østfold	6 (1.30)
Total included	470 (94.76)		463 (94.88)
Other counties[a]	26 (5.24)		25 (5.12)
Total	496 (100.00)		488 (100.00)

Data presented as number (percentage) of dogs surgically treated for orthopaedic diseases at the University Animal Hospital, Swedish University of Agricultural Sciences and the University Animal Hospital, Norwegian University of Life Sciences over a 5-year period

[a] 10 Swedish and 7 Norwegian counties < 1% of caseload not included in control group calculations

counties contributed with more than 1% each and were included in the calculations. The relative contributions of the 16 counties retained are given in Table 1.

Second, to select the most common surgically treated orthopaedic diseases and ensure statistical reliability, dogs with diagnoses with less than 100 individual recordings (comprising < 10% of the eligible cases) were excluded. Four diagnoses included more than 100 recordings; medial compartment disease (MCD), fractures of the radius/ulna, MPL and cranial cruciate ligament disease (CCLD). Since MCD is closely associated with the other developmental elbow joint diseases, we chose to also include humeral trochlear osteochondrosis (OC) and ununited anconeal process (UAP) in one combined elbow dysplasia (ED) category. These four conditions are further referred to as the diseases under study (Fig. 1a).

Third, the control group retracted from the ID-registries was restricted to breeds present in all the counties selected in the first step (Fig. 1b). In addition to mixed-breed dogs, the Border Collie, Cavalier king Charles spaniel (CKCS), Chihuahua, English cocker spaniel, Flat-coated retriever, German shepherd dog (GSD), Golden retriever, Jack Russell terrier (JRT), Labrador retriever,

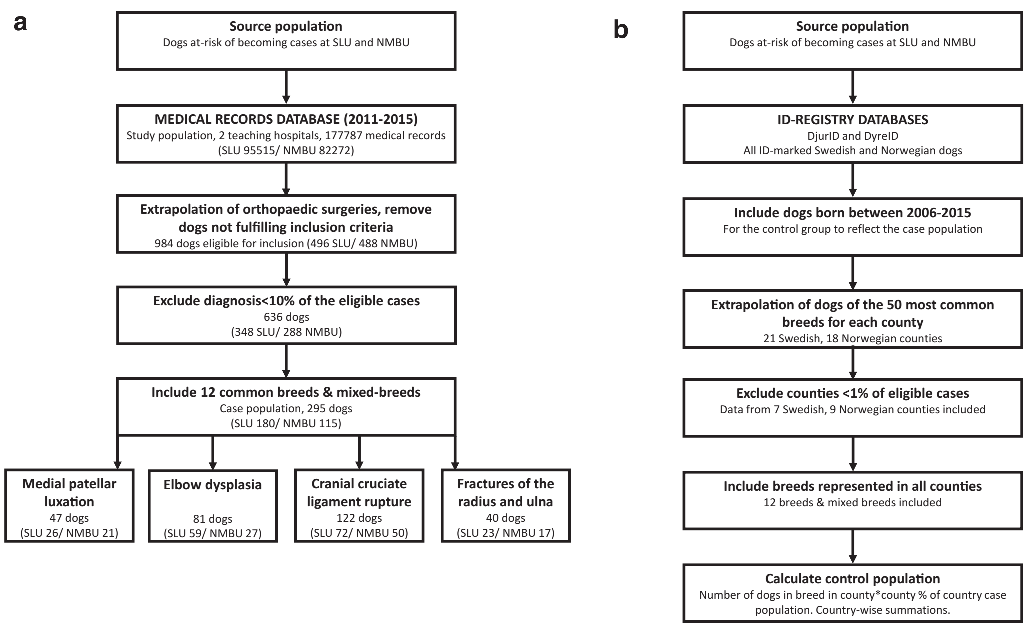


Fig. 1 Schematic illustration of the case- and control population selection. **a** Case population, **b** control population

Rottweiler, Shetland sheepdog, and the Staffordshire bull terrier were among the 50 most common breeds in all counties. These breeds are further referred to as the breeds under study.

Fourth, the control group retracted from the ID-registries was modified to reflect the breed distribution in the source population. The number of dogs in each of the breeds under study in the included counties were adjusted in accordance with the percentage of the eligible cases in the study population from the respective county (given in Table 1). While 55% of the eligible cases at SLU were from the county of Uppsala, 25% were from Stockholm, but only 1% from Västerbotten. In the national ID-registry, 755 Labradors were registered in Uppsala, 3331 in Stockholm and 452 in Västerbotten. These numbers where then multiplied (755 * 0.55 = 415, 3331 * 0.25 = 833 and 452 * 0.01 = 5) and similar calculations were performed for the other counties. Summed together the adjusted number of Labradors comprising the control population was 1277, which is closer to the raw registration numbers in Uppsala than in Stockholm. Calculations and raw registration numbers are provided separately (Additional file 1).

The final case population included all dogs in the study population of the breeds under study with the diagnosis of interests fulfilling the inclusion criteria.

Statistical analysis

Data were complied, cleaned and checked for errors in Microsoft Excel and imported into Stata 14.2 (Stata Corp., College Station, TX, USA), which was used for all statistical analyses. Age and weight of all dogs with the diseases under study are presented as median (range). The case population for each diagnosis was regarded as a separate population for the statistical analysis. Univariable logistic regression was used to compare the breed distribution between the case- and control population separately for each country for the diagnoses under study with mixed-breed dogs as the reference. Breeds without cases of the diagnoses under study were omitted from the analysis. Multivariable logistic regression, with a fixed effect for VTH to adjust for country differences, was performed for the combined case population. Results are presented as odds ratios (OR) with 95% confidence intervals. As this was not a planned hypothesis testing study, no predefined level of significance is reported.

Results

During the 5-year study period, a total of 82,272 individual patient records (average 16,455/year) were registered at NMBU and 95,515 (average 19,103/year) at SLU. Of these, 983 dogs (495 at SLU and 488 at NMBU) classified into 35 different diagnoses (Table 2), were eligible for inclusion in the study and 636 (64.6%) were treated for the diagnoses under study. ED, MPL and fractures of the radius/ulna occurred most frequently in young dogs, while CCLD had a median age of 5.8 years. ED and CCLD occurred most commonly in medium and large sized dogs, while the median weight for both MPL and fractures of the radius/ulna was below 5 kg (see Table 3 for more details).

Table 2 Distribution of orthopaedic disorders in surgically treated dogs at two Veterinary Teaching Hospitals

Disorder or injury	N (%)
Fracture tarsus	10 (1.02)
Infraspinatus contracture	11 (1.12)
Shoulder complex	15 (1.52)
Fracture MC/MT/Paw	19 (1.93)
OC Stifle	20 (2.03)
Luxation hip	21 (2.13)
Fracture humerus	22 (2.24)
Collateral ligament rupture	22 (2.24)
Fracture femur	34 (3.46)
Fracture tibia/fibula	48 (4.88)
OC Shoulder	52 (5.29)
Other diagnoses*	74 (7.52)
Total other diagnoses	348 (35.6)
Fracture radius/ulna	114 (11.59)
Elbow dysplasia	131 (13.31)
MCD	*103 (10.47)*
OC elbow	*23 (2.34)*
UAP	*5 (0.51)*
Medial patellar luxation	131 (13.31)
CCLD	260 (26.42)
Total diagnosis of interest	636 (64.6)
Total	984 (100)

Data presented as the number (percentage) of dogs surgically treated for orthopaedic diseases at the University Animal Hospital, Swedish University of Agricultural Sciences and the University Animal Hospital, Norwegian University of Life Sciences over a 5-year period

Italic is used to mark the diagnoses that is combined in the elbow dysplasia category

OC osteochondrosis, *UAP* ununited anconeal process, *MC* metacarpus, *MT* metatarsus, *MCD* medial compartment disease, *CCLD* cranial cruciate ligament disease

*Diagnoses with <1% of surgically treated orthopaedic cases summarised

The breeds under study comprised 43.7% (430 dogs) of the eligible cases (Table 4), 51.2% in Sweden (254 dogs) and 36.1% in Norway (176 dogs). Sixty-eight percent (295 dogs) had one of the diagnoses in question and were included in the case population.

Details from the logistic regression analyses including OR, confidence intervals and associated P-values are given in Table 5. The German shepherd dog, Labrador retriever, Rottweiler and the Staffordshire bull terrier

Table 3 Age and body weight in relation to orthopaedic diagnosis at two Veterinary Teaching Hospitals

Disorder or injury	Age (years)	Weight (kg)
ED	1.0 (0.4–8.8)	30.0 (10.0–52.7)
OC	*0.9 (0.5–8.4)*	*32.0 (15.0–52.0)*
MCD	*1.0 (0.4–8.8)*	*29.0 (10.0–52.7)*
UAP	*0.5 (0.4–2.2)*	*33.5 (19.0–36.7)*
Medial patellar luxation	2.0 (0.6–8.9)	4.9 (1.6–27.0)
CCLD	5.8 (0.9–12.0)	26.2 (4.0–66.0)
Fracture of the radius/ulna	1.0 (0.2–8.0)	3.0 (1.0–37.8)

Data presented as median (range) and includes 984 dogs surgically treated for four common orthopaedic diseases at the University Animal Hospital, Swedish University of Agricultural Sciences and the University Animal Hospital, Norwegian University of Life Sciences over a 5-year period

Italic is used to mark the diagnoses that is combined in the elbow dysplasia category

ED elbow dysplasia, *OC* osteochondrosis, *UAP* ununited anconeal process, *MCD* medial compartment disease, *CCLD* cranial cruciate ligament disease

were identified with an increased risk of ED (Table 5a). The highest risk was found for the Labrador (OR = 5.73) and Rottweiler (OR = 5.63). The Chihuahua was the only breed with an increased risk of MPL (OR = 2.80, Table 5c). Together with the GSD, the Chihuahua was also found to have a decreased risk of CCLD (Table 5b). The risk of CCLD in the Labrador retriever was lower than for mixed-breed dogs in Sweden (OR = 0.44), but higher in Norway (OR = 2.85) and the combined analysis gave an OR equal to mixed-breed dogs. The Rottweiler was the only breed where an increased risk of CCLD was identified (OR = 3.96). In addition to mixed-breeds, only three of the breeds under study (the CKCS, Chihuahua and the Shetland sheepdog) had cases of fractures of the radius and ulna (Table 5d), but no difference in risk could be identified. The OR for being treated for the diseases of interests were generally lower at NMBU compared to SLU (OR 0.50–0.67).

Discussion

Three of the four breeds identified in this study as having an increased risk of surgery for ED are the same as in several other studies. The German shepherd dog, Labrador retriever, and the Rottweiler are well-known breeds at risk [8–11]. An interesting finding is that the Staffordshire bull terrier had a high OR for ED. To the authors' knowledge, there is only one other study available reporting this breed among breeds predisposed for ED [9]. In Scandinavia, the Staffordshire bull terrier has gained

Table 4 Breed distribution of dogs surgically treated for orthopaedic diseases and a geographically adjusted control group

Breed	Eligible cases			Control population		
	Sweden	Norway	Combined	Sweden	Norway	Combined
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Mixed-breed	114 (44.9)	53 (30.1)	167 (38.8)	2964 (27.2)	4359 (37.4)	7323 (32.5)
Border collie	8 (3.2)	5 (2.8)	13 (3.0)	303 (2.8)	425 (3.7)	728 (3.2)
CKCS	5 (2.0)	9 (5.1)	14 (3.3)	522 (4.8)	556 (4.8)	1078 (4.8)
Chihuahua	14 (5.5)	18 (10.2)	32 (7.4)	1044 (9.6)	985 (8.5)	2029 (9.0)
English cocker spaniel	1 (0.4)	3 (1.7)	4 (0.9)	515 (4.7)	539 (4.6)	1054 (4.7)
Flat-coated retriever	3 (1.2)	4 (2.3)	7 (1.6)	433 (4.0)	356 (3.1)	789 (3.5)
German shepherd dog	12 (4.7)	7 (4.0)	19 (4.4)	1061 (9.7)	591 (5.1)	1652 (7.3)
Golden retriever	17 (6.7)	9 (5.1)	26 (6.1)	999 (9.2)	754 (6.5)	1753 (7.8)
Jack Russel terrier	9 (3.5)	6 (3.4)	15 (3.5)	430 (3.9)	710 (6.1)	1140 (5.1)
Labrador retriever	32 (12.6)	20 (11.4)	52 (12.1)	1277 (11.7)	823 (7.1)	2100 (9.3)
Rottweiler	19 (7.5)	22 (12.5)	41 (9.5)	502 (4.6)	469 (4.0)	971 (4.3)
Shetland sheepdog	8 (3.2)	7 (4.0)	15 (3.5)	475 (4.4)	319 (2.7)	794 (3.5)
Staff. bull terrier	12 (5.8)	13 (7.4)	25 (5.8)	394 (3.6)	763 (6.6)	1157 (5.1)
Total (BuS)*	254 (51.2)	176 (36.1)	430 (43.7)	10.525 (100.0)	10.886 (100.0)	21.411 (100.0)
Other breeds*	242 (48.8)	312 (63.9)	554 (56.3)			
Total	496 (100.0)	488 (100.0)	984 (100.0)			

Control population calculated from registration numbers of each breed in the national ID-registries adjusted to reflect the source population of dogs surgically treated for orthopaedic diseases at the University Animal Hospital, Swedish University of Agricultural Sciences and the University Animal Hospital, Norwegian University of Life Sciences over a 5-year period

Data presented as number of dogs (percentage of breeds under study)

BuS Breeds under study, *CKCS* Cavalier king Charles spaniel

*Data presented as number of dogs (percentage of total)

Table 5 Results from the logistic regression analyses of breed susceptibility for four common orthopaedic diseases in 12 dog breeds

a) Elbow dysplasia

Breed	SLU				NMBU				Combined			
	N (%)	OR	95% CI	P	N (%)	OR	95% CI	P	N (%)	OR	95% CI	P
Mixed-breed	13 (22.0)	1.00	Ref.	–	2 (7.41)	1.00	Ref.	–	15 (17.4)	1.00	Ref.	–
Flat-coated retriever	0 (0.0)	–	–	–	2 (7.41)	12.24	(1.72–87.18)	0.012	2 (2.3)	1.13	(0.26–4.96)	0.872
German shepherd dog	10 (17.0)	2.15	(0.94–4.92)	0.070	3 (11.11)	11.06	(1.84–66.35)	0.009	13 (15.1)	3.31	(1.56–7.02)	0.002
Golden retriever	7 (11.9)	1.60	(0.63–4.02)	0.319	2 (7.41)	5.78	(0.81–41.10)	0.080	9 (10.5)	2.26	(0.98–5.18)	0.055
Jack Russel terrier	0 (0.0)	–	–	–	0 (0.0)	–	–	–	0 (0.0)	–	–	–
Labrador retriever	19 (32.2)	3.39	(1.67–6.89)	0.001	9 (33.33)	23.83	(5.14–110.51)	< 0.001	28 (32.6)	5.73	(3.04–10.81)	< 0.001
Rottweiler	4 (6.8)	1.81	(0.59–5.59)	0.298	8 (29.63)	37.18	(7.87–175.58)	< 0.001	12 (14.0)	5.63	(2.62–12.07)	< 0.001
Staff. bull terrier	6 (10.2)	3.47	(1.31–9.19)	0.012	1 (3.7)	2.86	(0.25–31.54)	0.392	7 (8.1)	3.08	(1.25–7.59)	0.014
SLU	59 (68.9)								59 (45.0)	1.00	Ref.	–
NMBU					27 (60.0)				27 (20.6)	0.52	(0.33–0.83)	0.006
Other breeds	27 (31.1)				18 (40.0)				45 (34.4)			
Total	86 (100.0)				45 (100.0)				131 (100.0)			

b) Cranial cruciate ligament disease

Breed	SLU				NMBU				Combined			
	N (%)	OR	95% CI	P	N (%)	OR	95% CI	P	N (%)	OR	95% CI	P
Mixed-breed	32 (44.4)	1.00	Ref.	–	13 (26.0)	1.00	Ref.	–	45 (36.9)	1.00	Ref.	–
Border collie	0 (0.0)	–	–	–	1 (2.0)	0.79	(0.10–6.05)	0.820	1 (0.8)	0.22	(0.03–1.61)	0.136
CKCS	0 (0.0)	–	–	–	2 (4.0)	1.21	(0.27–5.36)	0.805	2 (1.6)	0.30	(0.07–1.23)	0.096
Chihuahua	1 (1.39)	0.09	(0.01–0.65)	0.017	1 (2.0)	0.34	(0.04–2.61)	0.299	2 (1.6)	0.16	(0.04–0.66)	0.011
English cocker spaniel	0 (0.0)	–	–	–	1 (2.0)	0.62	(0.08–4.76)	0.648	1 (0.8)	0.15	(0.02–1.11)	0.064
German shepherd dog	0 (0.0)	–	–	–	1 (2.0)	0.57	(0.07–4.34)	0.585	1 (0.8)	0.10	(0.01–0.70)	0.021
Golden retriever	7 (9.7)	0.65	(0.29–1.48)	0.302	5 (10.0)	2.22	(2.22–1.17)	0.130	12 (9.8)	1.09	(0.57–2.07)	0.796
Jack Russel terrier	7 (9.7)	1.51	(0.66–3.44)	0.329	2 (4.0)	0.94	(0.21–4.19)	0.940	9 (7.4)	1.29	(0.62–2.64)	0.495
Labrador retriever	6 (8.3)	0.44	(0.18–1.04)	0.062	7 (14.0)	2.85	(1.13–7.17)	0.026	13 (10.7)	1.00	(0.54–1.85)	0.991
Rottweiler	12 (16.7)	2.21	(1.13–4.33)	0.020	12 (24.0)	8.58	(3.89–18.91)	< 0.001	24 (19.7)	3.96	(2.39–6.56)	< 0.001
Shetland sheepdog	3 (4.17)	0.59	(0.18–1.92)	0.376	0 (0.0)	–	–	–	3 (2.5)	0.60	(0.19–1.95)	0.401
Staff. bull terrier	4 (5.6)	0.94	(0.33–2.67)	0.908	5 (10.0)	2.20	(0.78–6.18)	0.136	9 (7.4)	1.27	(0.62–2.62)	0.513
SLU	72 (50.3)								72 (27.7)	1.00	Ref.	–
NMBU					50 (42.7)				50 (19.2)	0.60	(0.42–0.87)	0.007
Other breeds	71 (49.7)				67 (57.3)				138 (53.1)			
Total	143 (100.0)				117 (100.0)				260 (100.0)			

c) Medial patellar luxation

Breed	SLU				NMBU				Combined			
	N (%)	OR	95% CI	P	N (%)	OR	95% CI	P	N (%)	OR	95% CI	P
Mixed-breed	13 (50.0)	1.00	Ref.	–	8 (38.1)	1.00	Ref.	–	21 (44.7)	1.00	Ref.	–
CKCS	1 (3.9)	0.44	(0.06–3.35)	0.425	3 (14.3)	2.94	(0.78–11.11)	0.112	4 (8.2)	1.25	(0.43–3.66)	0.679
Chihuahua	9 (34.6)	1.97	(0.83–4.61)	0.120	8 (38.1)	4.43	(1.66–11.82)	0.003	17 (36.2)	2.80	(1.47–5.32)	0.002
Jack Russel terrier	1 (3.9)	0.53	(0.07–4.06)	0.248	0 (0.0)	–	–	–	1 (2.1)	0.31	(0.42–2.30)	0.252
Shetland sheepdog	2 (7.7)	0.96	(0.21–4.27)	0.957	0 (0.0)	–	–	–	2 (4.3)	0.81	(0.19–3.49)	0.782
Staff. bull terrier	0 (0.0)	–	–	–	2 (9.5)	1.43	(0.30–6.74)	0.652	2 (4.3)	0.62	(0.14–2.65)	0.518
SLU	26 (36.1)								26 (19.8)	1.00	Ref.	–
NMBU					21 (35.6)				21 (16.0)	0.67	(0.38–1.20)	0.181
Other breeds	46 (63.9)				38 (64.4)				84 (64.1)			

Table 5 (continued)

c) Medial patellar luxation

Breed	SLU				NMBU				Combined			
	N (%)	OR	95% CI	P	N (%)	OR	95% CI	P	N (%)	OR	95% CI	P
Total	72 (100.0)				59 (100.0)				131 (100.0)			

d) Fractures of the radius and ulna

Breed	SLU				NMBU				Combined			
	N (%)	OR	95% CI	P	N (%)	OR	95% CI	P	N (%)	OR	95% CI	P
Mixed-breed	19 (82.6)	1.00	Ref.	–	9 (52.9)	1.00	Ref.	–	28 (70.0)	1.00	Ref.	–
CKCS	1 (4.4)	0.30	(0.04–2.24)	0.240	0 (0.0)	–	–	–	1 (2.5)	0.23	(0.32–1.71)	0.152
Chihuahua	3 (13.0)	0.45	(0.13–1.52)	0.197	6 (35.3)	2.95	(1.05–8.31)	0.041	9 (22.5)	1.09	(0.51–2.33)	0.816
Shetland sheepdog	0 (0.0)	–	–	–	2 (11.8)	3.04	(0.65–14.11)	0.156	2 (5.0)	0.59	(0.14–2.51)	0.480
SLU	23 (48.9)								23 (20.2)	1.00	Ref.	–
NMBU					17 (25.4)				17 (14.9)	0.58	(0.30–1.09)	0.090
Other breeds	24 (51.1)				50 (74.6)				74 (64.9)			
Total	47 (100.0)				67 (100.0)				114 (100.0)			

Results from country-stratified and combined logistic regression analyses presented as Odds ratios (OR) and 95% confidence intervals (CIs). Breeds without cases of the disease in question were omitted

CKCS Cavalier king Charles spaniel, *SLU* Swedish University of Agricultural Sciences, *NMBU* Norwegian University of Life Sciences, *ref* reference category

great popularity over recent years and from being a rare breed has now become one of the most common breeds in both Norway and Sweden.[4,5] If this is true also for other countries, it may help explain why this is the only other study to date concerning this breeds' predisposition to ED. The Staffordshire bull terrier shares a common ancestry with Mastiff breeds, which are reported to have the disease [10].

It should be mentioned that the collective diagnosis ED used in this study comprises three common developmental disorders in the dog, UAP, MCP, and OC. Joint incongruity and articular cartilage damage are also included in the group of conditions known as elbow dysplasia[6] but have not been evaluated in our study. However, since all conditions sorted under the collective term are believed to be highly interrelated [12] and articular cartilage damage and joint incongruity are unlikely to be seen as a separate entity, we believe this to be a minor limitation to the study. Moreover, conclusions about prevalence of the particular diagnoses in each breed has been addressed in previous studies [8–10].

Labrador retrievers, Rottweilers and Staffordshire bull terriers are reported to be at increased risk for CCLD, while Chihuahuas, GSDs, and Shetland sheepdogs have been claimed to be at lower risk [1, 2, 13–15]. Our study detected an increased risk of disease in the Rottweiler, and decreased in GSDs and Chihuahuas, which are consistent with the earlier reports. For some breeds the literature provides inconsistent results. Cocker spaniels were found to have a decreased risk of CCLD in one study [1], but not in another [15]. The risk among Golden retrievers have been described both as increased [1], same as in the reference population [14] and decreased [2, 15]. Despite the Labrador retriever being one of the most common breeds presenting with CCLD in our material, the combined OR was identical to mixed-breed dogs. Though mixed-breeds have been reported to have a slightly higher OR for CCLD than purebred dogs [8], this finding highlights the importance of having a comparable control population when reporting breed susceptibility. The country-specific OR for CCLD in the Labrador was lower than for mixed-breed dogs in Sweden, but higher in Norway. As for several other breeds originally bred for hunting, and the retriever breeds in particular, there are two quite different types of Labradors; a slim, lighter working type and a heavier built show type. It is not known whether the likelihood of orthopaedic diseases is the same for both types. Moreover, the relative frequencies

[4] Registration statistics, Swedish board of agriculture. http://www.jordbruksverket.se/amnesomraden/djur/olikaslagsdjur/hundarochkatter/hundregistret/statistik.4.45fb0f14120a3316ad78000672.html. (Accessed 28 November 2018).

[5] Norwegian Kennel Club registration data. https://www.nkk.no/statistikk/category1098.html. (Accessed 28 November 2018).

[6] International Elbow Working Group. http://www.vet-iewg.org/about/. (Accessed 29 October 2018).

of show and field bred Labradors in Norway and Sweden are unknown. This could be a contributing factor to the deviating results observed in the two countries and illustrates that breed susceptibility reported from single-centre studies and/or studies with a limited caseload should not be overemphasised. In general, minimally/borderline significant results in relation to breed susceptibility should be viewed with caution.

Medial patellar luxation is far more common than lateral luxation [16]. Among the breeds reported to have a higher prevalence are the CKCS, JRT and the Chihuahua [10, 16–18]. The results are conflicting for Staffordshire bull terriers [17, 18]. Even though the CKCS had a slightly higher OR than mixed-breed dogs in our study, the Chihuahua was the only breed where an increased risk of surgically treated MPL was identified. This is in concordance with a recent study reporting the prevalence of patellar luxation among Swedish Chihuahuas to be 23% [19]. The Labrador retriever is reported with an increased prevalence of MPL in some studies [17, 20, 21], but Labrador retriever is also the most common purebred dog registered in the UK Kennel Club [22]. Two of the aforementioned studies were conducted in the UK, but since neither included a comparable control population, no conclusions about breed predispositions in the source population should be drawn. Even though the Labrador retriever is one of the most popular breeds in Norway and Sweden as well, no Labrador retrievers presented with MPL in our material. It may therefore seem that Scandinavian Labrador retrievers have a decreased rather than increased risk of MPL.

Considering the low bodyweight of the dogs with fractures of the radius and ulna in our material (Table 3), it is not surprising that the Chihuahua, CKCS and the Shetland sheepdog were the only breeds under study with the diagnosis. The absence of fractures of the radius and ulna in larger breeds was expected since these are more common in small and miniature dogs [23, 24].

The discrepancy between earlier studies and our results could be attributed to several factors such as genetic variation between different geographical areas and genetic drift as a consequence of breeding strategies over time [22], but it could also be due to the lack of an appropriate control group in previously published studies. In addition, a change of breed popularity over time, as discussed for the Staffordshire bull terrier, needs to be taken into account. Breed predispositions reported in studies conducted decades ago should be viewed with caution since they are likely to lack validity today. Comparing breed susceptibility with a control population adjusted to match the geographical distribution of the case population could be extended to larger caseloads from different geographical regions to increase the external validity of the results and to be able to calculate odds ratios for breeds where the diagnosis of interest is rare. A larger case population would improve the accuracy of the estimations and make it a better tool to study breeds with decreased risks, without the need for more advanced statistical methods. The method described in our study provides a framework with a potential for exploring breed-specific disease predispositions further. It is not limited to orthopaedic disorders but could be extended to all diseases where breed predisposition is suspected.

Most studies that report breed predispositions acknowledge the lack of a representative control population as a limitation. The control group is often either completely missing with only raw prevalence being described or limited to randomly selected hospital controls. Hospital populations, in particular referral populations, are mostly composed of sick dogs. Since sick dogs can acquire a different condition of interest, the dogs being sick is not in itself a justified reason for excluding them as controls. However, a variety of different diseases in dogs are breed-related. This introduces selection bias since some breeds are likely to be overrepresented in a study population comprised of sick dogs, and hospital populations are therefore not the most representative population for control selection in regard to breed composition. A source population is defined as the population from which the study subjects are drawn [6]. In some cases, the source population is well-defined, but more often, as in the case of hospital populations, where some animals might come from afar, while others live nearby, the actual source population from which the cases originate is unknown [4]. Some studies have utilised larger clinical databases, such as the VetCompass system in the UK [1] and the Veterinary Medical Databases in the USA [15]. Although these databases include large numbers of animals, they only contain information about dogs admitted to veterinary care, and not the actual source population (the population of dogs that were likely to be included as cases if they had got the disease in question). Even when large clinical databases are used, the reported risk of disease can appear too high if the breed under investigation has a lower than average disposition for other diseases, and therefore is less frequently represented in the clinical database than in the source population. In recent years, a Swedish database of insured dogs has been used to compare breed predisposition to different diseases [25–27]. A limitation of using insured dogs as the reference is that the uninsured dogs are not included and there is a possibility that breeds with more health problems are more likely to be insured. Common for all the large databases is that the information recorded for each case and the details about the diagnostic workup can be sparse.

The reasoning behind calculating a geographically adjusted control group came from observations of different breed profiles at the two VTHs. SLU is situated in a middle-sized Swedish town, Uppsala, while NMBU is located in the city centre of Oslo, the capital of Norway. Registration numbers from different national kennel clubs reveal that breed distribution varies between countries. Even though the overall breed distribution is quite similar in Norway[7] and Sweden,[8] there are large regional variations (Additional file 1). Since both VTHs have a substantial number of referred patients, using the unadjusted registration numbers from the counties of Uppsala and Oslo, or the total numbers for each country, would create bias and not be representative of the actual source population. Adjusting the registration numbers from each of the counties by their relative contribution to the database of eligible cases, ensures this bias is kept at a minimum. The results from the logistic regression analysis (Table 5) show that the risk of becoming a case at NMBU is generally lower than at SLU. Since there are several other large small animal hospitals located near NMBU, while SLU is the largest hospital in Uppsala county, it is not surprising that the relative percentage of the control population seen at NMBU is smaller than at SLU.

Several limitations for this study must be acknowledged. Most importantly, only information from dogs examined at one of the participating VTHs were included. Therefore, information regarding dogs that were referred to other veterinary hospitals in the areas and for dogs whose owners did not pursue surgical treatment at the participating VTHs is lost. It is not unlikely that the treatment and referral strategies of dogs with the same orthopaedic disease might differ between breeds due to factors such as the complexity of the surgical procedure, size and temperament. It is therefore feasible that referral caseloads show a selection bias towards more complicated cases. For example, it is possible that small breed dogs with CCLD are underrepresented in our material because a substantial percentage of these dogs were treated conservatively or not referred in the first place. The information in the database cannot be retrospectively confirmed or rejected; therefore, all results rely on correct reporting of data. While ID-marking is mandatory for all Swedish dogs and for pure-breed Norwegian dogs to be registered in the national kennel club, it is voluntary for mixed-breed dogs in Norway. This discrepancy is a potential selection bias in the control group. However, the general Swedish and Norwegian dog populations are quite similar, and this is most likely true for mixed-breed dogs as well as pure-breeds. Moreover, a variety of cross-breeds (poodle mixes) have gained popularity over the last decades and are bred by breeders in a similar manner as pure-bred dogs. In addition, stray and shelter dogs are uncommon in Scandinavia; most dogs belong to an owner. Since the percentage of mixed-breed dogs in the Norwegian control population was higher than in the Swedish (Table 4), and with the aforementioned factors in mind, we believe the difference in ID-marking policy between Norway and Sweden to be of minor importance to our results. In addition, the control groups have been calculated separately for each country, and the logistic regression model adjusted for hospital.

Even though studies comparing the use of different control populations are available in the human literature [7], veterinary studies are lacking. The implications of using different control groups (i.e. hospital controls, insurance data, adjusted and unadjusted ID-registry data) in relation to breed susceptibility for disease should be addressed in future studies.

[7] Top 25 popular dog breeds in Norway 2017. https://www.nkk.no/getfile.php/131972994-1517566048/Dokumenter/Om%20NKK/Organisasjonen/Statistikk/Topp%2025%20registrerte%20raser%20i%202017.pdf. (Accessed 30 November 2018).

[8] Registreringsstatisik 2017. Available at https://www.skk.se/sv/om-skk/det-har-ar-skk/press/. (Accessed 30 November 2018).

Conclusions

Most of the results in the current study are in agreement with earlier reported breed predispositions for ED, MPL and CCLD, but in contrast to several other studies, an increased risk of CCLD was not identified for the Labrador retriever. The Staffordshire bull terrier was found to have an increased risk of ED. Although the country-specific results were mostly in concordance with each other, some discrepancies were noted. These findings highlight the importance of using large caseloads from different geographical regions and appropriate control groups when reporting breed susceptibility for disease.

Additional file

Additional file 1. Control population calculations and raw registration numbers.

Abbreviations

CCLD: cranial cruciate ligament disease; CKCS: Cavalier king Charles spaniel; ED: elbow dysplasia; GSD: German shepherd dog; MCD: medial compartment disease; MPL: medial patellar luxation; NMBU: Norwegian University of Life Sciences; OC: osteochondrosis; SLU: Swedish University of Agricultural Sciences; UAP: ununited anconeal process; VTH: Veterinary Teaching Hospital.

Authors' contributions

GSB registered the data originating at NMBU and ERM/MD the data at SLU. GSB conducted the data analysis and interpretation under supervision from ES. AB and GSB fostered the idea of the adjusted reference population, and AB established the initial database and coordinated the writing process. GSB and

ERM were major contributors to the manuscript, with substantial contributions from the other authors. All authors participated in the discussions and revisions of the entire text. All authors read and approved the final manuscript.

Author details
[1] Department of Companion Animal Clinical Sciences, Faculty of Veterinary Medicine, Norwegian University of Life Sciences, P.O. Box 369 sentrum, N-0102 Oslo, Norway. [2] Department of Clinical Sciences, Swedish University of Agricultural Sciences, P.O. Box 7054, SE-750 07 Uppsala, Sweden. [3] Department of Food Safety and Infection Biology, Faculty of Veterinary Medicine, Norwegian University of Life Sciences, P.O. Box 369 sentrum, N-0102 Oslo, Norway.

Acknowledgements
The authors wish to thank DyreID and DjurID for providing data from the ID-registries, Dr. Randi Krontveit for advising on the statistical analysis, and Karolina Engdahl for help in collecting data.

Competing interests
The authors declare that they have no competing interests.

Availability of data and materials
The original dataset analysed during the current study is available in the Mendeley Data repository, http://dx.doi.org/10.17632/txjvcc774j.2. The datasets generated during the current study are available from the corresponding author on reasonable request.

Consent for publication
Not applicable.

Ethics approval and consent to participate
This study did not require official or institutional ethical approval. The animals were handled according to high ethical standards and national legislation.

Funding
This study was funded by NMBU and SLU.

Prior publication
Data have not been published previously.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 6 December 2018 Accepted: 15 April 2019
Published online: 25 April 2019

References

1. Taylor-Brown FE, Meeson RL, Brodbelt DC, Church DB, McGreevy PD, Thomson PC, et al. Epidemiology of cranial cruciate ligament disease diagnosis in dogs attending primary-care veterinary practices in England. Vet Surg. 2015;44:777–83.
2. Witsberger TH, Villamil JA, Schultz LG, Hahn AW, Cook JL. Prevalence of and risk factors for hip dysplasia and cranial cruciate ligament deficiency in dogs. J Am Vet Med Assoc. 2008;232:1818–24.
3. Grimes DA, Schulz KF. Compared to what? Finding controls for case-control studies. Lancet. 2005;365:1429–33.
4. Wacholder S, McLaughlin JK, Silverman DT, Mandel JS. Selection of controls in case-control studies. I. Principles. Am J Epidemiol. 1992;135:1019–28.
5. Verani JR, Baqui AH, Broome CV, Cherian T, Cohen C, Farrar JL, et al. Case-control vaccine effectiveness studies: preparation, design, and enrollment of cases and controls. Vaccine. 2017;35:3295–302.
6. Dohoo IR, Martin SW, Stryhn H. Veterinary epidemiologic research. 2nd ed. Charlotte: VER, Inc.; 2014.
7. Li L, Zhang M. Population versus hospital controls for case-control studies on cancers in Chinese hospitals. BMC Med Res Methodol. 2011;11:167.
8. Bellumori TP, Famula TR, Bannasch DL, Belanger JM, Oberbauer AM. Prevalence of inherited disorders among mixed-breed and purebred dogs: 27,254 cases (1995–2010). J Am Vet Med Assoc. 2013;242:1549–55.
9. Kirberger RM, Stander N. Incidence of canine elbow dysplasia in South Africa. J S Afr Vet Assoc. 2007;78:59–62.
10. LaFond E, Breur GJ, Austin CC. Breed susceptibility for developmental orthopedic diseases in dogs. J Am Anim Hosp Assoc. 2002;38:467–77.
11. Oberbauer AM, Keller GG, Famula TR. Long-term genetic selection reduced prevalence of hip and elbow dysplasia in 60 dog breeds. PLoS ONE. 2017;12:e0172918.
12. Krotcheck UB, Peter. Surgical diseases of the elbow. In: Johnston SA, Tobias KM, editors. Veterinary surgery: small animal, vol. 1. 2nd ed. St. Lousis: Elsevier; 2017. p. 2600.
13. Adams P, Bolus R, Middleton S, Moores AP, Grierson J. Influence of signalment on developing cranial cruciate rupture in dogs in the UK. J Small Anim Pract. 2011;52:347–52.
14. Duval JM, Budsberg SC, Flo GL, Sammarco JL. Breed, sex, and body weight as risk factors for rupture of the cranial cruciate ligament in young dogs. J Am Vet Med Assoc. 1999;215:811–4.
15. Whitehair JG, Vasseur PB, Willits NH. Epidemiology of cranial cruciate ligament rupture in dogs. J Am Vet Med Assoc. 1993;203:1016–9.
16. Bosio F, Bufalari A, Peirone B, Petazzoni M, Vezzoni A. Prevalence, treatment and outcome of patellar luxation in dogs in Italy. A retrospective multicentric study (2009–2014). Vet Comp Orthop Traumatol. 2017;30:364–70.
17. Alam MR, Lee JI, Kang HS, Kim IS, Park SY, Lee KC, et al. Frequency and distribution of patellar luxation in dogs. 134 cases (2000 to 2005). Vet Comp Orthop Traumatol. 2000;2007(20):59–64.
18. O'Neill DG, Meeson RL, Sheridan A, Church DB, Brodbelt DC. The epidemiology of patellar luxation in dogs attending primary-care veterinary practices in England. Canine Genet Epidemiol. 2016;3:4.
19. Nilsson K, Zanders S, Malm S. Heritability of patellar luxation in the Chihuahua and Bichon Frise breeds of dogs and effectiveness of a Swedish screening programme. Vet J. 2018;234:136–41.
20. Bound N, Zakai D, Butterworth SJ, Pead M. The prevalence of canine patellar luxation in three centres. Clinical features and radiographic evidence of limb deviation. Vet Comp Orthop Traumatol. 2009;22:32–7.
21. Gibbons SE, Macias C, Tonzing MA, Pinchbeck GL, McKee WM. Patellar luxation in 70 large breed dogs. J Small Anim Pract. 2006;47:3–9.
22. Farrell LL, Schoenebeck JJ, Wiener P, Clements DN, Summers KM. The challenges of pedigree dog health: approaches to combating inherited disease. Canine Genet and Epidemiol. 2015;2:3.
23. Fox DB. Radius and ulna. In: Johnston SA, Tobias KM, editors. Veterinary surgery: small animal, vol. 1. 2nd ed. St. Louis: Elsevier; 2018.
24. Piras L, Cappellari F, Peirone B, Ferretti A. Treatment of fractures of the distal radius and ulna in toy breed dogs with circular external skeletal fixation: a retrospective study. Vet Comp Orthop Traumatol. 2011;24:228–35.
25. Egenvall A, Bonnett BN, Olson P, Hedhammar A. Gender, age, breed and distribution of morbidity and mortality in insured dogs in Sweden during 1995 and 1996. Vet Rec. 2000;146:519–25.
26. Heske L, Nødtvedt A, Jäderlund KH, Berendt M, Egenvall A. A cohort study of epilepsy among 665,000 insured dogs: incidence, mortality and survival after diagnosis. Vet J. 2014;202:471–6.
27. Hanson JM, Tengvall K, Bonnett BN, Hedhammar A. Naturally occurring adrenocortical insufficiency–an epidemiological study based on a swedish-insured dog population of 525,028 dogs. J Vet Intern Med. 2016;30:76–84.

Paper II

Original Article

jfms Journal of Feline Medicine and Surgery

Cranial cruciate ligament disease in cats: an epidemiological retrospective study of 50 cats (2011–2016)

Journal of Feline Medicine and Surgery
1–8

DOI: 10.1177/1098612X19837436
journals.sagepub.com/home/jfm

This paper was handled and processed by the European Editorial Office (ISFM) for publication in *JFMS*

SAGE

Gudrun S Boge[1*], Karolina Engdahl[2*], Elena R Moldal[1] and Annika Bergström[2]

Abstract

Objectives The aim of this study was to describe the characteristics and long-term outcome of surgically and conservatively treated cats with cranial cruciate ligament disease (CCLD).

Methods A retrospective cohort study of cats with CCLD, diagnosed at two university animal hospitals between January 2011 and December 2016, was performed. Signalment, history, treatment and follow-up information were retrieved. Cat owners were contacted for additional long-term follow-up information. The cases were divided into two groups; one conservatively managed and one surgically treated with the lateral fabellotibial suture technique. A quality of life questionnaire, the Feline Musculoskeletal Pain Index (FMPI), was distributed to the owners of cats alive at follow-up for assessment of chronic pain as a long-term outcome. Univariable statistical methods were used to evaluate the data.

Results Fifty cats were identified and were followed for a median of 41 months after diagnosis of CCLD. Seven cats (14%) developed bilateral CCLD. Twenty-eight cats (56%) were treated conservatively and 22 (44%) surgically. All surgically treated cats in which arthrotomy was performed (19/22) had total CCL rupture and 9/19 (47%) had meniscal injuries. Postoperative surgical complications were recorded in 6/22 cats (27%). Owners of 24/29 (83%) cats still alive at follow-up completed the FMPI questionnaire. The conservatively treated cats had a lower FMPI score, indicating less chronic pain, than those cats treated surgically ($P = 0.017$).

Conclusions and relevance Conservatively treated cats with CCLD experienced less chronic pain at long-term follow-up than surgically treated cats. Bilateral disease is not uncommon in cats with CCLD.

Keywords: Cranial cruciate ligament; lateral fabellotibial suture; meniscal disease; stifle joint; treatment; quality of life

Accepted: 21 February 2019

Introduction

While cranial cruciate ligament disease (CCLD) in dogs is one of the most discussed and studied topics in veterinary orthopaedics, the condition in cats has gained little attention. Even though the exact aetiopathogenesis of canine CCLD is unknown, multiple risk factors – including breed, sex, age and body weight – have been identified.[1–4] The aetiopathogenesis of CCLD in cats is unclear,[5,6] and although the disease is reported less frequently in cats than in dogs,[7] epidemiological studies are lacking. In dogs with CCLD, bilateral rupture is reported in approximately 20–50% of cases.[8–13] To our knowledge, the occurrence of bilateral disease in cats has not been reported, and the literature is limited to a few cases in

[1]Department of Companion Animal Clinical Sciences, Norwegian University of Life Sciences, School of Veterinary Science, Oslo, Norway
[2]Department of Clinical Sciences, Swedish University of Agricultural Sciences, Uppsala, Sweden

*Gudrun S Boge and Karolina Engdahl contributed equally to this work.

Corresponding author:
Gudrun Seeberg Boge DVM, Department of Companion Animal Clinical Sciences, Norwegian University of Life Sciences, School of Veterinary Science, Campus Adamstuen, PO Box 369 sentrum, N-0102 Oslo, Norway
Email: gudrun.seeberg.boge@nmbu.no

case series.[6,14] The incidence of meniscal injury in cats with CCLD[14] has been reported to be in the same range as for dogs.[15] Both conservative and different surgical treatments have been deemed successful in feline CCLD.[16–18] Extracapsular stabilisation with lateral suture is commonly used,[6] but different osteotomy procedures have been described.[17,19]

Objective measures of musculoskeletal function in cats can be challenging. Quality of life (QoL) questionnaires provide an opportunity for a standardised assessment of long-term outcome. One such QoL is the Feline Musculoskeletal Pain Index (FMPI),[20] which was designed to assess chronic pain caused by degenerative joint disease in cats. The questionnaire has been validated and undergone reliability testing,[20–24] and Swedish version is available.[25]

The objective of this study was to describe the characteristics and long-term outcome of surgically and conservatively treated cats with CCLD. We also aimed to evaluate if treatment method affected the QoL of cats with CCLD.

Materials and methods

Case selection

The medical records of cats with CCLD presented at two university hospitals (University Animal Hospital, Swedish University of Agricultural Sciences; and University Animal Hospital, Norwegian University of Life Sciences) between January 2011 and December 2016 were reviewed retrospectively between 1 March and 1 September 2018. The case population included both referral and primary cases. The diagnosis of CCLD was based on a cranial drawer during clinical examination. Exclusion criteria were an uncertain diagnosis, euthanasia at the time of diagnosis or incomplete follow-up information (eg, where information about whether the cat was alive or not was missing, or the owner could not be contacted).

The records were evaluated for signalment at presentation, including date of birth, breed, sex and body weight. The cats were registered as overweight if they had a body condition score >3.5/5 or >5/9. Neuter status was not registered. History and clinical examination findings were recorded and included onset of lameness, affected limb, time from injury to diagnosis and surgery, contralateral cranial cruciate ligament (CCL) status, insurance status and concurrent orthopaedic diagnosis. Date and cause of death were registered if available. If the cat was diagnosed with bilateral disease during the study period, the characteristics from the first injury was used. For all surgically treated cases, additional information was recorded, including surgeon, date of surgery, arthrotomy, multi-ligament injuries (caudal cruciate ligament [CaCL] rupture, collateral ligament rupture), meniscal injury, antimicrobial therapy, surgical technique and postoperative complications. Owing to the small number of complications, we chose not to classify the complications as major or minor.

Follow-up

Owners and referring veterinarians were contacted by telephone and/or email to obtain additional follow-up information between 1 August and 15 September 2018. Information regarding subsequent contralateral CCLD, additional complications after surgery, date and type of complications, whether the cat was alive or dead, and the date and cause of death was registered. Owners of conservatively treated cats were asked if the cats later had surgery of the affected stifle at other clinics. Follow-up time was calculated as the time from diagnosis to owner contact in the cases where the cat was alive and from diagnosis to euthanasia in the cases where the cat was dead. Cats were presumed to be alive if the information in the medical records was complete and the last registered veterinary visit was in 2018.

Owners of cats that were still alive were asked to complete the FMPI questionnaire in December 2018. The questionnaire contained 18 questions about the cats' ability to perform different activities, such as running, eating and jumping, and the cats' overall activity, on a 6 point Likert scale. The results were scored from −1 (above normal ability to perform the activity) to 4 (not at all able to perform the activity), according to Benito et al.[20] The questionnaire also contained two questions about pain in the last week and on the day of assessment, scored from 0 (no pain) to 4 (severe pain), and one question about the overall QoL, scored from 0 (excellent) to 3 (poor) A more detailed description of the questionnaire can be found in the supplementary material, Appendix S1. A low score indicated less chronic pain and a total score of 3 was used as the cut-off value for normal cats.[25] Three additional questions regarding treatment with non-steroid anti-inflammatory drugs (NSAIDs) were included in the questionnaire.

Statistical analysis

Data were compiled in Microsoft Excel and imported into Stata 15, which was used for all statistical analyses. A P value of <0.05 was considered statistically significant. Normality was assessed graphically for continuous variables and is presented as median (range). Categorical variables were described as percentages. Association between categorical and continuous variables were explored by the two-sample t-test and Wilcoxon rank sum test for normally and non-normally distributed variables, respectively. Associations between categorical variables were tested using the χ^2 test or Fisher's exact test. A multivariable analysis was not performed owing to the homogeneity of the material and lack of statistical power because of the limited number of cases.

Table 1 Descriptive features of 50 cats with cranial cruciate ligament disease presented at two university animal hospitals

Variable	Conservative	Surgery	Overall
Number of cats	28 (56.0)	22 (44.0)	50 (100.0)
Cats treated at SLU*	25 (89.3)	14 (63.6)	39 (78.0)
Cats treated at NMBU*	3 (10.7)	8 (36.4)	11 (22.0)
Age (years)	9.2 (0.4–15.3)	8.3 (1.6–14.2)	9.0 (0.4–15.3)
Weight (kg)	4.7 (2.0–8.3)	5.0 (3.5–7.5)	4.9 (2.0–8.3)
Overweight	9 (32.1)	11 (50.0)	20 (40.0)
Sex			
Female	17 (60.7)	8 (36.4)	25 (50.0)
Male	11 (39.3)	14 (63.6)	25 (50.0)
Insured	23 (82.1)	14 (63.6)	37 (74.0)
Time from injury to diagnosis in days (range)*†	2 (0–55)	7 (0–68)	4 (0–68)
Stifle affected			
Left	14 (50.0)	14 (63.6)	28 (56.0)
Right	14 (50.0)	8 (36.4)	22 (44.0)
Bilateral rupture	2 (7.1)	5 (22.7)	7 (14.0)
Time to bilateral rupture (months)	12.8 (6.9–18.8)	21.3 (4.4–37.7)	18.8 (4.4–37.7)
Follow-up time (months)	41.9 (0.5–83.1)	38.9 (3.5–86.6)	41.1 (0.5–86.6)
Cats alive at follow-up	15 (53.6)	14 (63.6)	29 (58.0)
Answers to QoL (% of cats alive)	12 (80.0)	12 (85.7)	24 (82.8)

Continuous variables reported as median (range) and categorical variables as n (%)
*P = 0.03. These were the only variables where a statistically significant difference was detected between the groups
†Missing value from one surgically treated cat, n = 49
SLU = Swedish University of Agricultural Sciences; NMBU = Norwegian University of Life Sciences; QoL = quality of life questionnaire

Results

Case inclusion

During the 6 year period, 60/493 (12.2%) of the patients diagnosed with CCLD were feline, of which 50 had complete follow-up information and were included in this study. Sex distribution was even. Median age at time of diagnosis was 9.0 years. Median weight was 4.9 kg and 20 cats were registered as overweight. Thirty-seven cats were insured (see Table 1). Seven breeds were represented. Thirty-nine cats (78.0%) were mixed breed (domestic shorthair and domestic longhair). The remaining cats included three British Shorthairs, two Maine Coons, two Norwegian Forest Cats and two Siberians, one European Shorthair and one Persian.

The left CCL was injured in 28 cats, and the right in 22. The most common clinical presentation was acute onset of lameness with duration <1 week prior to diagnosis (Table 1). Two cases of concurrent medial patellar luxation (MPL) and one case of femoral fracture were diagnosed. Both cats with MPL were conservatively treated, while the femoral fracture was treated surgically with a femoral head and neck resection during the same procedure.

Treatment

Of the 50 cats, 28 were treated conservatively and 22 received surgical treatment. None of the initially conservatively treated cats needed surgical intervention later. The time from injury to diagnosis was shorter for the conservatively compared to the surgically treated cats (P = 0.03) and conservative treatment was chosen more often at the Swedish University of Agricultural Sciences than at the Norwegian University of Life Sciences (P = 0.03). None of the other variables included was significantly different between the groups (Table 1).

Twelve surgeons with different levels of experience performed the procedures; the lateral fabellotibial suture (LFS) technique was used in all cats. Arthrotomy was performed in 19/22 surgeries and a complete CCL rupture was noted in all. Multi-ligament stifle injuries were diagnosed in five surgically treated cats; four had collateral ligament damage and two of these had an additional complete rupture of the CaCL. The fifth cat had CaCL rupture but intact collateral ligaments. Meniscal injury was noted in nine cats. However, information regarding treatment of the meniscal injuries, and the extent and type of meniscal damage was inconsistent in the records and was therefore not included. Further details for the surgically treated cats are given in Table 2.

Complications and follow-up

Postoperative complications were recorded in 6/22 (27.3%) surgically treated cats. There was no statistical difference in complication frequency between the two clinics (P = 0.35), or between the cases with multi-ligament

Table 2 Data from 22 surgically treated cats with cranial cruciate ligament disease presented at two university animal hospitals

	n	(%)
Implant material		
Nylon	12	54.5
Polypropylene	2	9.1
Polyethylene	7	31.8
Polyester	1	4.5
Arthrotomy	19	86.4
Meniscal injury*	9	47.4
CaCL rupture*	3	15.8
Antibiotic treatment	18	81.8
Only perioperative	11	50.0
Peri- and postoperative	7	31.8
Complications	6	27.3

*Percentage of cats with arthrotomy performed
CaCL = caudal cruciate ligament

stifle injuries and those without ($P = 0.59$). Two cats had one postoperative complication, while four cats had two. Three of the six cats with complications underwent a second surgery (Table 3).

Eighteen of the surgically treated cases received perioperative antibiotic treatment. Seven of these were also administered antibiotic treatment postoperatively. One of these cats had a wound injury, while no justification for antibiotic use was given in the others.

Two conservatively and five surgically treated cats developed bilateral disease (14.0%). The median interval between the bilateral injuries was 18.8 months. There was no difference in either median weight or percentage of overweight cats among the cats with bilateral disease vs cats with unilateral disease (5.1 kg and 42.9% vs 4.9 kg and 39.5%, respectively). The number of bilateral cases was not statistically different between the conservatively and surgically treated cats ($P = 0.12$).

The median follow-up time for the 50 cats was 41.1 months (Table 1). Twenty-nine were alive and 21 were dead at follow-up.

QoL questionnaire

The FMPI questionnaire was completed by 24/29 (82.8%) of the cat owners with a median total score of 3 (range of −6 to 15). The FMPI was answered by the owners of 2/5 cats with multi-ligament injuries. These two cats had a median total score of 13 (range of 11–15) vs 4 (range of 0–15) in the 10 surgically treated cats without multi-ligament injuries. The median total score of all the surgically treated cats was 5 (range of 0–15) vs 0.5 (range of −6 to 7) in the conservatively treated cats ($P = 0.02$).

When the two cats with multi-ligament injuries were excluded the difference between the groups was still significant ($P = 0.05$). Three of 12 conservatively treated and 8/12 surgically treated cats had a total score >3, with the difference in proportions being statistically significant ($P = 0.04$). None of the cats received NSAIDs treatment at time of follow-up. Further results are given in Table 4, and the FMPI scores from the cats with postoperative complications in Table 3.

Discussion

CCLD is considered an uncommon disease in cats. Even though several sources state that CCLD is less common in cats than in dogs,[7,26,27] this is the first time a comparison has been published. The low percentage (12.2%) of feline patients with CCLD in our study supports the previous assumption that CCLD is more common in dogs than in cats.

The age of the cats in our study is comparable to earlier reports,[6,14,17] and the weight is similar to that of randomly selected healthy controls in two earlier studies of CCLD in cats.[5,6] A greater proportion of cats in our study was insured vs the general insurance coverage (35.7% in 2012) of cats in Sweden.[28] This discrepancy in insurance coverage could indicate that owners of insured cats are more likely to seek veterinary advice in cases of CCLD. This is in agreement with Taylor-Brown et al,[3] who reported that insured dogs had four times higher odds of a CCLD diagnosis than uninsured dogs. As the number of insured cats in our study was approximately equal in the two treatment groups (Table 1), we can assume that insurance status did not influence the choice of treatment.

The incidence (47%) of meniscal injury in surgically treated cats in our study was somewhat lower than an earlier report of 67% meniscal injuries in cats surgically treated for CCLD,[14] but in the same range as the percentage of meniscal injuries reported in canine studies.[15,29] It should also be noted that another study with a limited number of cats identified meniscal tears in only 2/11 cats.[17]

None of the surgically treated cats in the current study had partial CCL ruptures. This is in agreement with an earlier study in cats,[14] but in contrast to the higher proportion of partial CCL ruptures in dogs.[15] As the degree of rupture was unknown in the conservatively managed cats, it is possible that this group had a higher percentage of partial ruptures than the cats treated with surgery. Other studies have suggested that partial ruptures can be clinically silent and thus not detected by the owners.[14,17] If a partial rupture produces only mild or no clinical signs, it is likely that the actual proportion of partial CCL rupture in cats is higher than reported in this study. To address this question, a post-mortem examination of a larger number of cats would have to be performed.

A degenerative process in the ruptured CCL has been reported in dogs,[30,31] and there is an ongoing discussion about the aetiology of CCLD in cats.[5,6] A recent study by

Table 3 Details for the six surgically treated cases with postoperative complications in a retrospective study of 50 cats with cranial cruciate ligament disease

Case	Comorbidities	Arthrotomy	Meniscal injury	CaCL rupture	First complication			Second complication			Alive/dead at follow-up	FMPI score	Follow-up	Remarks
					Type	Time from surgery to complication (days)	Treatment	Type	Time from surgery to complication (days)	Treatment				
1	None	Yes	No	No	Neurological deficits hindlimb	1	NSAIDs	Postoperative meniscal injury	15	Reoperation	Alive	15	27.3	Acute lameness after being outdoor before second complication
2	None	Yes	Yes	No	Operation wound seroma	14	None	Moderate to severe lameness, severe OA	532	NSAIDs, rehabilitation	Alive	4	57.2	
3	Collateral ligament rupture, wound injury, febrile	Yes	Yes	Yes	Stifle luxation chronic at presentation	532	NSAIDs, reoperation not recommended	NA	NA	NA	Alive	15	45.1	Several extra capular sutures initially. Reduced stifle ROM since operation
4	None	Yes	Yes	No	Moderate to severe chronic lameness, suspected to be implant related	175	Reoperation, line removed	Moderate to severe chronic lameness, unspecified	547	Amputation	Dead	NA	19.3	Dyspnoea after second reoperation, euthanased 1 day postoperatively
5	None	Yes	No	No	Moderate to severe lameness, unspecified	155	NSAIDs	NA	NA	NA	Dead	NA	24.1	FeLV, anaemia cause of death
6	Collateral ligament injury	Yes	Yes	Yes	Medial collateral ligament rupture	10	Reoperation	Implant related, line ruptured	55	Reoperation, line replaced	Alive	11	79.1	Medial collateral ligament injury, not ruptured at initial operation

CaCL = caudal cruciate ligament; FMPI = Feline Musculoskeletal Pain Index; NSAIDs = non-steroidal anti-inflammatory drugs; OA = osteoarthritis; NA = not applicable; ROM = range of motion; FeLV = feline leukaemia virus

Table 4 Comparison of Feline Musculoskeletal Pain Index (FMPI) results at long-term follow-up between conservative and surgically treated cats with cranial cruciate ligament disease

	Conservative	Surgery	*P* value
	n = 12	n = 12	
FMPI – activity	0 (–6 to 7)	4 (0–14)	0.017
FMPI – pain	0 (0–3)	0 (0–2)	NA
FMPI – QoL	0 (0–1)	0.5 (0–2)	0.080
FMPI – total score	0.5 (–6 to 7)	5 (0–15)	0.017

Results from 18 activity questions (scored –1 [above normal activity] to 4 [no activity at all]), two pain questions (scored 0 [no pain] to 4 [severe pain]) and one quality of life (QoL) question (scored 0 [excellent] to 3 [poor]). A low total score indicated less chronic pain.
P values from Wilcoxon signed rank test
NA = not analysed owing to high number of zero values

Wessely et al[5] found no histological evidence of a degenerative process in the CCL of cats, while a study by Harasen[6] supported both a traumatic and a degenerative aetiology of the disease. However, only a single CCL was examined histologically in the latter study.

The percentage of cats with bilateral disease in our study was substantially lower than the 20–50% typically reported in canine studies,[8–13] despite a long follow-up. In addition, several of the cats had CaCL ruptures and collateral ligament injuries, which is rare in dogs with CCLD.[32,33] Together, this could support a degenerative aetiology in dogs and a traumatic aetiology in cats. However, with CCLD being an uncommon disease in cats, 14% of bilateral disease is a substantial number if the aetiology is solely traumatic. We emphasise the need for prospective studies of potential risk factors for CCLD in cats, preferably with a larger number of cases, including histological examinations of the ruptured ligaments.

Postoperative complications were relatively common in our study. Even though the reason for this is unknown, several surgeons with different levels of experience performed the procedures and we cannot exclude the possibility that the low number of LFS surgeries per surgeon contributed to the complication risk.

The results from the QoL investigation showed that a substantial proportion of the cats had a FMPI score indicative of chronic pain. However, none of the cats received NSAID treatment at follow-up. Moreover, most of the owners with cats scoring high on the FMPI did not perceive their cat as being painful. This implies that signs of chronic pain in cats can be subtle and may go unnoticed by the owners.

This is the first epidemiological study of CCLD in cats including both surgically and conservatively treated cats. A higher proportion of the surgically than the conservatively treated cats had a FMPI score >3, indicating chronic pain. It is perhaps not surprising that all the cats with postoperative complications had high scores.

Previous studies have reported a normal locomotion pattern 1 year after experimental CCL transection in cats,[34] and good functional recovery after conservative treatment of CCLD.[16] This is in contrast to the study by Ruthrauff et al,[14] which suggested that surgical stabilisation with stifle exploration should be considered in cases of feline CCLD due to the progression of degenerative joint disease as a result of meniscal injury. As mentioned, meniscal injuries were common among the surgically treated cats in our study. Nevertheless, the FMPI scores indicated that chronic pain was more common in the surgically treated than in the conservatively treated cats. Even though the degree of meniscal injury was unknown in the conservatively treated cats, these findings do not support meniscal injury as an argument for surgical treatment is cases of feline CCLD.

In cats where multi-ligament injuries result in a severely unstable stifle joint, surgical stabilisation is recommended.[35] The FMPI results of the cats with multi-ligament injuries in the current study show that chronic pain could be expected in these cats, even after surgical correction. However, even after excluding these cats, the median FMPI scores were significantly higher for the surgically treated than the conservatively treated cats.

Cats treated conservatively were not evaluated by arthrotomy, and information about partial or full CCL rupture or meniscal injury is therefore not available. A possible selection bias due to a clinical decision to treat less lame cats with less severe joint disease conservatively cannot be excluded. It is unknown whether this has affected the long-term FMPI score.

Surgical procedures are always associated with some degree of stress and pain for the animal, in addition to substantial costs for the owner. From this perspective, the current findings support conservative treatment in cases of isolated CCLD in cats. However, one should refrain from drawing definite conclusions owing to the risk of bias, the small number of cats and the lack of a clinical assessment of long-term function in our study.

Our study has several important limitations. The retrospective study design introduces several potential sources of bias, such as recall bias and misclassification errors. Another limitation is the unbalanced number of cats at the two clinics and the relatively small number of cases. In addition, information regarding the severity of lameness at initial presentation was not available and it is possible that the degree of lameness affected treatment choice and consequently the FMPI scores. Even though the response rate to the FMPI questionnaire was high, there is a risk of non-responder bias. Moreover, the cats in our study may not reflect the general population as both clinics are referral hospitals. Even though cats with osteoarthritis often do not show signs of overt lameness,[36] the absence of osteoarthritis grading in the cats in our study is another limitation. The degree of osteoarthritis in relation to treatment and long-term outcome in cats with CCLD should be addressed in the future.

Conclusions

In the present study, conservatively treated cats with CCLD experienced less chronic pain at long-term follow-up compared to surgically treated cats, according to a QoL assessment. Multi-ligament stifle injuries, meniscal disease and postoperative complications were frequently observed in surgically treated cats. Subsequent CCLD in the contralateral stifle occurred in 14% of the cats. Prospective studies with an objective assessment of different treatment strategies and risk factors for bilateral CCLD are warranted.

Acknowledgements The authors would like to acknowledge the assistance of Professor Ulf Emanuelson and Professor Eystein Skjerve in the preparation of this manuscript and for advising on the statistical analysis, and Caroline Mason for help in collecting data.

Supplementary material The following files are available: Appendix S1: Shortened English version of the quality of life questionnaire with descriptive rating scale. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of interest The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding The PhD-project of one of the authors (KE) is financed by Agria Pet Insurance Research Foundation. No other financial support for the research, authorship, and/or publication of this article was received.

ORCID iD Gudrun S Boge https://orcid.org/0000-0001-6889-4002
Karolina Engdahl https://orcid.org/0000-0003-2800-9990
Elena R Moldal https://orcid.org/0000-0001-6626-9801
Annika Bergström https://orcid.org/0000-0003-1133-8747

References

1 Witsberger TH, Villamil JA, Schultz LG, et al. **Prevalence of and risk factors for hip dysplasia and cranial cruciate ligament deficiency in dogs**. *J Am Vet Med Assoc* 2008; 232: 1818–1824.
2 Whitehair JG, Vasseur PB and Willits NH. **Epidemiology of cranial cruciate ligament rupture in dogs**. *J Am Vet Med Assoc* 1993; 203: 1016–1019.
3 Taylor-Brown FE, Meeson RL, Brodbelt DC, et al. **Epidemiology of cranial cruciate ligament disease diagnosis in dogs attending primary-care veterinary practices in England**. *Vet Surg* 2015; 44: 777–783.
4 Duval JM, Budsberg SC, Flo GL, et al. **Breed, sex, and body weight as risk factors for rupture of the cranial cruciate ligament in young dogs**. *J Am Vet Med Assoc* 1999; 215: 811–814.
5 Wessely M, Reese S and Schnabl-Feichter E. **Aetiology and pathogenesis of cranial cruciate ligament rupture in cats by histological examination**. *J Feline Med Surg* 2017; 19: 631–637.
6 Harasen GLG. **Feline cranial cruciate rupture**. *Vet Comp Orthop Traumatol* 2005; 18: 254–257.
7 Umphlet RC. **Feline stifle disease**. *Vet Clin North Am Small Anim Pract* 1993; 23: 897–913.
8 Grierson J, Asher L and Grainger K. **An investigation into risk factors for bilateral canine cruciate ligament rupture**. *Vet Comp Orthop Traumatol* 2011; 24: 192–196.
9 Moore KW and Read RA. **Cranial cruciate ligament rupture in the dog – a retrospective study comparing surgical techniques**. *Aust Vet J* 1995; 72: 281–285.
10 Harasen GL. **A retrospective study of 165 cases of rupture of the canine cranial cruciate ligament**. *Can Vet J* 1995; 36: 250–251.
11 Buote N, Fusco J and Radasch R. **Age, tibial plateau angle, sex, and weight as risk factors for contralateral rupture of the cranial cruciate ligament in Labradors**. *Vet Surg* 2009; 38: 481–489.
12 Mölsä SH, Hielm-Björkman AK and Laitinen-Vapaavuori OM. **Use of an owner questionnaire to evaluate long-term surgical outcome and chronic pain after cranial cruciate ligament repair in dogs: 253 cases (2004–2006)**. *J Am Vet Med Assoc* 2013; 243: 689–695.
13 Muir P, Schwartz Z, Malek S, et al. **Contralateral cruciate survival in dogs with unilateral non-contact cranial cruciate ligament rupture**. *PLoS One* 2011; 6: DOI: 10.1371/journal.pone.0025331.
14 Ruthrauff CM, Glerum LE and Gottfried SD. **Incidence of meniscal injury in cats with cranial cruciate ligament ruptures**. *Can Vet J* 2011; 52: 1106–1110.
15 Gatineau M, Dupuis J, Plante J, et al. **Retrospective study of 476 tibial plateau levelling osteotomy procedures. Rate of subsequent 'pivot shift', meniscal tear and other complications**. *Vet Comp Orthop Traumatol* 2011; 24: 333–341.
16 Scavelli TD and Schrader SC. **Non-surgical management of rupture of the cranial cruciate ligament in 18 cats**. *J Am Anim Hosp Assoc* 1987; 23: 337–340.
17 Mindner JK, Bielecki MJ, Scharvogel S, et al. **Tibial plateau levelling osteotomy in eleven cats with cranial cruciate ligament rupture**. *Vet Comp Orthop Traumatol* 2016; 29: 528–535.

18 De Sousa R, Sutcliffe M, Rousset N, et al. **Treatment of cranial cruciate ligament rupture in the feline stifle. Biomechanical comparison of a standard fabella-tibial suture and lateral sutures placed between quasi-isometric points**. *Vet Comp Orthop Traumatol* 2015; 28: 401–408.

19 Hoots EA and Petersen SW. **Tibial plateau leveling osteotomy and cranial closing wedge ostectomy in a cat with cranial cruciate ligament rupture**. *J Am Anim Hosp Assoc* 2005; 41: 395–399.

20 Benito J, Depuy V, Hardie E, et al. **Reliability and discriminatory testing of a client-based metrology instrument, feline musculoskeletal pain index (FMPI) for the evaluation of degenerative joint disease-associated pain in cats**. *Vet J* 2013; 196: 368–373.

21 Benito J, Hansen B, Depuy V, et al. **Feline musculoskeletal pain index: responsiveness and testing of criterion validity**. *J Vet Intern Med* 2013; 27: 474–482.

22 Zamprogno H, Hansen BD, Bondell HD, et al. **Item generation and design testing of a questionnaire to assess degenerative joint disease-associated pain in cats**. *Am J Vet Res* 2010; 71: 1417–1424.

23 Gruen ME, Griffith E, Thomson A, et al. **Detection of clinically relevant pain relief in cats with degenerative joint disease associated pain**. *J Vet Intern Med* 2014; 28: 346–350.

24 Gruen ME, Griffith EH, Thomson AE, et al. **Criterion validation testing of clinical metrology instruments for measuring degenerative joint disease associated mobility impairment in cats**. *PLoS One* 2015; 10: DOI: 10.1371/journal.pone.0131839.

25 Stadig S. **Evaluation of physical dysfunction in cats with naturally occurring osteoarthritis**. PhD Thesis, Swedish University of Agricultural Sciences, 2017.

26 Kunkel KA, Basinger RR, Suber JT, et al. **Evaluation of a transcondylar toggle system for stabilization of the cranial cruciate deficient stifle in small dogs and cats**. *Vet Surg* 2009; 38: 975–982.

27 McLaughlin RM. **Surgical diseases of the feline stifle joint**. *Vet Clin North Am Small Anim Pract* 2002; 32: 963–982.

28 Sweden S. **Hundar, katter och andra sällskapsdjur**. https://www.skk.se/globalassets/dokument/om-skk/scb-undersokning-hundar-katter-och-andra-sallskapsdjur-2012.pdf (2012, accessed November 1, 2018).

29 Fitzpatrick N and Solano MA. **Predictive variables for complications after TPLO with stifle inspection by arthrotomy in 1000 consecutive dogs**. *Vet Surg* 2010; 39: 460–474.

30 Ichinohe T, Kanno N, Harada Y, et al. **Degenerative changes of the cranial cruciate ligament harvested from dogs with cranial cruciate ligament rupture**. *J Vet Med Sci* 2015; 77: 761–770.

31 Comerford EJ, Smith K and Hayashi K. **Update on the aetiopathogenesis of canine cranial cruciate ligament disease**. *Vet Comp Orthop Traumatol* 2011; 24: 91–98.

32 Pacchiana PD, Morris E, Gillings SL, et al. **Surgical and postoperative complications associated with tibial plateau leveling osteotomy in dogs with cranial cruciate ligament rupture: 397 cases (1998–2001)**. *J Am Vet Med Assoc* 2003; 222: 184–193.

33 Johnson JA, Austin C and Breur GJ. **Incidence of canine appendicular musculoskeletal disorders in 16 veterinary teaching hospitals from 1980 through 1989**. *Vet Comp Orthop Traumatol* 1994; 7: 56–69.

34 Suter E, Herzog W, Leonard TR, et al. **One-year changes in hind limb kinematics, ground reaction forces and knee stability in an experimental model of osteoarthritis**. *J Biomech* 1998; 31: 511–517.

35 Schulz KS. **Diseases of the joint**. In: Fossum TW, Duphrey LP and Huff TG (eds). Small animal surgery. St Louis, MO: Elsevier, 2012, pp 1215–1374.

36 Clarke SP, Mellor D, Clements DN, et al. **Prevalence of radiographic signs of degenerative joint disease in a hospital population of cats**. *Vet Rec* 2005; 157: 793–799.

Paper III

The effect of treatment strategy on long-term outcome in dogs with cranial cruciate ligament disease, an epidemiological study of 333 dogs

Karolina Engdahl*[1], Gudrun S Boge*[2], Annika Bergström[1], Ulf Emanuelson[1], Jeanette Hanson[1], Odd Höglund[1], Elena R Moldal[2], Eystein Skjerve[3], Randi Krontveit[4]

[1]Department of Clinical Sciences, Swedish University of Agricultural Sciences, Uppsala, Sweden

[2]Department of Companion Animal Clinical Sciences, Norwegian University of Life Sciences – School of Veterinary Science, Oslo, Norway

[3]Department of Food Safety and Infection Biology, Norwegian University of Life Sciences – School of Veterinary Science, Oslo, Norway

[4]Norwegian Medicines Agency, Oslo, Norway

* These authors contributed equally to this work

Corresponding Author:

Karolina Engdahl

Academic qualifications: DVM

E-mail address: karolina.engdahl@slu.se

Phone number: +4618671892

Address: Department of Clinical Sciences, Swedish University of Agricultural Sciences, Ulls väg 12, 75007 Uppsala, Sweden

Acknowledgment

The authors would like to thank all participating dog owners and referring veterinarians for their cooperation and Caroline Mason for help in collecting data.

Conflict of interest

The authors declare no conflict of interest.

Funding

The PhD-project of one of the authors (K.E.) is financed by Agria Pet Insurance Research Foundation. No other financial support for the research, authorship, and/or publication of this article was received.

Author contributions

All authors contributed to the study design. KE and GSB registered the data under supervision from OH, AB and ERM. KE and GSB also carried out the data analysis and interpretation under supervision from RK with contribution from UE, ES and JH. KE and GSB was major contributors to the manuscript, with substantial input from the other authors. All authors participated in the discussions and revisions of the entire text. All authors read and approved the final manuscript.

The effect of treatment strategy on long-term outcome in dogs with cranial cruciate ligament disease, an epidemiological study of 333 dogs

Abstract

Objective: To analyse the long-term outcome of dogs treated surgically or conservatively for cranial cruciate ligament disease (CCLD).

Methods: A retrospective cohort study of 333 dogs presenting with CCLD at two University Hospitals was performed (2011-2016). Signalment, history, treatment and follow-up details were retrieved from medical records and dog owners contacted for further information. Treatment groups were defined; conservative or surgical with either lateral fabellotibial suture technique or osteotomy procedures. A multivariable Cox proportional hazards model was applied to evaluate risk factors for CCLD-related euthanasia (CRE) with 6 years maximum follow-up time.

Results: Sixty-five dogs were conservatively managed and 125/143 treated with LFS/osteotomy, respectively. At follow-up, 164 dogs (49.3%) were alive and 169 (50.7%) were dead. CRE occurred in 61 dogs (18.3%); 19 (29.2%) in the conservative, 19 (15.2%) in the LFS and 23 (16.1%) in the osteotomy group. The Cox model included treatment, orthopaedic comorbidities, age and weight. The hazard of CRE was lower for surgically compared to conservatively treated, with the hazard for the osteotomy group being significantly lower (HR 0.40, $p = 0.012$). The hazard increased with other orthopaedic comorbidities (HR 3.09, $p = 0.001$), age (HR 1.12, $p = 0.039$) and weight (HR 1.03, $p = 0.001$).

Conclusion: Treatment strategy, age, weight and other orthopaedic comorbidities were risk factors for CRE in dogs with CCLD.

Introduction

Cranial cruciate ligament disease (CCLD) is one of the most common orthopaedic conditions in dogs(1). Many factors including anatomical configuration, genetic and environmental factors are thought to affect the development of CCLD, but the exact aetiopathogenesis is still unclear(2-5). The disease can be treated conservatively or surgically. More than 60 variations of surgical procedures have been described(6), including lateral fabellotibial suture stabilisation (LFS), tibial plateau levelling osteotomy (TPLO) and tibial tuberosity advancement techniques such as the tibial tuberosity advancement (TTA) and the modified maquet procedure (MMP). TPLO and LFS are the surgical techniques most commonly studied, followed by TTA(6). Progressive osteoarthritis is reported to occur in the affected stifle regardless of treatment method(7).

Most studies assessing the outcome after CCLD surgery have a follow-up time of less than six months and/or focus on risk factors for postoperative complications(6, 8-11). Information obtained from interviews/questionnaires with owners and visual gait observations are commonly used for assessment of long-term outcome, while objective measurements such as force plate gait evaluation and thigh circumference are less often reported(6). Only a few studies comparing long-term outcomes from three (or more) treatment methods have been published(12-15). In addition, few studies have evaluated the outcome for conservatively treated dogs with CCLD(16-18).

In general, only small differences in kinematic measures between the surgical techniques have been found at follow-up evaluation(12, 15). Consequently, no general agreement on which surgical method yields the best outcome exists, although there is some evidence in favour of TPLO(6, 19). Common for all previously mentioned outcome measures is that they evaluate lameness, chronic pain or loss of function in the affected hind limb, which could eventually result in euthanasia in severe cases. The risk of euthanasia in dogs with CCLD is unknown, and there are currently no studies evaluating the effect of treatment strategy on life expectancy in dogs with CCLD.

The current study was designed to analyse the long-term outcome after CCLD-treatment. We hypothesised that CCLD-related euthanasia would be affected by treatment method and preoperative factors.

Materials and Methods

Study design

A retrospective cohort study was performed utilising electronic medical records of all dogs examined at two Veterinary University Hospitals (VHs, Hospital 1: University Animal Hospital, Norwegian University of Life Sciences and Hospital 2: University Animal Hospital, Swedish University of Agricultural Sciences) between January 2011 and December 2016.

Data collection

The medical records were reviewed between January 1 and August 31, 2018. Inclusion criteria was a diagnosis of CCLD, confirmed by a positive cranial drawer test or a positive tibial thrust. Routine clinical data including age, breed, sex and body weight was retrieved. Neuter status was not consistently registered in the records and hence not included. Clinical examination and history were noted when available.

The surgical technique was recorded for all surgically treated cases. Follow-up information such as subsequent contralateral CCLD, post-operative complications and date and reason for death/euthanasia was retrieved from the records. Bilaterally affected dogs were included as a single case at the time of the first CCLD treated at the VHs. Standardised written postoperative care and rehabilitation recommendations were available at both VHs and routinely provided to owners; however, this could not be verified in all medical records.

Dogs where information about lameness before treatment initiation was missing, dogs euthanised at time of diagnosis or with less than 14 days follow-up time, dogs with collateral ligament rupture or where joint inspection revealed less than 10% CCL rupture, dogs diagnosed at the hospitals but surgically treated at other clinics or surgically treated at the VHs for contralateral CCLD prior to the study period, were excluded.

Follow-up information was obtained via telephone interviews with the owners between August 1 and October 15, 2018. Standardised questions about additional complications, contralateral CCLD, and date and reason for death/euthanasia were asked. Referring veterinarians were contacted for additional information when deemed necessary. Dates were recorded as 1st of the month if the exact date was unknown.

Outcome

Reason for death/euthanasia was retrospectively classified as related to CCLD or not. Euthanasia related to CCLD was defined as all deaths where lameness from the affected hindlimb(s) was contributing to the decision of euthanasia. CCLD-related euthanasia was the end-point of the study and classified into five different subcategories (Table 1). Classification of death/euthanasia unrelated to CCLD was performed according to Fleming et al. (2011)

(20), with a few modifications: the original categories for organ system and pathophysiological process were used, but additional categories for “high age” and “behaviour-related” were added. If the reason for death/euthanasia could not be classified, it was recorded as “unclassified” rather than excluded.

Risk factors

Treatment method was defined as the main exposure variable. All dogs without surgical correction of the CCLD were defined as conservatively treated. Surgically treated dogs were categorised into two groups; LFS and osteotomy (TPLO, TTA and MMP). Initial data exploration showed that further categorisation of the osteotomies was not feasible, due to the relatively small number of dogs in each group that were euthanised of CCLD-related causes.

A tentative causal diagram was made to identify possible confounding and intervening variables for the association of treatment method with the outcome. In addition, a change of >20% in the coefficients in the model with the potential confounder present was used to assess confounding. All post-surgical related variables (such as postoperative complications and bilateral disease) were considered as intervening variables, since they lay on the causal path between the main exposure variable (treatment) and the outcome (CCLD-related euthanasia), and thus not considered for inclusion in the statistical analyses(21). The variables hospital, age, sex, weight, orthopaedic and non-orthopaedic comorbidities, lameness more than eight weeks prior to treatment initiation, insurance status, overweight, laterality of the affected stifle, and joint inspection were considered as potential determinants for CCLD-related euthanasia. The variable for orthopaedic comorbidity included four categories (patellar luxation, stifle osteochondrosis, hip dysplasia and other orthopaedic conditions).

Statistical analysis

All statistical analyses were conducted in Stata 15(22). The distribution of dogs by descriptive variables in each treatment group was calculated. Continuous variables are presented as median (range) and categorical variables as number (percentage). Graphical assessment of the continuous variables age and weight showed deviance from normality, hence a non-parametric Kruskal-Wallis one-way ANOVA was used to compare the difference in medians between the treatment groups. One-sample test of proportions was used to compare the number of female and male dogs and Chi-square tests to examine the relationship between categorical determinants and treatment. A Bonferroni correction was applied to adjust for pairwise comparison between the treatment groups with an alpha level of 0.0167

(0.05/3). The number, percentage and median time to death/euthanasia and censoring was calculated. Kaplan-Meier survival curves were used to describe differences in time-to-event for the treatment groups. Follow-up time was calculated as the time from treatment initiation to euthanasia, or owner-contact/latest follow-up in the medical records when the dog was alive. Maximum follow-up time was set to 6 years (72 months) for the analysis.

A Cox proportional hazards model was applied to estimate the effect of possible risk factors on time to CCLD-related euthanasia. Dogs alive at the end of the study period, lost to follow-up or dead/euthanised due to causes unrelated to CCLD were censored. A female Gordon setter had a missing value for weight, and the weight for female Gordon setters according to the breed standard[1] was used in the analysis. Collinearity between variables was evaluated by Goodman and Kruskal's gamma for categorical or dichotomous variables and by Pearson's correlation coefficient for continuous variables. A hazard ratio (HR), 95% confidence interval and p-value were calculated for each variable. All variables with $p < 0.15$ in univariable analyses were considered for inclusion into a multivariable model. Hospital was forced into the final model to account for differences between the two hospitals.

Manual stepwise backward elimination was applied for selection of variables. Biologically plausible interactions were considered for inclusion. The Wald test was used to evaluate the significance of the predictors. A p-value of <0.05 was considered statistically significant. Schoenfeld residuals for each variable in the final model were used to evaluate the assumption of proportional hazards. Sensitivity analysis was performed to evaluate the assumption of individual censoring. Plots of martingale residuals were used to test the functional form of the predictors. Deviance and scaled score residuals were plotted against time at risk for detection of outliers and influential observations, respectively. The model was fit with and without the suspected outlying observations. Linear combinations of the coefficients from the model were used to check for differences between the treatment methods after the final model was fitted.

Results

Animals and treatment

[1] Fédération Cynologique Internationale breed standard Gordon setter, accessed 13.02.2019: http://www.fci.be/Nomenclature/Standards/006g07-en.pdf

A total of 333 dogs (Hospital 1: 121, Hospital 2: 212) fulfilled the inclusion criteria and were enrolled in the study (Table 2). Sixty-five (19.5%) were conservatively treated, 125 (37.6%) treated with LFS and 143 (42.9%) with osteotomy (71 TPLOs, 54 TTAs, 18 MMPs, Supplementary table 1). The most common breeds were mixed-breed (n = 66), Rottweiler (n = 24), Labrador Retriever (n = 15), Golden Retriever (n = 15) and Jack Russel Terrier (n = 13). The median age of dogs treated conservatively and with LFS were significantly higher than dogs treated with osteotomy (7.6 and 7.7 years vs. 4.2 years, $p < 0.001$). The median weight in the osteotomy group was significantly higher than in the other groups (35.0 kg vs. 11.3 kg (LFS) and 17.9 kg (conservative), $p < 0.001$). There were significantly more female than male dogs ($p = 0.03$).

In total 134 dogs (40.2%) had a comorbidity recorded at the time of treatment initiation. Of the conservatively treated dogs, 18 (27.7%) had concurrent orthopaedic conditions while 20 (30.8%) had other non-orthopaedic diseases. The corresponding numbers for the LFS group were 34 (27.2%) and 19 (15.2%), and for the osteotomy group 30 (21.0%) and 24 (16.8%), respectively. Non-orthopaedic comorbidities were significantly more common among conservatively treated dogs compared to dogs treated by LFS ($p=0.012$), but not compared to dogs treated with osteotomy ($p=0.022$, not significant after Bonferroni correction). The most common non-orthopaedic comorbidity was various dermatological diseases.

Outcome

At follow-up, 164 dogs (49.3 %) were still alive, while 108 (32.4%) were dead/euthanised due to reasons unrelated to CCLD (Table 3). The most common non-CCLD-related reasons were high age or related to the urogenital organs, gastrointestinal system or the musculoskeletal system (lameness of the affected hindlimb excluded). The reason for euthanasia was CCLD-related in 61 dogs (18.3%); 19 (29.2%) in the conservatively treated group, 19 (15.2%) in the LFS group and 23 (16.1%) in the osteotomy group. The most common CCLD-related reason for euthanasia was persistent lameness (Table 1). Nine (47.4%) of the conservatively treated dogs, 6 (31.6%) of the dogs treated by LFS and 7 (30.4%) of the dogs treated with osteotomy had concurrent comorbidities that contributed to the decision of euthanasia. None of the dogs excluded due to <14 days follow-up time were dead/euthanised of reasons related to CCLD.

Survival analysis

A Kaplan-Meier survival plot for the different treatment groups is presented in Figure 1. [insert Figure 1]. Collinearity between variables was not detected. The p-values from the univariable Cox model is presented in Supplementary table 2. The final model included variables for treatment method, orthopaedic comorbidities, age and weight (Table 4, $p < 0.05$). None of the tested interactions were significant. Weight and age were found to be confounders for treatment method. The overall effect of treatment had a p-value of 0.035. The hazard of CCLD-related euthanasia for dogs treated by osteotomy was significantly lower than for the conservatively treated dogs (HR 0.40, $p = 0.012$). It was also lower for the dogs treated by LFS, but the difference was not statistically significant (HR 0.56, $p = 0.109$). No significant difference was found between the two surgical techniques ($p = 0.370$). The hazard of CCLD-related euthanasia increased with other orthopaedic comorbidities (HR 3.09, $p = 0.001$), age (HR 1.12, $p = 0.039$) and weight (HR 1.03, $p = 0.001$). The model validation did not reveal violations of the model assumptions.

Discussion

Chronic clinical dysfunction due to a persistent lameness which results in euthanasia is the most serious outcome of CCLD. This study is the first to evaluate disease-related euthanasia in relation to treatment method in dogs with CCLD. In total, 61 (18.1%) of the dogs were euthanised due to CCLD-related causes within the follow-up time. This is substantially higher than in a study by Mölsa et al.(2013), which is one of a few long-term studies available(23). In that study, a questionnaire was completed by owners of 253 surgically treated dogs (mean follow-up time 2.7 years). Only 2% of the owners reported their dogs as dead due to problems related to CCLD. However, it might be that owners of euthanised dogs were less likely than owners of dogs still alive to return such a questionnaire, which could explain the discrepancy. At one-year follow-up, 43 (12.9%) of the dogs in the current study had died or been euthanised. This finding supports the fact that exclusion of euthanised dogs has the potential to bias the results in long-term studies evaluating clinical function of dogs with CCLD. Thus, survival analysis is an appropriate statistical method.

Results from the multivariable Cox proportional hazards model show that surgically treated dogs have a lower risk of CCLD-related euthanasia than conservatively treated dogs. This implies that, in this referral population, there is a risk of treatment failure resulting in euthanasia following conservative treatment. Surgical treatment resulted in longer survival, and osteotomies had lowest hazard of CCLD-related euthanasia. It is also worth noticing that the hazard increased with weight, age and other concurrent orthopaedic diseases.

According to current recommendations, conservative treatment of CCLD is most suitable for small dogs (<15 kg) with mild and resolving lameness or if there is a contraindication for surgical treatment(24). In the present study material, dogs with concurrent disease were more likely to be treated conservatively. This is in agreement with the recommendations, since concurrent disease can be a contraindication for surgical treatment.

Joint exploration was rarely performed in the conservatively treated cases, and thus, a lower percentage of meniscal injury was reported in these dogs than in the dogs treated by surgery. Joint exploration with meniscal inspection is generally recommended and has been performed in most studies of surgically treated CCLD in dogs(8, 11, 12). Hence, undetected meniscal injury may have been a possible reason for treatment failure due to persisting lameness in the conservatively treated dogs. However, a recent study evaluating long-term outcome after TPLO surgery without joint exploration reported a low incidence of persistent lameness and questioned the need for routine meniscal examination(25).

In our study, surgeons with different levels of experience performed the procedures. The literature provides conflicting results regarding the impact of the surgeon's experience on the outcome. While a few studies have reported a positive correlation between surgeon experience and outcome(13), no association has been found in several(9, 12, 19, 26, 27). We could not determine the level of experience of the primary surgeons; and thus, we were not able to evaluate this effect on CCLD-related euthanasia. Although it should be acknowledged as a limitation, this could also result in better external validity since there will always be variability between surgeons in clinical settings. The outcome after procedures performed by surgeons with variable experience levels may more accurately reflect common practice, compared to studies evaluating outcome after surgeries performed by a single surgeon.

Time to CCLD-related euthanasia only represents one aspect of treatment outcome. The quality of life for animals with CCLD must also be taken into consideration. Several standardised quality of life (QoL) questionnaires have been evaluated for pain assessment in dogs(23, 28, 29). However, due to the long follow-up time in our study, a high percentage of the dogs were dead at the time of owner contact and consequently QoL assessments were not considered relevant.

Some additional aspects of our study should be mentioned. Importantly, the categorisation of the reasons for death/euthanasia relied on the authors' judgement of the owners' and/or referral veterinarians' assessment, without further investigation or post-mortem examinations. CCLD-related euthanasia is not a completely objective endpoint, since the decision of euthanasia is often complex. However, a misclassification bias thus introduced is likely to be non-differential and consequently only reduce the likelihood to observe differences. This study was not conducted on a randomised group of patients, and therefore, the treatment decision could have been influenced by the inherent bias of the attending veterinarian, in addition to owner financial considerations and the perceived risk and prognosis associated with the surgical procedure. Although measured factors which could have influenced the treatment decision such as insurance status, concurrent diseases, weight and age of the dog were controlled for, unmeasured factors are likely to have influenced the obtained results. Since most of the dogs in the present study were referred, a bias toward surgical referral was evident and it is possible that the true success of conservative treatment for dogs with CCLD could have been underestimated.

Conclusion

Euthanasia related to CCLD in dogs is not uncommon and shows that the disease can result in such a severe lameness that it affects life-expectancy. Both treatment strategies and variables related to signalment and history of the dog were identified as risk factors for the hazard of CCLD-related euthanasia. The risk was lower for dogs surgically treated with osteotomy procedures compared to conservatively treated dogs and increased with age and weight. Information regarding life expectancy in relation to risk factors and treatment methods is valuable for a dog owner facing a decision about treatment of CCLD.

References

1. Johnson JA, Austin C, Breur GJ. Incidence of Canine Appendicular Musculoskeletal Disorders in 16 Veterinary Teaching Hospitals from 1980 through 1989. Vet Comp Orthop Traumatol. 1994;07(02):56-69.
2. Witsberger TH, Villamil JA, Schultz LG, Hahn AW, Cook JL. Prevalence of and risk factors for hip dysplasia and cranial cruciate ligament deficiency in dogs. J Am Vet Med Assoc. 2008;232(12):1818-24.
3. Whitehair JG, Vasseur PB, Willits NH. Epidemiology of cranial cruciate ligament rupture in dogs. J Am Vet Med Assoc. 1993;203(7):1016-9.
4. Taylor-Brown FE, Meeson RL, Brodbelt DC, Church DB, McGreevy PD, Thomson PC, et al. Epidemiology of Cranial Cruciate Ligament Disease Diagnosis in Dogs Attending Primary-Care Veterinary Practices in England. Vet Surg. 2015;44(6):777-83.
5. Duval JM, Budsberg SC, Flo GL, Sammarco JL. Breed, sex, and body weight as risk factors for rupture of the cranial cruciate ligament in young dogs. J Am Vet Med Assoc. 1999;215(6):811-4.
6. Bergh MS, Sullivan C, Ferrell CL, Troy J, Budsberg SC. Systematic review of surgical treatments for cranial cruciate ligament disease in dogs. J Am Anim Hosp Assoc. 2014;50(5):315-21.
7. Schulz KS. Diseases of the Joint. In: Fossum TW, Duphrey LP, Huff TG, editors. Small Animal Surgery. St. Louis: Elsevier; 2012. p. 1215-374.
8. Stauffer KD, Tuttle TA, Elkins AD, Wehrenberg AP, Character BJ. Complications Associated With 696 Tibial Plateau Leveling Osteotomies (2001–2003). J Am Anim Hosp Assoc. 2006;42(1):44-50.
9. Pacchiana PD, Morris E, Gillings SL, Jessen CR, Lipowitz AJ. Surgical and postoperative complications associated with tibial plateau leveling osteotomy in dogs with cranial cruciate ligament rupture: 397 cases (1998–2001). J Am Vet Med Assoc. 2003;222(2):184-93.
10. Hans EC, Barnhart MD, Kennedy SC, Naber SJ. Comparison of complications following tibial tuberosity advancement and tibial plateau levelling osteotomy in very large and giant dogs 50 kg or more in body weight. Vet Comp Orthop Traumatol. 2017;30(4):299-305.
11. Fitzpatrick N, Solano MA. Predictive variables for complications after TPLO with stifle inspection by arthrotomy in 1000 consecutive dogs. Vet Surg. 2010;39(4):460-74.
12. Conzemius MG, Evans RB, Besancon MF, Gordon WJ, Horstman CL, Hoefle WD, et al. Effect of surgical technique on limb function after surgery for rupture of the cranial cruciate ligament in dogs. J Am Vet Med Assoc. 2005;226(2):232-6.
13. Christopher SA, Beetem J, Cook JL. Comparison of long-term outcomes associated with three surgical techniques for treatment of cranial cruciate ligament disease in dogs. Vet Surg. 2013;42(3):329-34.
14. Moore KW, Read RA. Cranial cruciate ligament rupture in the dog--a retrospective study comparing surgical techniques. Aust Vet J. 1995;72(8):281-5.
15. Mölsä SH, Hyytiainen HK, Hielm-Bjorkman AK, Laitinen-Vapaavuori OM. Long-term functional outcome after surgical repair of cranial cruciate ligament disease in dogs. BMC Vet Res. 2014;10:266.
16. Pond M, Campbell J. The canine stifle joint I. Rupture of the anterior cruciate ligament: an assessment of conservative and surgical treatment. J Small Anim Pract. 1972;13(1):1-10.
17. Wucherer KL, Conzemius MG, Evans R, Wilke VL. Short-term and long-term outcomes for overweight dogs with cranial cruciate ligament rupture treated surgically or nonsurgically. J Am Vet Med Assoc. 2013;242(10):1364-72.
18. Vasseur PB. Clinical Results Following Nonoperative Management for Rupture of the Cranial Cruciate Ligament in Dogs. Vet Surg. 1984;13(4):243-6.
19. Gordon-Evans WJ, Griffon DJ, Bubb C, Knap KM, Sullivan M, Evans RB. Comparison of lateral fabellar suture and tibial plateau leveling osteotomy techniques for treatment of dogs with cranial cruciate ligament disease. J Am Vet Med Assoc. 2013;243(5):675-80.

20. Fleming J, Creevy K, Promislow D. Mortality in North American dogs from 1984 to 2004: an investigation into age-, size-, and breed-related causes of death. J Vet Intern Med. 2011;25(2):187-98.

21. Dohoo IR, Martin SW, Stryhn H. Veterinary epidemiologic research. 2nd ed. Charlotte, P.E.I.: VER, Inc.; 2014.

22. StataCorp. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC; 2017.

23. Mölsä SH, Hielm-Björkman AK, Laitinen-Vapaavuori OM. Use of an owner questionnaire to evaluate long-term surgical outcome and chronic pain after cranial cruciate ligament repair in dogs: 253 cases (2004–2006). J Am Vet Med Assoc. 2013;243(5):689-95.

24. McKee MW, Cook JL. The stifle. In: Houlton J, Cook JL, Innes JF, Langley-Hobbs SJ, editors. BSAVA Manual of Canine and Feline Musculoskeletal Disorders 1ed: Blackwell Professional Publishing; 2006.

25. Bureau S. Owner assessment of the outcome of tibial plateau levelling osteotomy without meniscal evaluation for treatment of naturally occurring cranial cruciate ligament rupture: 130 cases (2009 to 2013). J Small Anim Pract. 2017;58(8):468-75.

26. Wilson ML, Roush JK, Renberg WC. Comparison of the Effect of Dog, Surgeon and Surgical Procedure Variables on Improvement in Eight-Week Static Weight-Bearing following Tibial Plateau Levelling Osteotomy. Vet Comp Orthop Traumatol. 2018;31(06):396-404.

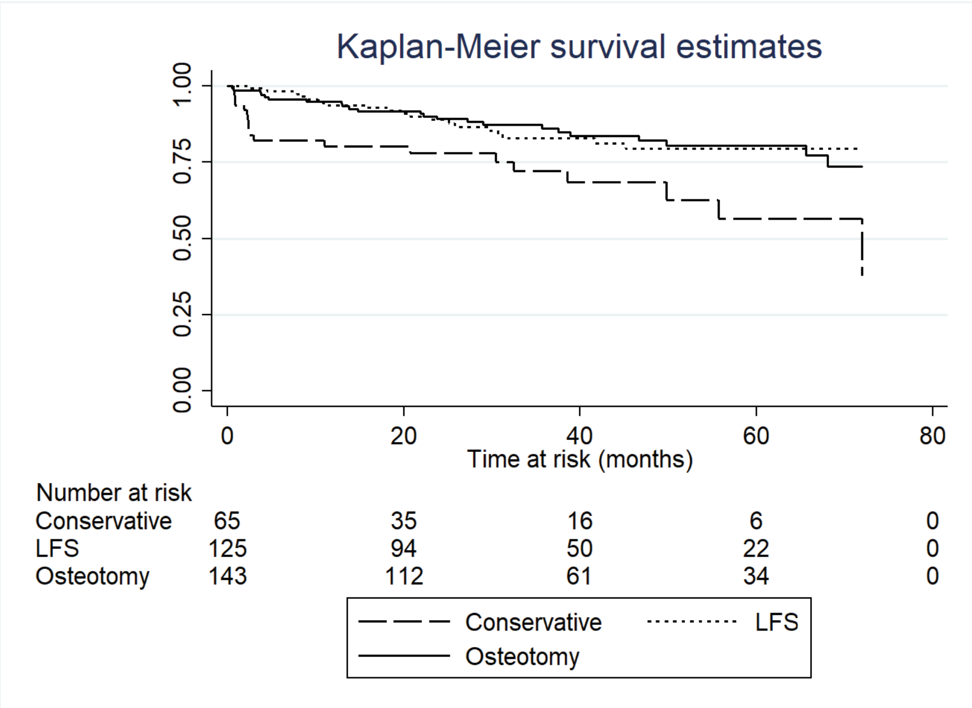
27. Casale SA, McCarthy RJ. Complications associated with lateral fabellotibial suture surgery for cranial cruciate ligament injury in dogs: 363 cases (1997-2005). J Am Vet Med Assoc. 2009;234(2):229-35.

28. Innes JF, Bacon D, Lynch C, Pollard A. Long-term outcome of surgery for dogs with cranial cruciate ligament deficiency. Vet Rec. 2000;147(12):325-8.

29. Hudson JT, Slater MR, Taylor L, Scott HM, Kerwin SC. Assessing repeatability and validity of a visual analogue scale questionnaire for use in assessing pain and lameness in dogs. Am J Vet Res. 2004;65(12):1634-43.

Figure legend

Figure 1. Kaplan-Meier curves by treatment describing disease-related survival in a retrospective cohort of dogs treated for CCLD. Time at risk is from treatment initiation to 72 months.



Tables

Table 1. Disease-related euthanasia of dogs with cranial cruciate ligament disease

Reason for euthanasia	CCLD only N (%)	Comorbidity N (%)	Combined N (%)
Persistent lameness	13 (52.0)	12 (48.0)	25 (41.0)
Contralateral CCLD	16 (94.1)	1 (5.9)	17 (28.9)
Other	2 (22.2)	7 (77.8)	9 (14.8)
Post-operative complications	7 (87.5)	1 (12.5)	8 (13.1)
Risk won't return to function	2 (100.0)	0 (0.0)	2 (3.3)
Total	40 (65.6)	21 (34.4)	61 (100)

CCLD = Cranial cruciate ligament disease
Comorbidity = additional non-CCLD related factors contributing to the decision of euthanasia.

Table 2. Descriptive features at time of diagnosis of 333 dogs with cranial cruciate ligament disease (2011-2016).

Variable	**Surgery**				**Conservative**		**Total**	
	LFS		Osteotomy					
Number of dogs (% of overall)	125	(37.5)	143	(43.0)	65	(19.5)	333	(100.0)
Dogs treated at Hospital 1 (%)	*25*	*(20.0)*	*77*	*(53.9)*	*19*	*(29.2)*	*121*	*(36.3)*
Dogs treated at Hospital 2 (%)	*100*	*(80.0)*	*66*	*(46.2)*	*46*	*(70.8)*	*212*	*(63.7)*
Age in years (min-max)	7.7	(0.9-12.8)	4.2	(0.9-10.7)	7.6	(0.2-13.3)	6.5	(0.2-13.3)
Weight in kg (min-max)	11.3	(3.3-49.3)	35.0	(10.1-80.3)	17.9	(3.8-76.0)	23.6	(3.3-80.3)
Overweight (%)	41	(32.8)	35	(24.5)	19	(29.2)	95	(28.5)
Sex (%)								
Female	74	(59.2)	71	(49.7)	40	(61.5)	185	(55.6)
Male	51	(40.8)	72	(51.3)	25	(38.5)	148	(44.4)
Insured (%)	112	(89.6)	118	(82.5)	52	(80.0)	282	(84.3)
Stifle affected (%)								
Left	60	(48.0)	82	(57.3)	28	(43.1)	170	(51.0)
Right	62	(49.6)	59	(41.3)	34	(52.3)	155	(46.6)
Bilateral	3	(2.4)	2	(1.4)	3	(4.6)	8	(2.4)
Lameness >8 w prior to treatment initiation (%)	47	(37.6)	74	(51.8)	33	(50.8)	154	(46.3)
Orthopaedic comorbidities (%)	34	(27.2)	30	(21.0)	18	(27.7)	82	(24.61)
Hip dysplasia	*7*	*(5.6)*	*9*	*(6.3)*	*2*	*(3.1)*	*18*	*(5.4)*
Patellar luxation	*19*	*(15.2)*	*2*	*(1.4)*	*5*	*(7.7)*	*26*	*(7.8)*
OC Stifle	*0*	*(0.0)*	*7*	*(4.9)*	*4*	*(6.2)*	*11*	*(3.3)*
Other	*8*	*(6.4)*	*12*	*(8.4)*	*7*	*(10.8)*	*27*	*(8.1)*
Non-orthopaedic comorbidities (%)	19	(15.2)	24	(16.8)	20	(30.8)	63	(18.9)

Categorical variables presented as number of dogs (% total number of dogs by treatment method if not specified). Continuous variables as median (min-max).
LFS = Lateral Fabellotibial suture; OC = Osteochondrosis.
Weight missing for one dog, N=332 for this variable

Table 3. Treatment and follow-up of 333 dogs with cranial cruciate ligament disease presented to two veterinary teaching hospitals (2011-2016).

Variable	**Surgery**		**Conservative**	**Total**
	LFS (N=125)	Osteotomy (N=143)	(N=65)	(N=333)
Follow-up time in months (min-max)	34.0 (0.8-91.3)	36 (0.5-89.3)	23.5 (0.6-90.4)	34 (0.5-91.3)
Bilateral rupture (% of dogs with unilateral CCLD)*	47 (38.5)	49 (34.8)	10 (16.1)	106 (32.6)
Joint inspection (%)	115 (92.0)	104 (72.7)	5 (7.7)	224 (67.3)
Hospital 1	*16 (64.0)*	*38 (49.4)*	*4 (21.1)*	*58 (47.9)*
Hospital 2	*99 (99.0)*	*66 (100.0)*	*1 (2.2)*	*166 (78.3)*
Arthrotomy (%)	101 (80.1)	42 (29.4)	2 (3.1)	145 (43.5)
Arthroscopy (%)	21 (16.8)	73 (51.1)	3 (4.6)	97 (29.1)
Meniscal injuries (%)	29 (23.2)	29 (20.3)	1 (1.5)	59 (17.7)
Post-operative complications	32 (25.6)	52 (36.4)	NA	NA
Dogs alive (%)	69 (55.2)	76 (53.2)	19 (29.3)	164 (49.3)
Dogs dead/euthanised (%)	56 (44.8)	67 (46.8)	46 (70.7)	169 (50.7)
CCLD-related	19 (15.2)	23 (16.1)	19 (29.2)	61 (18.3)
Other causes	37 (29.6)	44 (30.7)	27 (41.5)	108 (32.4)
Months to CCLD-related euthanasia (min-max)	19.9 (2.3-45.1)	21.9 (0.5-68.1)	2.4 (0.6-74.0)	15.6 (0.5-74.0)
Months to censoring (min-max)	37.4 (0.8-91.3)	38.7 (0.8-89.2)	25.4 (0.6-90.3)	36.2 (0.6-91.3)

Continuous variables reported as median (range), categorical variables as number of dogs (percentage).

CCLD = Cranial Cruciate Ligament Disease; LFS = Lateral Fabellotibial suture; NA = Not applicable; OC = Osteochondrosis.

Table 4. Results from a multivariable Cox proportional hazards model comparing disease-related euthanasia in a retrospective cohort of dogs with surgically and conservatively treated CCLD (maximum follow-up time 6 years).

Variable and level	HR	95% CI	P
Treatment			0.035*
Conservative	1.00	-	-
LFS	0.56	(0.28-1.14)	0.109
Osteotomy	0.40	(0.19-0.81)	0.012
Hospital			
Hospital 1	1.00	-	-
Hospital 2	1.21	(0.65-2.25)	0.547
Orthopaedic comorbidity			<0.001*
None	1.00	-	-
Patellar luxation	1.57	(0.52-4.73)	0.420
Hip dysplasia	1.10	(0.34-3.59)	0.873
OC Stifle	0.78	(0.22-2.80)	0.706
Other	3.09	(1.59-6.00)	0.001
Age (years)	1.12	(1.01-1.25)	0.040
Weight (kg)	1.03	(1.01-1.05)	0.001

CCLD = cranial cruciate ligament disease, HR= Hazard ratio, OC = Osteochondrosis. Age, weight and orthopaedic comorbitidies at time of diagnosis.

* Wald-test

Supplementary table 1. Surgical CCLD-procedures at two Veterinary University Hospitals in a retrospective cohort of dogs with surgically and conservatively treated CCLD.

	LFS (N=125)				TPLO (N=71)				TTA (N=54)				MMP (N=18)			
Year	S	P	M	(min-max)	S	P	M	(min-max)	S	P	M	(min-max)	S	P	M	(min-max)
2011	8	24	5	(1-6)	6	15	5	(1-5)	3	12	8	(1-8)	1	5	5	(5-5)
2012	8	19	3	(1-4)	4	13	4	(2-4)	2	15	10	(5-10)	2	2	1	(1-1)
2013	8	25	5	(1-6)	5	10	3	(1-3)	2	10	6	(4-6)	1	2	2	(2-2)
2014	6	14	4	(1-4)	5	9	2	(1-3)	3	9	5	(2-5)	1	3	3	(3-3)
2015	8	16	2.5	(1-5)	3	8	3.5	(1-4)	2	6	4	(2-4)	2	5	4	(1-4)
2016	8	27	7	(1-8)	4	16	6	(1-8)	1	2	2	(2-2)	1	1	1	(1-1)
Total	**15**	**125**	**4**	**(1-8)**	**10**	**71**	**3**	**(1-8)**	**4**	**57**	**5**	**(1-10)**	**2**	**18**	**3.5**	**(1-5)**

S = Number of individual surgeons, P = Total number of procedures, M (min-max) = Median number of procedures/surgeon CCLD = Cranial cruciate ligament disease, LFS = Lateral fabellotibial suture, TPLO = Tibial plateau leveling osteotomy, TTA = Tibial tuberosity advancement, MMP = Modified maquet procedure

Supplementary table 2. Univariate Cox proportional hazard model for selection of variables

Variable	P-value
Age (years)	0.019
Lameness >8 w prior to treatment	0.008
Hospital	0.074
Joint inspection	0.124
Insurance	0.144
Laterality of affected limb[†]	0.774
Meniscal injury	0.250
Non-orthopaedic comorbidiy	0.963
Orthopaedic comorbidity[†]	0.014
Overweight	0.900
Sex	0.135
Treatment[†]	0.003
Year of treatment[†]	0.464
Weight (kg)	0.034

[†]p-value from Wald test presented for multilevel categorical variables

ISBN: 978-82-575-1638-3
ISSN: 1894-6402

Norwegian University
of Life Sciences

Postboks 5003
NO-1432 Ås, Norway
+47 67 23 00 00
www.nmbu.no

105219 / ANDVORDGRAFISK.NO