Evaluation of physical dysfunction in cats with naturally occurring osteoarthritis

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(Photo: S. Stadig)

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Abstract

Osteoarthritis (OA) is a common cause of chronic pain and physical dysfunction in cats. Clinical signs are often subtle and lameness is rarely the chief complaint. The main clinical features consist of gradual changes in the cat's behaviour and everyday living. The changes are often misinterpreted as part of normal ageing. In a clinical setting, the diagnosis is based on information from the owner, physical examination and radiography. However, conflicting physical and radiographic signs makes feline OA challenging to diagnose. Improved tools are needed as diagnostic aid and to evaluate treatment efficacy.

The overall aim of the thesis was to improve methods for diagnosis and evaluation of treatment in cats with naturally occurring OA. Since chronic pain can only be measured indirectly, physical dysfunction caused by OA was measured. The alteration in physical dysfunction was evaluated using physical examination, objective pressure mat technique and subjective owner assessment questionnaires. The specific aims were to: establish reference values from gait analysis in sound cats, compare kinetic data from sound cats walking on the pressure mat with results from OA cats, evaluate four different questionnaires regarding validity and reliability, and in a clinical pilot study evaluate the effects of pain relieving treatment in OA cats using the pressure mat and the questionnaires.

The acquired reference values from sound cats confirmed that cats have a similar gait symmetry and front-hind asymmetry as dogs. Peak vertical force and vertical impulse were reliable gait parameters to analyse. Cats with OA and cranial cruciate ligament injury were compared to sound control cats. The cats with OA put load on their paws more unevenly and had a different behaviour in the home environment, compared to sound cats. The four questionnaires that were evaluated all had sound validity and reliability. The clinical pilot study comparing meloxicam and robenacoxib, showed that osteoarthritic cats that received pain-relieving drugs improved significantly.

The thesis contributes to evaluation of physical dysfunction in osteoarthritic cats by using objective pressure mat technique and subjective questionnaires. This leads to improved management of chronic pain in cats with OA and improved feline welfare.

Keywords: feline, pressure mat, questionnaire, clinical metrology instrument, DJD

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Utvärdering av funktionsnedsättning hos katt med naturligt förekommande osteoartrit

Sammanfattning

Osteoartrit (OA) är en vanlig orsak till kronisk smärta och funktionsnedsättning hos katt. Symtomen är ofta vaga och hälta ses sällan. De huvudsakliga symptomen består av successiva förändringar i kattens beteende och livsstil. Ofta tolkas de gradvisa förändringarna som tecken på ett normalt åldrande. Kliniskt baseras diagnosen på information från kattägaren, klinisk undersökning och röntgen. Fynden från den kliniska undersökningen överensstämmer inte alltid med fynden från röntgenundersökningen, vilket försvårar diagnostiken. Förbättrade metoder behövs för diagnostik av OA hos katt samt för utvärdering av behandlingseffekt.

Det övergripande syftet med avhandlingen var att förbättra metoderna för diagnostik och utvärdering av behandling hos katt med naturligt förekommande OA. Eftersom kronisk smärta enbart kan mätas indirekt, mättes funktionsnedsättning orsakad av OA. Funktionsnedsättningen utvärderades med klinisk undersökning, objektiv tryckmatteteknik samt subjektiv ägarbedömning via frågeformulär. De specifika syftena var att etablera referensvärden från tryckmätningsmattan för friska katter, att jämföra kinetisk data från friska katter med data från OA katter, utvärdera validitet och reliabilitet för fyra olika frågeformulär samt i en klinisk pilotstudie utvärdera smärtlindrande behandling med hjälp av tryckmatta och frågeformulär.

Referensvärdena från friska katter bekräftade hypotesen att katter har samma gångartssymmetri och bak-framdelsasymmetri som hundar. Maximal vertikal kraft och vertikal impuls var tillförlitliga parametrar att analysera. Katter med OA och korsbandsskada jämfördes med en grupp friska viktmatchade kontrollkatter. Katterna med OA belastade sina tassar mer ojämnt och hade ett annorlunda beteende i hemmiljön, jämfört med de friska katterna. De fyra frågeformulären som utvärderades hade samtliga god validitet och reliabilitet. Den kliniska pilotstudien där effekten av meloxikam och robenacoxib jämfördes visade att katterna med OA fick en signifikant smärtlindring av läkemedlen. Avhandlingen bidrar till att utvärdera funktionsnedsättning hos katter med OA genom att använda objektiv tryckmatteteknik och subjektiv ägarbedömning. Detta leder till förbättrade metoder för att bedöma och utvärdera behandling av kronisk smärta på grund av OA hos katt och på sikt förbättrad välfärd för katter.

Sökord: feline, pressure mat, questionnaire, clinical metrology instrument, DJD

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Dedication

To Henrik, Carl & John – with love

But the wildest of all the wild animals was the Cat. He walked by himself, and all places were alike to him.

Rudyard Kipling “Just so stories” 1902

Contents

List of publications

This thesis is based on the work contained in the following papers, referred to by Roman numerals in the text:

I Stadig, S.M.*, Bergh A.K. (2014). Gait and jump analysis in healthy cats using a pressure mat system. Journal of Feline Medicine and Surgery, 17 (6), pp. 523-529.

II Stadig S.*, Lascelles B.D.X., Bergh A. (2016). Do cats with a cranial cruciate ligament injury and osteoarthritis demonstrate a different gait pattern and behaviour compared to sound cats? Acta Veterinaria Scandinavica. 58 (Suppl 1):70, pp. 72-79.

III Stadig S.*, Lascelles B.D.X., Nyman G., Bergh A. (2017). Evaluation and Comparison of Pain Questionnaires in Cats with Osteoarthritis. (Manuscript)

IV Stadig S.*, Lascelles B.D.X., Nyman G., Bergh A. (2017). Multimodal evaluation of treatment with meloxicam and robenacoxib in osteoarthritic cats – a pilot study. (Manuscript)

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The contribution of Sarah Stadig to the papers included in this thesis was as follows:

I Involved in hypothesis generation and planning of the study, shared responsibility and took part in all data collection, main responsibility for data analysis, shared responsibility for interpretation and summarizing results, main responsibility for writing manuscript and corresponding with the journal and critically revising the article with input from co-authors.

II Shared responsibility for design and planning of the study, shared responsibility and took part in all data collection, shared responsibility for data analysis, shared responsibility for interpretation and summarizing results, main responsibility for writing manuscript and corresponding with the journal and critically revising the article with input from co-authors.

III Shared responsibility for the planning of the study, main responsibility and took part in all data collection, main responsibility for data collection and interpretation, shared responsibility for data analysis and summarizing results, main responsibility for writing manuscript.

IV Shared responsibility for the hypothesis generation and design of the study, main responsibility and took part in all data collection, main responsibility for data analysis and interpretation, shared responsibility for data analysis and summarizing results, main responsibility for writing manuscript.

Abbreviations

AM	Activity monitor
BCS	Body condition score
BW	Body weight
CCL	Cranial cruciate ligament
CKD	Chronic kidney disease
CMI	Clinical metrology instrument
CNS	Central nervous system
COX	Cyclooxygenase
CS	Central sensitization
CSOM	Client-specific outcome measure
CT	Computed tomography
CVI	Content Validity Index
DJD	Degenerative joint disease
DLH	Domestic longhair
DSH	Domestic shorthair
E.g.	*Exempli gratia* (For example)
FeLV	Feline leukaemia virus
FeSFV	Feline syncytium-forming virus
FHD	Feline hip dysplasia
FIV	Feline immunodeficiency virus
FMPI	Feline musculoskeletal pain index
FPFF	Feline physical function formula
GRF	Ground reaction force
ICC	Intra-class correlation
ICD	International classification of diseases
I.e.	*Id est* (In other words)
KG	Kilogram
L	Left
LF	Left front

LH	Left hind
MRI	Magnetic resonance imaging
NO	Nitric oxide
NRS	Numerical rating scale
NSAID	Nonsteroidal anti-inflammatory
OA	Osteoarthritis
OBW	Owner behaviour watch
PS	Peripheral sensitization
PVF	Peak vertical force
R	Right
RF	Right front
RH	Right hind
ROM	Range of motion
SD	Standard deviation
THR	Total hip replacement
VAS	Visual analogue scale
VGA	Visual gait analysis
VI	Vertical impulse
ZQB	Zamprogno question bank
WHO	World health organization

1 Introduction

1.1 General background

The World Small Animal Veterinary Association (WSAVA) state in their Guidelines for recognition, assessment and treatment of pain that for "members of the veterinary healthcare team it is our moral and ethical duty to mitigate this suffering to the best of our ability. This begins by evaluating for pain at every patient contact. However, and despite advances in the recognition and treatment of pain, there remains a gap between its occurrence and its successful management…" (Mathews *et al.*, 2014).

The domestic cat (*Felis catus*) is currently the most common pet globally (FEDIAF Facts & Figures, 2014). The cat's life expectancy has increased during the last decades (Egenvall *et al.*, 2009; Gunn-Moore, 2006; Kraft, 1998) and advanced age is currently, the only identified risk factor for feline osteoarthritis (OA) (Slingerland *et al.*, 2011; Lascelles *et al.*, 2010). OA is a common cause of chronic pain and physical dysfunction in cats. Both retrospective and more recent prospective studies demonstrate that radiographic prevalence of feline degenerative joint disease is almost 90%. Many cat owners are concerned about the quality of life in their aging cat, however, cat ownership is multifaceted. There is research indicating that in some circumstances cats become more of a family member than a companion animal (Turner, 2017; Stammbach & Turner, 1999). At the same time many cats suffer from suboptimal welfare, lacking adequate supervision and veterinary care taking (Howell *et al.*, 2016; Clark *et al.*, 2012). The clinical signs of naturally occurring OA are often subtle, appear gradually and lameness is not common (Clarke *et al.*, 2005; Godfrey, 2005; Hardie *et al.*, 2002). The main clinical features consist of gradual changes in the cat's behaviour and activities of daily living (Klinck *et al.*, 2012; Slingerland *et al.*, 2011; Zamprogno *et al.*, 2010; Bennett & Morton, 2009; Lascelles *et al.*,

2007a; Clarke & Bennett, 2006). These changes are often misinterpreted as part of the normal ageing process. In a clinical setting, the diagnosis is based on information from the cat owner, physical examination and radiography. Cats visiting veterinary clinics are often subjected to a substantial stress response (Quimby *et al.*, 2011; Belew *et al.*, 1999). During physical examination it can be difficult to establish whether a cat is withdrawing the paw or an extremity due to pain and discomfort or just feel uncomfortable being handled. Some cats cower on the examination table and a rewarding lameness examination can be hard to perform (Bennett *et al.*, 2012). Conflicting physical and radiographic signs makes feline OA challenging to diagnose (Lascelles *et al.*, 2007a; Clarke & Bennett, 2006; Budsberg, 1997). Improved diagnostic tools are required to identify cats that suffer from physical dysfunction, such as movement asymmetries, decreased joint range of motion and muscle atrophy, due to OA. At present there are no diagnostic tools that can measure chronic pain directly in cats. However, physical dysfunction as we know it, is one of the many effects of chronic pain and thus an indirect measure of pain. Even if physical dysfunction is affected by other parameters than pain, it is still valuable in order to reduce the gaps between the occurrence and the successful management of pain, as WSAVA states (Mathews *et al.*, 2014).

This is why we have chosen to investigate objective and subjective assessment methods to assess physical dysfunction due to OA in cats. Pressure mat technique is a method that has proven to be valuable evaluating physical function in dogs with OA (Abdelhadi *et al.*, 2013; Oosterlinck *et al.*, 2011; Bockstahler *et al.*, 2009; Lequang *et al.*, 2009). Using questionnaires for the cat owner to fill in regarding the cat's ability to function in the familiar home environment circumvents many of the limitations with examining the cat at the veterinary clinic. This is a tool that has showed promising results (Stadig *et al.*, 2016; Gruen *et al.*, 2015; Sul *et al.*, 2014; Benito *et al.*, 2013b; Benito *et al.*, 2012; Zamprogno *et al.*, 2010; Bennett & Morton, 2009), but needs further evaluation. By evaluating pressure mat technique and questionnaires improved feline welfare can be achieved.

1.2 Osteoarthritis – general definitions & nomenclature

OA is the most common form of arthritis that affects synovial joints in mammalian species (Nganvongpanit *et al.*, 2017; Johnson *et al.*, 2016; Rothschild Bruce M, 2012). Previously OA has been termed osteoarthrosis, degenerative joint disease (DJD), degenerative arthritis and arthritis deformans with varying specificity. Standardized nomenclature and consistent terminology is essential in describing the disease and comparing epidemiological studies.

Publications on epidemiology and prevalence of feline OA has room for improvement regarding the use of common terminology. Frequently, the lack of standardization makes interpretation and comparison of results difficult. In the past, the term DJD has been most commonly used for the disease. However, DJD is now considered a comprehensive term including several kinds of degenerative joint pathology. OA is a form of DJD that affects synovial or appendicular joints, whereas *spondylosis deformans* is a form of DJD that affects intervertebral disc or axial joints (Bennett *et al.*, 2012). The osteoarthritic disease has been defined by the Osteoarthritis Research Society International (OARSI) as follows: "Osteoarthritis is a common disease affecting many or possibly all mammals. Osteoarthritis is a disorder involving movable joints characterized by cell stress and extracellular matrix degradation initiated by micro- and macro-injury that activates maladaptive repair responses including pro-inflammatory pathways of innate immunity. The disease manifests first as a molecular derangement (abnormal joint tissue metabolism) followed by anatomic, and/or physiologic derangements (characterized by cartilage degradation, bone remodeling, osteophyte formation, joint inflammation and loss of normal joint function), that can culminate in illness" (Kraus *et al.*, 2015).

It has been questioned whether OA is a degenerative disease (Brandt *et al.*, 2009) and in the future it is possible that OA will no longer fit under the umbrella term DJD. While describing the osteoarthritic disease, that can occur asymptomatically, it is important to distinguish between the osteoarthritic disease and the illness caused by OA. Eric J. Cassell stated already in 1976, "…let us use the word "illness" to stand for what the patient feels when he goes to the doctor and "disease" for what he has on the way home from the doctor´s office. Disease, then, is something an organ has; illness is something a man has" (Helman, 1981). Distinguishing between the osteoarthritic "disease" and the osteoarthritic "illness" is fundamental to standardizing concepts concerning a heterogeneous disease. In humans, once clinical signs of chronic pain and physical dysfunction appears the osteoarthritic disease process is far advanced (Kraus *et al.*, 2015). This also resembles the case with feline OA, numerous cats have an ongoing disease process, which will not be detected due to lack of illness (Bennett *et al.*, 2012).

Different definitions of OA exist, based on diagnostic parameters and the purpose of the definition. Clinical or symptomatic OA is based on clinical signs of pain, loss of function and disability, whereas radiographic OA is defined on predetermined criteria such as osteophytes, sclerosis and bone remodeling. Pathophysiological OA is based on cartilage damage, synovitis, osteophyte formation and hypertrophy of the joint capsule. Radiographic OA has long been considered the gold standard, however the relationship between radiographic

findings and clinical or symptomatic OA is poor (Kraus *et al.*, 2015; Bennett *et al.*, 2012). These definitions of OA, DJD, disease and illness are the ones that will be used hereafter, in this thesis.

1.3 Feline osteoarthritis - aetiology

Feline OA is commonly classified as primary or secondary depending on its aetiology. The term primary or idiopathic OA is used when there is no apparent cause for the disease development. Scottish Fold osteochondrodysplasia (Gandolfi *et al.*, 2016; Chang *et al.*, 2007; Malik *et al.*, 1999) and mucopolysaccharidosis (Vinayak *et al.*, 2005; Macri *et al.*, 2002; Crawley *et al.*, 1998) are considered primary forms of OA in cats. These kinds of primary OA are, however, not common in clinical practice. The vast majority of cases with feline OA are primary OA seen in older cats with no obvious initiating factor, sometimes referred to as age-related cartilage degeneration (Lascelles, 2010). Some authors question the categorization into primary and secondary OA in humans, and suggest all types of OA to be secondary (Brandt *et al.*, 2009).

Secondary OA in cats can be caused by several predisposing conditions such as congenital abnormality or joint deformity and frequently appear subsequent to traumatic joint injury (Lascelles, 2010). One predisposing condition is hypervitaminosis A, due to feeding liver-rich diets. This was commonly reported during the 1960s. Nowadays most pet cats are fed commercial diets mainly, hence only isolated cases are seen (Guerra *et al*., 2014; Polizopoulou *et al.*, 2005; Seawright *et al.*, 1965). Breeds that are prone to developmental diseases such as hip dysplasia (Main Coon, Persians and Himalayans) frequently develop secondary OA as a sequelae (Table 1.) (Loder & Todhunter, 2017; Perry, 2016; Keller *et al.*, 1999). Elbow dysplasia has been suggested (Staiger & Beale, 2005) as a predisposing cause of OA in cats, but fragmented coronoid process, which is the most common predisposing elbow dysplasia in dogs, has currently not been shown in cats (Freire *et al*., 2014a). Occasional cases of congenital elbow luxation are reported, but are unlikely to be a common underlying cause for elbow OA (Valastro *et al.*, 2005; Rossi *et al.*, 2003). Burmese cats are frequently reported to be more prone to develop elbow OA, yet supporting evidence is hard to find in the literature. Abyssinians and Devon Rex cats have been reported to be more prone to suffer from patellar luxation, another developmental anomaly that frequently leads to secondary OA (Engvall & Bushnell, 1990; Prior, 1985). Non-pedigree cats and other breeds are also occasionally affected by patellar luxation (Smith *et al.*, 1999; Houlton & Meynink, 1989; Davies & Gill, 1987; Johnson, 1986).

Table 1. *Summary of studies on prevalence of feline hip dysplasia and/or DJD with variations in study design, breeds and age cohorts.*

Author	Study design	Number of cats	Age	Breed	FHD	FHD and DJD
Langenbach *et al*., 1998	Pro-spective	78	Mean 2 years, median 2.5 years	17 (22%) DSH; 61 (78%) purebred	25 (32%)	15 (19%)
Keller *et al*., 1999	Retro-spective	684	Mean 67.4 months; (range 1-256) months	603 (88%) DSH; 81 (12%) purebred	45 (6.6%)	43/45 (96%)
Loder & Todhunter, 2017	Retro-spective	2548	20.4 ± 11.6 months	Maine Coon	635 (24.9%)	-

Feline hip dysplasia (FHD); Degenerative joint disease (DJD); Standard deviation (SD); Domestic shorthair (DSH)

Infectious agents and defective immune system have been investigated as potential causes of DJD in cats. Gao and co-authors investigated a defective immune response that could, potentially, both cause and exacerbate an arthritic condition (Gao *et al.*, 2013). There are case reports of cats with polyarthritis that were infected with *Mycoplasma* spp. (Zeugswetter *et al.*, 2007; Moise *et al.*, 1983). Liehmann and co-authors describe two cases with immunocompetent cats that were diagnosed with monoarthritis caused by *Mycoplasma felis* (Liehmann *et al.*, 2006). *Bartonella* spp. exposure has been investigated in cats with DJD, since a positive relationship between arthritis and *Bartonella* spp. seroreactivity has been shown in dogs (Henn *et al.*, 2005). A positive association between previous exposure to *Bartonella* spp. and DJD in cats could, however, not be verified (Tomas *et al.*, 2015). A study by Pedersen *et al.* (1980) indicated an aetiological link between feline leukaemia virus (FeLV) and feline syncytia-forming virus (FeSFV). Twenty cats with chronic progressive polyarthritis were studied, and all cats suffered from previous or concurrent FeSFV infection and 60% of the cats were infected with FeLV (Pedersen *et al.*, 1980). The findings of chronic progressive polyarthritis and concomitant viral infection has been corroborated by subsequent case reports, but further research is required. Inkpen published a case report on chronic progressive polyarthritis in a cat that was positive for FeSFV (Inkpen, 2015) and Oohashi and co-authors published a case report with a cat with chronic progressive polyarthritis that was seropositive for both FeLV and feline immunodeficiency virus (Oohashi *et al.*, 2010). The suppression of the immune system caused by the virus was suggested to contribute to the disease development in this case.

1.4 Feline osteoarthritis – pathogenesis

Few publications on the pathogenesis of naturally occurring OA in cats exist, yet several publications on the feline synovial joint as an experimental model. The feline elbow joint seems more prone to develop greater osteoarthritic changes than other synovial joints (Lascelles *et al.*, 2010). Hence, histopathological changes in the feline humeral condyle have been studied. The pathological changes affect mainly the medial part of the joint and changes in the subchondral bone contributes to the disease process. The subchondral bone has proved important in the osteoarthritic disease process in other mammals suffering from OA. Ryan and co-authors also showed that the articular cartilage was thicker, but had reduced chondrocyte density in the OA cats, compared to normal cats (Ryan *et al.*, 2013). This corroborates an earlier publication by Clark *et al.* (2005), who reported a thickening of the articular cartilage and a reduction in chondrocyte density in an experimental model of the feline cranial cruciate ligament (CCL) deficient stifle joint (Clark *et al.*, 2005). Concurrent changes in the subchondral bone and degeneration of the articular cartilage have been studied in the feline CCL deficient stifle joint. The results suggest that the subchondral bone may contribute to the development of post-traumatic OA (Boyd *et al.*, 2005). Freire and co-authors reported that mild to moderate cartilage lesion in the elbow joint without concurrent osteophytes were not detected radiographically and the distribution of the lesions in the cartilage indicated medial compartment joint disease. They also established that osteochondromatosis secondary to DJD was probably the cause of osteochondral fragments within the joint (Freire *et al.*, 2014b). More research into the pathogenesis of cats with naturally occurring OA is required, partly to establish cause, partly to tailor treatment.

1.5 Feline Osteoarthritis – prevalence

Feline OA is generally considered to have a high radiographic prevalence (Table 2.). However, the prevalence differs between publications and is likely to be biased for several reasons (Godfrey, 2008; Clarke *et al.*, 2005; Godfrey, 2005; Hardie *et al.*, 2002). More recent prospective, cross-sectional studies are likely to be less biased. Lascelles *et al.* (2010) performed a prospective study where all appendicular joints and the spine were radiographed in 100 randomly selected cats regardless of health status (Lascelles *et al.*, 2010). Slingerland *et al.* (2011) also performed a prospective study where the appendicular joints were radiographed in 100 cats where the locomotor system was examined and the owner-perceived behavioural changes were evaluated (Slingerland *et al.*, 2011). Establishing the prevalence of clinical OA in cats that causes pain and physical

dysfunction is most relevant from a clinical point of view, yet challenging. Gruen and co-authors established that, with the use of clinical metrology instruments, cat owners could detect reoccurrence of clinical signs due to DJD after removal of medical treatment (Gruen *et al.*, 2014). This is a novel idea of identifying cats affected by chronic pain caused by DJD and needs to be investigated further.

Table 2. *Summary of studies on radiographic prevalence of feline OA and/or DJD with variations in study design and age cohorts.*

Author	Study design	Number of cats	Age (years)	OA (%)	Joint most commonly affected by OA	SD (%)	DJD (%)
Hardie *et al*., 2002	Retro-spective	100	Mean 15.2 SD ± 1.9	64	Elbow (17 %)	26	90
Pacchiana *et al*., 2004	Clinical study	52	25 cats: < 1; 14 cats: 1 – 3; 11 cats: 3-6; 2: > 6	30	Elbow	-	-
Godfrey, 2005	Retro-spective	292	-	22	Elbow (21.8 %)	-	-
Clarke *et al*., 2005	Retro-spective	218	Median 10.2 Range 0.6-16.4	16.5	Hip (51.0%)	20.6	33.9
Clarke & Bennet, 2006	Pro-spective	28	Median 11	-	Elbow (45.0%); Hip (38.0%)	-	-
Godfrey, 2008	Retro-spective	100	Mean 10.1 Median 10.0 Range 1-22	57	Hip (34%); Elbow (24%); Shoulder (21%); Stifle (19%); Tarsus (17%); Carpus (3%)	-	-
Lascelles *et al*., 2010	Pro-spective	100	Range 0.5-20	91	Hip (65 %); Stifle (50 %); Tarsus 40.0%); Elbow (35 %)	55	-
Slingerland *et al*., 2011	Pro-spective	100	≥ 6	61	Shoulder; Elbow; Hip; Tarsus	-	-

Osteoarthritis (OA); *Spondylosis deformans* (SD); Degenerative joint disease (DJD)

1.6 Feline osteoarthritis – signs of disease

1.6.1 Understanding feline coping strategies

In order to appreciate the clinical signs presented by osteoarthritic cats, it is important to be aware of the cat's innate behaviour as a solitary, territorial species. The domestic cat is a mid-level predator, thus both a hunter and a prey species (Bradshaw, 2016). Cats are known for their ability to disguise overt signs of disease, possibly as a consequence of being a prey species, thereby increasing self-preservation (Ashley *et al.*, 2005). This is a coping strategy caused by a survival instinct for self-preservation (Gowan & Iff, 2016). There is research indicating that this kind of sickness-behaviour is an organized motivational response from the animal in order to minimize the effects of disease and promote recovery (Dantzer & Kelley, 2007; Johnson, 2002; Aubert, 1999).

Clinical signs of feline OA are known to be subtle (Klinck *et al.*, 2012). In addition to this, removing the cat from its home territory and taking it to the veterinary practice subjects the cat to stress that affects physiological parameters (Quimby *et al.*, 2011; Belew *et al.*, 1999). The stress response is likely to add to the difficulties in recognizing clinical manifestations of chronic pain. It has been shown that the assessor's ability to recognize signs of pain requires familiarity with and knowledge of the species concerned (Roughan & Flecknell, 2003). Canines are the most common species seen in small animal practices, and the most common clinical sign of OA in dogs is lameness. This is a potential bias regarding what clinical signs to look for when screening and diagnosing feline OA.

1.6.2 Owner perceived clinical signs

Frequently cat owners mainly observe and interact with their cats in a home environment. Few cats regularly walk on a leash and the owners therefore rarely see them walk on an even surface for an extended period of time, thereby being able to determine possible gait disturbances (Rochlitz, 2005). In order for pet owners to recognize lameness it often requires a gait asymmetry. Few cats show lameness as a clinical sign and OA is frequently a bilateral disease (Clarke *et al.*, 2005). Clarke & Bennett showed that lameness was not a common clinical sign of OA in cats, instead alterations in the ability to jump up and the height of jump were the most frequent features (Clarke & Bennett, 2006). Of the cats with radiographic signs of OA, 4.0 – 17.5% were lame (Slingerland *et al.*, 2011; Clarke *et al.*, 2005; Godfrey, 2005; Hardie *et al.*, 2002). In addition to lameness, Godfrey reported stiff gait, difficulty in jumping, limb weakness, shuffling gait

and inactivity as presenting complaints (Godfrey, 2008). In addition to these complaints, Bennett & Morton reported on changes in temperament and inappropriate elimination (Bennett & Morton, 2009). Depending on what questions the clinician asks he or she may inappropriately bias the owner towards questions regarding the cat's level of activity or mobility. Benito and co-authors showed that 60% of cat owners considered items not relating to activity, such as rest for instance, important to the cat's quality of life (Benito *et al.*, 2012).

1.7 Feline osteoarthritis – diagnostic methods

Feline OA is usually diagnosed from a triad of information, combining information from physical examination, radiography and the cat owner (Figure 1.). All three are necessary since no single examination is decisive in diagnosing a painful osteoarthritic feline joint. Medical decision making is a process known to be subjected to various kinds of biases (Klein, 2005; Bornstein & Emler, 2001). Making maximum use of the information provided by the cat owner requires asking the right questions in a systematic way and assigning each piece of information with its proper weight. Gradual and subtle behavioural changes indicative of OA are often not the chief complaint when the cat owner brings the geriatric cat to the veterinarian.

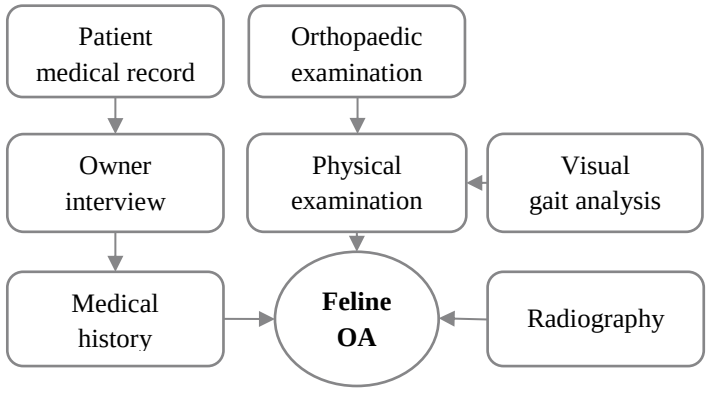

Figure 1. Illustrating the diagnostic process, with various techniques, used to diagnose feline OA.

1.7.1 Physical and orthopaedic examination

If it is suspected that only a limited amount of examination can be performed, it is important to select appropriate parts that are potentially rewarding. If the locus

of pain can be identified in the locomotor apparatus in the wake cat, it is often advantageous to continue the examination with the cat sedated.
The physical and orthopaedic examination must be performed in a systematic and feline friendly manner to avoid false results. False-positive and false negative results are common. A false-positive result arises when the examiner interprets the cat's response as painful or disabled, whereas it really is caused by the cat being angry, fearful, or just uncomfortable. A false-negative response arises when the cats refrains from showing signs of pain (Kerwin, 2012). If the cat will not walk at all, the last resort can be to ask the cat owner to film the cat in the safe and familiar home environment.

Even when a systematic, thorough orthopaedic examination has been performed, the results show a discrepancy with the radiographic findings of OA. In a study by Clarke and Bennett (Clarke & Bennett, 2006) 34% of the joints that had findings on clinical examination did not have any signs of radiographic OA. In another study only 33% of the joints that had radiographic OA were painful on manipulation (Lascelles *et al.*, 2007a). These results were confirmed by Lascelles and co-authors in a later publication, and they concluded that negative findings from palpation combined with goniometry tend to predict radiographically normal joints. The same authors showed that palpatory findings of crepitus, joint effusion and joint thickening could predict radiographic findings of OA (Lascelles *et al.*, 2012).

1.7.2 Radiography

In 2000, Allan claimed that radiographic signs of OA in cats are similar to those reported in dogs (Allan, 2000). At that time, relatively little was published specifically concerning feline radiographic criteria for OA. Several subsequent authors have made the same assumption and traditionally feline joint radiographs have been evaluated using the same assessment criteria as for canine joint radiographs (Clarke & Bennett, 2006; Godfrey, 2005; Hardie et al., 2002). Later, there have been suggestions that the radiographic appearance of feline OA differs from canine OA (Lascelles et al., 2010b).

Osteophytes are generally considered a hallmark feature of radiographic OA (Kellgren & Lawrence, 1957), however osteophytes are possibly a radiographic feature that appears differently in cats. In cats, osteophytes have been suggested to form less readily than in dogs (Bennett et al., 2012; Lascelles *et al*., 2010b; Clarke & Bennett, 2006; Hardie *et al.*, 2002; Allan, 2000). There is also speculation regarding radiographically visible soft tissue mineralisation and intra-articular mineralized bodies, as to whether they are indicative of feline radiographic OA and clinically significant or not. Medial meniscal

mineralisation is regarded as a normal feature in non-domestic cats (Rahal *et al*., 2013; Kirberger *et al.,* 2005) and *small* medial meniscal mineralisations in domestic cats are considered an incidental finding with unlikely clinical significance (Leijon *et al*., 2017; Freire *et al*., 2011). Several publications during the last decade, however, conclude that medial meniscal calcification in cats are probably pathologic findings (Lascelles *et al.,* 2010b). Freire and co-authors found that medial meniscal mineralisation seems to indicate medial compartment DJD (Freire *et al.,* 2010). Voss and co-authors supported this in their conclusion for large mineralisations in the feline stifle joint, finding that they were associated with DJD (Voss *et al.,* 2017). Several publications corroborate that meniscal mineralisation is a pathologic finding, by demonstrating an association between meniscal mineralisation and CCL rupture (Reinke, 1994; Scavelli & Schrader, 1987; Whiting & Pool, 1985).

In 2002, Hardie *et al*. published a paper on radiographic evidence of feline OA (Hardie *et al*., 2002). The authors used Morgan's scoring system which is based on the presence and severity of radiographic features consistent with OA (Morgan, 1999). The following radiographic features were used: effusion, or soft-tissue swelling or thickening around the joint, osteophytes, enthesophytes, subchondral sclerosis, remodelling of articular surfaces, perichondral bone erosion, intracapsular, capsular or extraarticular mineralisation was also taken into account (Hardie *et al.,* 2002). Clarke used the same radiographic criteria in both his papers, namely: radiographic presence of osteophytes, with or without subchondral sclerosis, soft tissue mineralisations and enthesophytes (Clarke & Bennett, 2006; Clarke *et al*., 2005). Godfrey assessed the joints as either having or not having OA based on whether radiographic signs of increased subchondral bone density or periarticular new bone (osteophytes) were present or not (Godfrey, 2008).

Freire and co-authors brought together a group of board-certified veterinary radiologists and a board-certified veterinary surgeon to discuss what radiographic criteria were indicative of feline OA. The following radiographic features were decided upon: joint effusion, osteophytes, and enthesophytes, joint associated mineralisation, sclerosis, subluxation, subchondral bone erosions/cysts, intraarticular mineralisation and new bone formation in the tarsal joint (Freire *et al*., 2011; Lascelles *et al.,* 2010b). Slingerland and co-authors used the same radiographic score as Hardie *et al.,* (2002) in their cross-sectional study on the prevalence of feline OA (Slingerland *et al.,* 2011). Information regarding the presence of a sesamoid bone in the tendon of origin of *Musculus supinator*, meniscal ossicles, soft tissue mineralisation, periarticular new bone formation, sclerosis and fusion of intertarsal joints were recorded independently from findings that indicated OA.

Table 3. summarises findings from the various publications regarding feline OA. The terminology in the table is the same as used by the authors in their original publications. This illustrates the difficulties in lacking terminology consensus. At the same time it illustrates a significant advancement, since Allan's first publication in 2000. Reading the table, bear in mind that currently, the term periarticular new bone formation generally means osteophyte. However, enthesophytes located on the articular margin are also periarticular bone formation and enthesophytes are also considered a type of osteophyte. Generally, osteophytes can be considered an umbrella term (Kirberger & McEvoy, 2016);[1].

Table 3. *Radiographic criteria used to define feline OA.*

Author(s) Criteria	Allan, 2000	Hardie *et al.*, 2002	Godfrey, 2005	Clarke *et al.*, 2005	Godfrey, 2008	Lascelles *et al.*, 2010	Slingerland *et al.*, 2011	Freire *et al.*, 2011
Joint effusion	✓	✓				✓		✓
Osteophytes		✓	✓	✓	✓	✓		✓
Enthesophytes	✓(1)	✓		✓		✓		✓
Periarticular new bone formation		✓					✓	
JAM (2)		✓				✓	×(3)	✓
Sclerosis	✓	✓	✓(4)	✓		✓	✓	✓
Subluxation coxofemoral joint						✓		✓
Subchondral bone erosions/cysts	✓	✓				✓		✓
IAM (5)	✓	✓		✓		✓	×(6)	✓
New bone formation, tarsal joint						✓	✓	✓

(1)Referred to as: periarticular new bone formation; (2) Joint-associated mineralisation (JAM); (3) referred to as soft tissue mineralisation; (4) referred to as increased subchondral bone density; (5) Intraarticular mineralisation (IAM) (including meniscal mineralisation in the stifle joint); (6) referred to as meniscal ossicles. ×Including sesamoid bone in the tendon of origin of *Musculus supinator*, recorded separately from findings indicative of OA.

1. Personal communication, C. Ley, 2017.

1.8 Motion analysis techniques used in cats

1.8.1 Visual lameness examination

Traditionally clinicians have used visual gait analysis (VGA) to assess lameness in quadrupeds. However, meagre concordance on moderate to low grade lameness, even amongst experienced assessors is a limitation. Quinn and co-authors showed a generally low agreement among independent observers when comparing numerical rating scales (NRS) and visual analogue scales (VAS) with force plate data in dogs (Quinn *et al.*, 2007). Other studies have shown low agreement between dog owners and clinicians assessments of unilateral lameness in dogs (Burton *et al.*, 2009), as well as between subjective VGA and objective force platform analysis (Waxman *et al.*, 2008). Oosterlinck *et al.* (2011) however, showed contradictory findings, comparing healthy dogs with dogs with unilateral lameness due to CCL rupture. The dogs were assessed subjectively with VGA and objectively using a pressure plate. The correlation between the VGA and the pressure plate data was high (Oosterlinck *et al.*, 2011). In this case however, the dogs had a moderately well-defined unilateral lameness and was only observed by one experienced observer, which potentially could bias the results. It is likely that the agreement between VGA and objective gait analysis is even less in cats than in dogs, due to differences in gait and willingness to participate in the gait examination procedure.

Orthopaedic disease is known to redistribute the body weight supported by the limbs in dogs (Abdelhadi *et al.*, 2013; Fischer *et al.*, 2013; Oosterlinck *et al.*, 2011; Bockstahler *et al.*, 2009; Rumph *et al.*, 1995; Griffon *et al.*, 1994) and cats (Carroll *et al.*, 2008; Romans *et al.*, 2005; Romans *et al.*, 2004) but is generally hard to detect visually (Oosterlinck *et al.*, 2011; Burton *et al.*, 2009; Quinn *et al.*, 2007; Hudson *et al.*, 2004). The need for valid and reliable objective methods for gait analysis is particularly essential in cats, a species frequently affected by OA in multiple joints and hard to direct when performing lameness examinations.

1.8.2 Force plate technique

A force plate measures the ground reaction forces (GRF) in three dimensions during stance phase; the vertical force (Fz) the cranio-caudal force (Fy) and the medio-lateral force (Fx). The most commonly calculated parameters are Peak Vertical Force (PVF) and Vertical Impulse (VI) (Gillette & Angle, 2008; Besancon *et al.*, 2003). PVF measures the force in one direction, is not related to time and commonly presented in (%BW) units. VI also measures the force,

yet related to time. The unit commonly used for VI is (%BW x seconds). Since the PVF and VI are directly influenced by the velocity (Colborne *et al.*, 2006; Riggs *et al.*, 1993), there is a need for repetitive trials to ensure trails with a consistent velocity, or to register the animal on a treadmill supplied with force sensors. Further, repetition of the trials matter and an inter-week variation has been shown (Nordquist *et al.*, 2011). Trial repetition and acceleration are other parameters that need to be constant in order not to influence the PVF or the VI (Renberg *et al.*, 1999; Rumph *et al.*, 1997; McLaughlin *et al.*, 1996; McLaughlin & Roush, 1994; Budsberg *et al.*, 1993).

A limitation in using force plates in cats is the cat´s nature. The cat is often difficult to direct, rarely accustomed to walking on a leash and has a limited duration in being able to repeat the number of trails needed to acquire representative readings on all four limbs. Another disadvantage using single force plates embedded in the floor is the techniques inability to measure stride or step length. In small animals like cats, there is always a risk of the animal striking the force plate with more than one foot simultaneously (Carr & Dycus, 2016). Therefore there are now treadmills that are supplied with force sensors, thus enabling registrations of sequential strides at a constant speed.

Force plates have been used extensively in dogs, yet to a lesser extent in cats. Quite a few of the publications where force plates are used for gait analysis in cats are using a small number of healthy cats as experimental models in comparative biomechanical and neurophysiological research (Dimiskovski *et al.*, 2017; Pantall *et al.*, 2012; Holinski *et al.*, 2011; Prilutsky *et al.*, 2011; Maas *et al.*, 2009; Suter *et al.*, 1998; Lavoie *et al.*, 1995; Herzog *et al.*, 1993).

Corbee *et al.*, (2014) published a fundamental paper regarding gait analysis in 24 healthy cats using a force plate, and video recordings. They found that the results were highly repeatable. The cats differed in that they had a more crouched position with flexion of the stifle and tibio-tarsal joints, in the hind limbs compared to dogs. Furthermore cats supinated their forepaws during the swing phase and pronated their paws immediately before the stance phase. The cats also showed increased diagonality of the pawfalls (placement of the forepaw in front of the contralateral forepaw) in their gait compared to the dogs (Corbee *et al.*, 2014).

Few publications exist, to the author’s knowledge, using force plates to evaluate orthopaedic conditions and their treatment in cats. Kalis and co-workers used force plates to evaluate the outcome after total hip replacement (THR) in four DSH cats (Kalis *et al.*, 2012).

1.8.3 Pressure mat technique

A pressure mat consists of sensors embedded in a low profile mat that registers sequential paw strikes. The scanning electronics and thin-film sensors measure the vertical force (Fz) and pressure distribution when the paw comes in contact with the surface. Pressure mats for quadrupeds have a range of different sensors with different shapes, sizes resolutions, and pressure ranges. High resolution pressure mats are commonly used in cats, due to the small size of their paws. The information usually retrieved with the pressure mat is information regarding the stance and stride for each paw, symmetry index (or ratio) between front/hind, and left/right sides, and PVF and VI (Tekscan, 2017).

Several authors have performed gait analysis with healthy dogs on pressure mats in order to validate the technique, establish reliable parameters and to create reference values (Kim *et al.*, 2011a; Oosterlinck *et al.*, 2011; Light *et al.*, 2010; Voss *et al.*, 2010; Lascelles *et al.*, 2006; Besancon *et al.*, 2004). As with force plate analysis, factors that influence the GRF are velocity, acceleration and trial repetition (Kim *et al.*, 2011b). In addition, species differences amongst breeds and sizes of dogs have also been established (Kim *et al.*, 2011a; Voss *et al.*, 2010; Besancon *et al.*, 2004).

To avoid the limitations with the force plate in cats, pressure mats have been increasingly used for feline gait analysis. Studies on healthy cats have established what parameters are reliable for objective gait analysis (Schnabl-Feichter *et al.*, 2017; Stadig & Bergh, 2014; Verdugo *et al.*, 2013; Lascelles *et al.*, 2007b). PVF and VI are the most commonly used parameters in cats, and have proven to be reliable once certain parameters such as, constant velocity and sufficient numbers of valid steps have been standardized. Most studies provide information regarding the vertical forces in relation to the body mass *e.g*. PVF (%BW) and vertical impulse as VI (%BW x seconds). Schnabl-Feichter and co-authors suggest a modified version where PVF (%BW) is normalized to the cat´s body mass and the total force from the four limbs (Schnabl-Feichter *et al.*, 2017). Normalizing PVF in relation to various parameters is an attempt to account for variations in body weight, body size and velocity. This is vital when comparing results from the same individual at different weight (Meijer *et al.*, 2014) or in dogs where there are large morphometric differences between breeds (Voss *et al.*, 2011; Voss *et al.*, 2010). Cats tend to be of a more uniform size within the species, yet breed variations effect on GRF have not yet been investigated. It is important to be aware of the fact that GRF data retrieved with force plates seem to be higher than the GRF data retrieved with pressure mats (Lascelles *et al.*, 2006). Furthermore, that the pressure mat only measures Fz (Guillot *et al.*, 2013; Kano *et al.*, 2013; Guillot *et al.*, 2012; Lascelles *et al.*, 2007b).

Verdugo and co-authors showed that male cats had an increased stride length compared to female cats (Verdugo *et al.*, 2013). The publications on healthy cats support the front/hind limb asymmetry previously established in other quadrupeds (Schnabl-Feichter *et al.*, 2017; Stadig & Bergh, 2014; Verdugo *et al.*, 2013; Lascelles *et al.*, 2007b). Differences amongst cat breeds or cats with different body condition scoring still remains to be explored, particularly body height and its effect on GRF, which is emphasized in the paper by Schnabl-Feichter *et al.*, (2017).

The pressure mat technique has been used in onychectomized cats to evaluate different surgical techniques (Robinson *et al.*, 2007), to evaluate long-term pain post operatively (Romans *et al.*, 2004) and to evaluate different analgesic protocols (Enomoto *et al.*, 2017; Romans *et al.*, 2005). Studies demonstrate that orthopaedic disease leads to a redistribution of the body weight (Carroll *et al.*, 2008; Romans *et al.*, 2005). In these studies, the induced lameness or lameness due to disease was unilateral.

It has been established in healthy dogs what way the vertical forces within the pads are distributed (Schwarz *et al.*, 2017; Souza *et al.*, 2013). Comparing healthy Labrador retrievers and Greyhounds, there were no breed differences and the pads of digit-3 and -4 were the major weight-bearing pads (Besancon *et al.*, 2004). To the author's knowledge, there is only one publication that deals with the distribution of the vertical forces in the pads of dogs with orthopaedic disease. Souza and co-authors compared the vertical forces in the pads of ten Pitbulls with cranial cruciate ligament (CCL) rupture with ten healthy Pitbulls. Results showed that PVF was lower in the metatarsal pad of the affected limb, and that the PVF in the pads of the forelimb and the contralateral hindlimb increased, likely due to a compensatory effect (Souza *et al.*, 2014). A similar result has been shown in one of our own publications, where the pressure distribution within the paws of cats with OA (with previous CCL injury) had a significantly lower PVF and a longer duration of stance phase, compared to sound cats. As previously reported, cats with OA (with previous CCL injury) increased the force in the vertical plane towards their forelimbs; however, the distribution within the front paws did not change significantly (Stadig *et al.*, 2016). Several publications have used the pressure mat technique as an objective outcome measurement to evaluate the efficacy of treatment with meloxicam in cats (Monteiro *et al.*, 2016; Guillot *et al.*, 2013; Carroll *et al.*, 2011).

1.9 Owner assessment questionnaires

1.9.1 Questionnaires design & development

Survey questionnaires is a common method for data collection, in research and in clinical practice. In human medicine questionnaires are mainly used to assemble information on self-reported observations from individual patients. In veterinary medicine, the animal owner or caretaker acts as a secondary assessor to obtain information regarding the issue at stake for the individual animal. The development of a structured questionnaire frequently follows a common step-wise approach (Song *et al.*, 2015) (Figure 2.).

Item generation

The first stage consists of a systematic literature review, combined with a number of experts, a list of relevant questionnaire items is generated. The list should contain the most appropriate words for describing *e. g.* the symptoms or clinical signs of a certain disease. Frequently the item generation involves generating items both for healthy and sick patients. If the questionnaire is going to measure a condition within a relatively unexplored area, it can be advantageous to select the items regarding the sick patients, from patients that are quite severely affected by the disease. The information can be compiled by using several different sources of expertise. Clinicians with specialist knowledge within the area, affected patients, relatives or animal owners or caretakers or focus groups can all provide a list of questionnaire items (Goncalves *et al.*, 2016; Anthoine *et al.*, 2014; Bennett & Morton, 2009; Brown *et al.*, 2007; Rattray & Jones, 2007). Sometimes the questionnaire items are condensed into few larger domains, but the reverse process can also occur where comprehensive domains initially generated are split up into single questionnaire items. Statistical analysis of the items generated from the two groups is performed, to identify what items are significantly different (Zamprogno *et al.*, 2010; Bennett & Morton, 2009).

Item refinement & condensation

The identified questionnaire items are thereafter presented to a focus group or a group of specialists within the area combined with animal owners or relatives or caretakers, which have previously not been exposed to the questionnaire items. The group reviews the items in order to condense the numbers and to complement with missing items. The constitution of the group and its credibility makes it frequently suitable to assess face validity *i.e*. whether the items selected

subjectively covers what the test is aimed to assess (Bolarinwa, 2015; Zamprogno *et al.*, 2010; Bennett & Morton, 2009; Rattray & Jones, 2007).

Construction of a pilot questionnaire

The method of contacting the respondents and the mode of delivering the questionnaire affects the outcome and the data quality. The actual design of the questionnaire has major impact on the actual results of the questionnaire and on the reply rate. A crucial feature to whether the respondent will fill out the entire questionnaire or not is the length of it. Keeping the questionnaire brief and relevant will increase the likelihood of the respondent fulfilling it. Factors that will increase the likelihood of the respondent completing the questionnaire are things like presenting questions that will raise an interest early in the questionnaire, make the initial questions easy to answer, have a logical order of the questions and group them together when possible. There are also suggestions that questions asking for personal data should be left towards the end of the questionnaire (Burgess, 2001).

The wording in the question design must be carefully selected in order to facilitate completion of the questionnaire and to minimize misunderstandings, generating low quality data and incomplete questionnaires. Complex and lengthy questions can cause the respondent to interrupt filling out the questionnaire. Technical jargon, uncommon words and difficult words should be avoided (Choi & Pak, 2005; Fallowfield, 1995). Forced choice, or so called insufficient category options *i.e*. questions that have limited options that potentially forces the respondent to select an option that is not completely correct should be avoided. Missing intervals in the answering options and overlapping intervals are also design errors that compromises the data quality (Burgess, 2001).

The way the respondent is able to answer the questions will have impact on both the quality of the data and the ease of data analysis. Whether the type of question is open or closed or the answering options are single or multiple will affect the answer provided. Asking open ended questions provides extensive information, but can be time consuming to analyse and interpret. Categorical scales using “Yes”/”No” or “True”/”False” are suitable for clear and unambiguous questions. This type of answer is easy to interpret, score and process. However, if the nature of the response in reality is continuous, this kind of binary or dichotomous answers are misleading (Rattray & Jones, 2007; Fallowfield, 1995).

There are several kinds of well-established simple dimensional pain scales available. Visual analogue scales (VAS) requires the patient to select a point on a line representing the intensity of pain. The VAS scale has been extensively

researched and is currently the most commonly used scale. Regarding scales for providing answering options, Likert scales are commonly used. The Likert scale provides five, seven or nine answering options ranging from "Strongly disagree" to "Strongly agree" with one option representing "Neither agree nor disagree" (Salaffi *et al.*, 2012; Fallowfield, 1995; Likert, 1952).

Preliminary testing of pilot questionnaire

Once a preliminary questionnaire design has been established one of the first tests to perform is a reliability retest *i.e.* does the outcome of the questionnaire remain stable over time, provided that the circumstances for the patient and the state of health or disease is unaltered. Does the questionnaire give the same results within tester (intra-tester reliability) and between different testers (inter-tester reliability) (Kliniska FoU gruppen, 2011).

Validity & reliability testing

Once the results from the pilot questionnaire have been processed, several aspects of validity and reliability must be taken into account. *Face validity* is the lowest level of superficial validity and is based on the subjective assessment of whether the questionnaire seems to measure what it is supposed to. This process is performed by using common sense and no statistical processing is involved. *Content validity* concerns whether the questionnaire covers all the aspects of what it is intended to measure. It should answer the question whether the questionnaire measures all the various features of the disease (Kliniska FoU gruppen, 2011; Karras, 1997). The content validity can be estimated by using factor analysis or by an expert group performing an extensive literature research. Using this information a Content Validity Index (CVI) can be calculated. *Criterion related validity* (sometimes referred to as *predictive validity*) is established by comparing the test with a "gold standard" or an external reference criterion standard. If an external standard exists, then measuring criterion related validity is a straight forward process calculating a correlation coefficient. In reality there is frequently a lack of a "gold standard" to compare with. *Construct validity* is generally defined as to what degree the test measures what it is supposed to be measuring. For tests that lack a standard criterion to compare with, other tests that aim to measure the same outcome, can be used for comparison to estimate construct validity. Another way is to use 'known-group technique', by comparing healthy and sick individuals. If the test is aimed at measuring presence of disease, these two groups would have differing results on the test (Kliniska FoU gruppen, 2011; Karras, 1997).

Finalizing the questionnaire

Once the statistical analysis of the pilot questionnaire has been taken into account, the questionnaire is refined and improved using these facts. This is a process that is frequently performed several times (Burgess, 2001). Frost and co-authors provide a summary of some of the requirements for patient reported outcomes, *e.g.* proof of reliability in clinical trials should include a minimum correlation coefficient threshold of 0.70 (0 – 1.0), and to establish validity and reliability a sample of at least 200 patient cases should test the tool (Frost *et al.*, 2007).

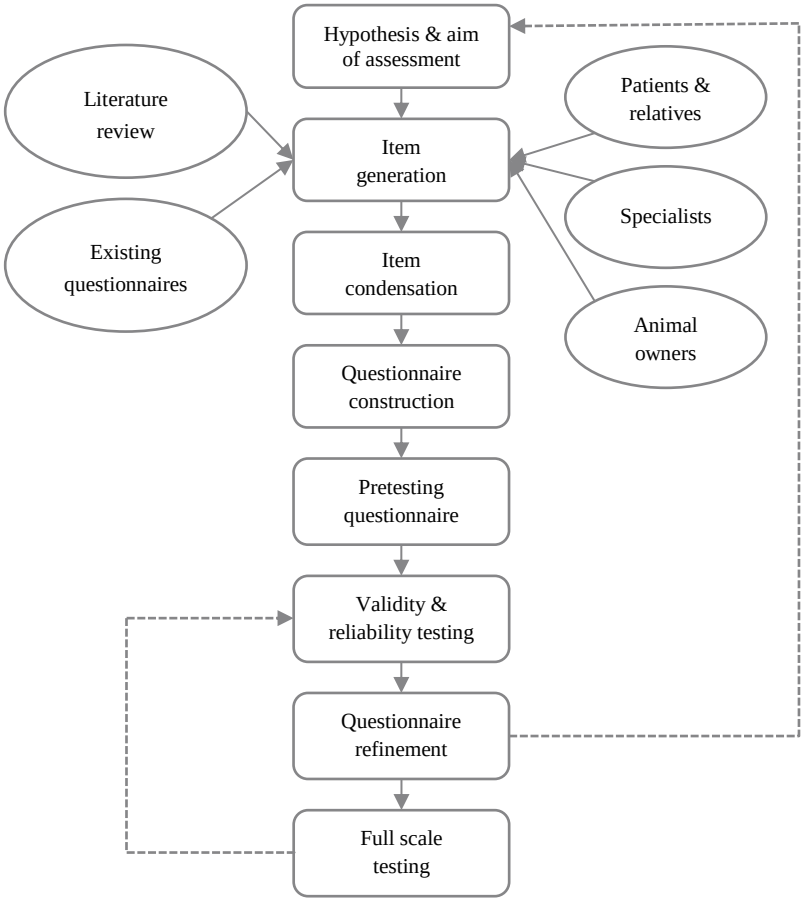

Figure 2. The methodological process for construction and evaluation of a questionnaire.

1.9.2 Disease specific questionnaires

There are several publications assessing chronic pain due to canine OA that has compared subjective assessment by the dog owner using a questionnaire with objective gait analysis and physical examination performed by a veterinary clinician. The objective gait analysis were in these cases considered the gold standard. The dog owner's assessment using the disease specific questionnaire correlated better with the objective assessment method, than did the clinician's physical examination (Waxman *et al.,* 2008; Quinn *et al.,* 2007). This illustrates the difficulty in assessing chronic pain in the musculoskeletal system caused by a disease that frequently affects several joints and limbs and has fluctuating clinical signs (Kee *et al.,* 1998).

In humans, it is well recognized that chronic pain has a negative impact on mood and Quality of Life (QoL) (Kuffler, 2017; Ataoglu *et al.,* 2013). The question in animals is no longer whether they can experience pain (Robertson, 2002; Bateson, 1992), but rather how it influences their QoL. In feline veterinary medicine there are several questionnaires developed to assess QoL in cats with various medical conditions such as chronic kidney disease (Bijsmans *et al.,* 2016), hyperthyroidism (Boland *et al.,* 2014), neoplastic disease (Vols *et al.,* 2016; Lynch *et al.,* 2011; Bowles *et al.,* 2010; Tzannes *et al.,* 2008; Slater *et al.,* 1996), cardiac disease (Rush *et al.,* 2015; Freeman *et al.,* 2012; Reynolds *et al.,* 2010), diabetes mellitus (Niessen *et al.,* 2010) and skin disease (Noli *et al.,* 2016).

Assessment tools for chronic pain caused by OA or musculoskeletal disease have been developed in cats. The Owner behaviour watch (OBW) was developed by Bennet & Morton, who constructed the questionnaire and evaluated effects of treatment with meloxicam in cats with OA (Bennett & Morton, 2009). The results from the questionnaire were corroborated by Sul and co-authors who evaluated the effect of meloxicam and glucosamine-chondroitin sulphate (Sul *et al.,* 2014). The Feline musculoskeletal pain index (FMPI) has been developed according to current psychometric methodology and has undergone validity and reliability testing (Gruen *et al.,* 2015; Gruen *et al.,* 2014; Benito *et al.,* 2013a; Benito *et al.,* 2013b; Benito *et al.,* 2012; Zamprogno *et al.,* 2010). The Feline physical function formula (FPFF) is mainly based on the four domains identified by Bennet & Morton and designed with binary answering options (Stadig & Bergh, 2011). The development of questionnaires to assess QoL in cats during the last two decades illustrates the recognition of the detrimental effects that disease and chronic pain can have on the cats QoL.

1.10 Feline OA & chronic pain

1.10.1 Chronic pain terminology

The terms acute and chronic pain have previously been based on the duration of pain. Pain has arbitrarily being categorized as chronic if it has persisted for more than 3 – 6 months (Robertson & Lascelles, 2010a). This definition is gradually shifting towards defining chronic pain as a disease state or even syndrome in itself (Ruan & Kaye, 2016; Mathews *et al.*, 2014). Chronic pain is currently defined as pain that persists beyond normal time of healing, and therefore lacks function as an alarm system for physiologic nociception and tissue damage (Mathews *et al.*, 2014). The terminology adaptive and maladaptive pain has emerged during the last decade (Robertson & Lascelles, 2010b). However, the International Classification of Diseases (ICD) of the World Health Organization (WHO) stated in the publication in 2015 that chronic pain "…is persistent or recurrent pain lasting longer than 3 months". The definition of chronic pain is recognized to have shortages, but this definition according to time has the advantage that it is clear and unambiguous (Treede *et al.*, 2015). It is likely that the terms acute, chronic, adaptive and maladaptive are inseparable on a continuous scale. I will henceforth use the term chronic as defined by ICD.

1.10.2 Pain mechanisms

Translational modelling of pain pathophysiology

According to the "structure – symptom discordance" there is a meagre correlation between the perception of osteoarthritic pain and joint damage. Even if there is a substantial knowledge regarding the pain mechanisms in human OA, there are still vast areas that are unexplored. Even if the knowledge of pathophysiological pain mechanisms in feline OA are scarce (Adrian *et al.*, 2017), mammals seem to have a fair amount of common features regarding the pathophysiology of both pain and OA. A vast amount of the knowledge on the osteoarthritic pain pathophysiology has been retrieved from experimental models using rodents and other mammals to approximate the human condition (Malfait *et al.*, 2013). Natural animal models, such as osteoarthritic cats, have even been suggested as the possible missing link that could provide vital information within the area of translational pain assessment (Klinck *et al.*, 2017). It is reasonable to believe that a substantial amount of what is known regarding human osteoarthritic pain pathophysiology can be applied to feline OA (Adrian *et al.*, 2017). Previous research has established that pain mechanisms are

complex, involving both peripheral and central mechanisms. The osteoarthritic pain is also recognized as being both nociceptive, neuropathic and of mixed origin (Perrot, 2015; Dimitroulas *et al.*, 2014).

Peripheral pain mechanisms & Primary hyperalgesia

Stimulation of free axonal nerve endings located in the subchondral bone, ligaments, periosteum, synovial membrane and tendons can initiate the osteoarthritic pain peripherally. The cartilage has traditionally been the prime focus of OA pathology, yet being aneural and avascular, other tissue structures and mechanisms are involved in the osteoarthritic pain experience (Dimitroulas *et al.*, 2014).

Pain perception is the central processing of painful sensory stimuli. Perception is dependent on sensation, through a receptor that detects sensation from different types of stimuli. The receptor can be free nerve endings, nociceptors, thermoreceptors or mechanoreceptors that are sensitive to both touch, pressure and vibration. The nerve fiber that transmit nociceptive impulses can be Aδ or group III afferents, as well as C or group IV afferents. The nerve fibers that transmit impulses elicited by touch and pressure can be Aα or group IA and IB afferents, as well as Aβ or group II afferents. Mechanoreceptors and thermoreceptors that are not primary nociceptors can however, when highly stimulated or when affected by neuropeptides act as pain receptors.

There are four types of nerve fiber afferents (I-IV) in the synovial joint: type I and II are corpuscular organs situated in the joint capsule, ligaments and meniscus, responding to mechanical stimuli. On the ligament surface there are Aδ myelinic fibers, referred to as type III receptors, acting as high threshold mechanoreceptors. This receptor is involved in pain sensation caused by injuries in the joint. The type IV receptor is a polymodal receptor formed by free nerve endings of unmyelinated C fibers (Trouvin & Perrot, 2017; Perrot, 2015). Half of the unmyelinated fibers in the synovial joint are C fibers and the other half are sympathetic fibers. Together the unmyelinated fibers make up more than 80 % of the fibers in the joint. (Grigg, 2001; Mapp, 1995). The type IV receptor is present in all structures in the synovial joint, except the cartilage. They are only active during inflammation and respond to mechanical, chemical and thermal stimuli. This receptor is also involved in pain sensation due to joint injuries. In the osteoarthritic joint, pain can be elicited by both mechanical stimuli, such as increased intra-articular pressure, and by inflammatory stimuli. Any abnormal mechanical stress on the joint can stimulate mechanoreceptors and elicit a pain reaction. Local inflammation with the release of inflammatory mediators, such as phospholipases, cyclooxygenases, lipoxygenases, free radicals and nitric oxide (NO) contribute to the pain (Perrot, 2015). Opioid and cannabinoid

receptors are also present in the joint and the numbers increase with inflammation. Increasing numbers of receptors, activation of dormant receptors and reducing the threshold for activation are all features of primary hyperalgesia and peripheral sensitization due to OA (Miller *et al.*, 2015). The changed local environment in the joint leads to increased innervation and vascularisation of the synovial joint tissues, including the cartilage where vascularized channels appear (Miller *et al.*, 2015). The vascular channels in the osteoarthritic cartilage contain both sympathetic and sensory nerves (Arendt-Nielsen *et al.*, 2015). The prevailing hypothesis is that degrading of the cartilage matrix leads to free cartilage fragments that come into contact with the synovium and elicits inflammation. Exposure of the chondrocytes to inflammation, oxidative stress and abnormal biomechanical loading makes them more vulnerable to further damage and creates a vicious circle. Eventually this leads to the patient experiencing primary hyperalgesia and allodynia (Berenbaum, 2013). Primary hyperalgesia in *e.g.* cutaneous tissue occurs in the area where the injury has occurred and the hyperalgesia is elicited by mechanical and heat stimuli. The hyperalgesia occurring due to inflammatory processes corresponds to primary hyperalgesia (Campbell & Meyer, 2006; Treede *et al.*). Conclusively, the peripheral sensitization contributes to the general sensitization of the nociceptive system, and is part of the explanation for the primary hyperalgesia occurring in inflamed tissue (Latremoliere & Woolf, 2009).

Central pain mechanisms & secondary hyperalgesia

Central sensitization (CS) is suggested to occur later in the nociceptive process, after the peripheral sensitization, mainly in the late or chronic stages of OA (Arendt-Nielsen *et al.*, 2010). Secondary hyperalgesia occurs outside, peripherally of the injured *e.g.* cutaneous tissue and is only elicited by mechanical stimuli. The processes occurring in neuropathic pain are similar to secondary hyperalgesia (Campbell & Meyer, 2006; Treede *et al.*).

Neuropathic & functional pain

Some patients with chronic pain due to OA suffer from multiple pain mechanisms integrated with the PS and the CS. Chronic or maladaptive pain is sometimes divided into neuropathic and functional pain. Neuropathic pain originates when there is actual neural tissue damage in the synovial joint and functional pain appears when there is no actual tissue damage, but the pain process is generated by dysfunction in the nervous system itself. Injury to peripheral nervous tissue in the synovial joint can occur either due to direct damage to sensory nerve endings in the tissues in the joint or due to damage of

the nerves innervating the remodeled joint (Adrian *et al.*, 2017). Understanding neuropathic and functional pain is fundamental to tailoring analgesic treatment with centrally acting drugs (Dimitroulas *et al*., 2014).

1.11 Non-steroidal anti-inflammatory drugs (NSAIDs)

1.11.1 Mechanism of action

Inflammatory processes lead to interleukin mediated release of enzymes from leucocytes and macrophages in the damaged tissue. The enzyme system regulates the breakdown of phospholipids from the damaged cell membranes. The enzyme phospholipase-A converts phospholipids to arachidonic acid. Arachidonic acid is in turn enzymatically converted to prostanoids.The prostanoids include prostaglandins, thromboxanes, leukotrienes and several related compounds that have a pro-inflammatory effect. This conversion is catalysed by the enzyme cyclooxygenase (COX). Cyclooxygenase exists as several isoenzymes, COX-1 is the physiologic enzyme that is responsible for producing prostaglandins that protects the gastric mucosa, regulates the renal blood flow and the thrombocyte function. COX-2 production is induced by inflammation and is responsible for the production of inflammatory prostaglandins. Traditional acetylsalicylic acid inhibit both COX-1 and 2. When the two isoenzymes were discovered in 1990, there were expectations that anti-inflammatory drugs could be fully tailored to selectively inhibit merely the COX-2 system. Currently, additional COX enzymes have been discovered and the COX-2 selective drugs have in many cases fewer side effects, even if the selectivity is not as complete as expected (Duke-Novakovski *et al.*, 2016; Gaynor & Muir III, 2015; Werner & Leden, 2010).

Meloxicam

Meloxicam is a COX-2 selective substance with anti-inflammatory, analgesic, anti-exudative and antipyretic effects by inhibiting prostaglandin synthesis. In vitro and in vivo studies demonstrated that meloxicam inhibits COX-2 more than COX-1. Meloxicam is registered for pain relief in cats with acute and chronic pain due to musculoskeletal disease. The recommended dose is a single oral dose of 0.1 mg meloxicam/kg BW on the first day, continued with a maintenance dose of 0.05 mg/kg BW orally once daily. Treatment with meloxicam should be avoided in cats with hepatic, renal, cardiac, gastrointestinal and haemorrhagic disorders due to increased risk of side effects. Treatment of dehydrated or

hypovolaemic cats should also be avoided (Metacam: EPAR Product information, 2017).

Meloxicam has been evaluated for treatment of chronic pain in cats with musculoskeletal disorders where cat owners and veterinarians have reported a pain relieving effect (Sul *et al.*, 2014; Bennett & Morton, 2009; Gunew *et al.*, 2008; Clarke & Bennett, 2006). Lascelles and co-workers showed in their publication that the pain relieving effect of meloxicam, when dosed according to the manufacturer's instructions, did result in pain relief that could be detected activity monitors (AM) and client-specific outcome measurements (Lascelles *et al.*, 2007c). Guillot and co-workers (2013) showed that meloxicam had a pain relieving effect when administered for four weeks and objectively measured with AMs (Guillot *et al.*, 2013). When meloxicam was compared to ketoprofen the pain relieving effect was assessed as being equal. Meloxicam was, however, considered more palatable an easier to administer by the cat owners. In this study the cats received treatment for five days and the meloxicam dosage was 0.3 mg/kg as a starting dose and 0.1 as a maintenance dose (Lascelles *et al.*, 2001). Gruen and co-authors (2015) evaluated meloxicam treatment in cats with DJD for 21 days, with AMs and questionnaires. The study included a placebo group and meloxicam was dosed at 0.035 mg/kg/day. The AMs showed that the cats receiving meloxicam were significantly more active (Gruen *et al.*, 2015). The same authors compared a group of cats that received meloxicam with a placebo group in a study aiming to detect clinically relevant pain. The pain reliving effect was evaluated using questionnaires and the results showed that owners detected signs of DJD once the meloxicam was withdrawn compared to when the placebo treatment was withdrawn (Gruen *et al.*, 2014). Meloxicam has also been used in an oral transmucosal formulation to treat cats with chronic pain caused by OA. Using objective pressure mat technique to evaluate the effect, the results showed that the transmucosal way of administering meloxicam had the same effect as the oral solution, which was shown by increased PVF on the affected limb (Monteiro *et al.*, 2016).

Robenacoxib

Robenacoxib is COX-2 selective inhibitor with analgesic, anti-inflammatory and antipyretic properties in cats. It is registered for treatment of acute pain and inflammation concurrent with musculoskeletal disorders in cat. The recommended dose is 1 mg/kg/day (dose interval 1–2.4 mg/kg/day) orally for a maximum of six days. Concurrent treatment with angiotensin converting enzyme ace inhibitors or drugs that could potentially have renal toxicity should be avoided. Overdosing could cause renal, hepatic and gastrointestinal toxicity

and have a negative effect on coagulation. Treatment of dehydrated cats should be avoided (Onsior: EPAR Product information, 2017).

Several publications regarding pharmacokinetics, safety, analgesic effect and adverse effects of robenacoxib in cats have been published (King *et al.*, 2016b; Pelligand *et al.*, 2016; Pelligand *et al.*, 2014; King *et al.*, 2013; Pelligand *et al.*, 2012; Schmid *et al.*, 2010; Giraudel *et al.*, 2009). Speranza *et al.*, (2015) published a non-inferiority study using a single dose of robenacoxib compared to meloxicam for the control of peri-operative pain. Results showed that robenacoxib did not have an inferior efficacy (Speranza *et al.*, 2015). Kamata and co-authors published a similar study where they compared robenacoxib and meloxicam for peri-operative use in cats. Results showed that both drugs were well tolerated as a single injection, robenacoxib however had superior pain relieving efficacy for post-operative pain (Kamata *et al.*, 2012). Robenacoxib was studied in osteoarthritic cats in a randomized blinded, placebo controlled study. A total of 194 cats participated and they received robenacoxib according to the manufacturer's dosage instructions for 30 days. Results established sound clinical safety even in cats with evidence of chronic kidney disease. The pain reliving effect of the drug was not evaluated (King *et al.*, 2016a).

2 Aims of thesis

The general aim of the thesis was to improve methods for diagnosis and evaluation of treatment in cats with naturally occurring OA. It is currently, not possible to directly measure chronic pain in cats, caused by OA. It is, however, possible to measure physical dysfunction instigated by chronic pain. Physical dysfunction in cats was measured using physical examination, objective pressure mat technique and subjective owner assessment questionnaires.

The specific aims were to:

- Establish a reference material for sound cats walking and jumping on the pressure mat, including analysis of the distribution of the vertical force within the paws (paper I).

- Establish what gait analysis parameters are reliable to study in sound cats and investigate possible sources of errors with the pressure mat analysis in sound cats (paper I).

- Compare kinetic data and behavioural traits in cats with OA (with previous CCL injury) with a matched control group of sound cats (paper II).

- Evaluate four owner assessment questionnaires designed for cats with musculoskeletal disease regarding validity and reliability, by comparing a group of sound cats with a group of OA cats (paper III).

- Evaluate the effects of treatment with NSAIDs in osteoarthritic cats using physical examination, pressure mat technique and questionnaires as outcome measures (paper IV).

3 Hypotheses

The following hypothesis were raised:

- The first hypothesis was that sound cats have a symmetrical gait, a front/hind limb asymmetry and that the gait parameters PVF and VI are reliable parameters to study (paper I).
- The second hypothesis was that cats with OA (with previous CCL injury) have:
    - more asymmetrical front/hind symmetry indices for PVF and VI, compared to sound cats
    - decreased PVF and VI on the affected hind limb compared to the unaffected hind limb
    - a different way of distributing the pressure under the paws, compared to sound cats
    - a different behaviour in the home environment, compared to sound cats (paper II).
- The third hypothesis was that:
    - neither sound nor osteoarthritic cats display a difference in the outcome of the four questionnaires when retested, provided that the cats state of health or disease was unaltered
    - the questionnaires could discriminate between healthy and osteoarthritic cats, when cut-off values were established with sound sensitivity and specificity
    - all four questionnaires had satisfying internal consistency (paper III).
- The last hypothesis was that treatment with NSAIDs would decrease the osteoarthritic cat's pain when measured objectively with the pressure mat and subjectively with the owner assessment questionnaires and that both drugs evaluated would have satisfying pain relieving effect (paper IV).

4 Material & methods

This chapter summarizes the material and methods used in the research which the thesis is founded upon. Detailed descriptions of the procedures used are presented in each paper I-IV. All procedures were approved by the local Ethical Review Board on Animal Experiment. Each cat owner signed an informed client consent form prior to inclusion.

4.1 Study design (papers I-IV)

Paper I: A prospective cross-sectional study was designed to define appropriate parameters for pressure mat analyses during walk and jump, and to define reference values for gait parameters of 46 healthy cats. Further, the distribution of the vertical force within the paws and the influence of a non-centered head position were investigated. The registrations were done with a pressure mat technique, and the cat was filmed from the side. The cat walked until two valid trials were attained. The jump was done from a 1.0 m high examination table. Prior to inclusion, the cat had a complete physical examination, performed by the same veterinarian, who also scored the cat´s body condition.

Paper II: The aim of this case-control study was to investigate if cats with OA (with previous CCL injury) walked differently on the pressure mat and showed different behaviour compared to sound cats according to the owner´s subjective assessment. The registrations were done with the pressure mat, and the 25 cats were filmed from the side. Each cat walked until five valid trials were attained. Prior to inclusion, the cat had a complete physical examination, performed by the same veterinarian, who also scored the cat´s body condition. Thereafter, a blood sample was taken from the osteoarthritic cats. The joints that were found to be affected on the orthopaedic examination were radiographed. In addition, the owner filled out The Owner Behaviour Watch (OBW)

questionnaire, a clinical metrology instrument (CMI), regarding the cat´s mobility, activity, grooming and temperament.

Paper III: The prospective cross-sectional study was designed to evaluate discriminatory ability, reliability and internal consistency of four CMIs, assessing the cat´s behaviour. Each of the 122 cats that contributed with data, underwent a physical examination, performed by the same veterinarian, who also evaluated the cat´s body condition score (BSC). Thereafter, a blood sample was collected. The appendicular joints that were found to be affected on the orthopaedic examination were radiographed, during sedation. In addition, the cat owner filled out four CMIs on two occasions: the FMPI, the OBW, the FPFF and the ZQB.

Paper IV: The aim of this randomized, controlled, clinical cross-over pilot study was to use multimodal assessment to evaluate the effects of treatment with meloxicam and robenacoxib in 6 osteoarthritic cats. Prior to inclusion, the cat had a complete physical examination, performed by the same veterinarian, who also scored the cat´s body condition. In addition, a blood sample was taken before sedation. The joints that were found to be affected on the orthopaedic examination were radiographed during sedation. The cats were evaluated using physical examination, pressure mat technique and four questionnaires. The recordings were done before and after treatment with the two drugs. The four questionnaires used before and after treatment were: the FMPI, the OBW, the FPFF and the ZQB.

4.2 Study population (paper I-IV)

A summary of information regarding the cats in studies I-IV are presented in Table 4. Cats that were potential study subjects were identified from the patient data base at the local animal hospitals, referred from primary care veterinarians, or self-referred from students and staff at the University. The University's Facebook page was used to advertise the project. Breeders associations were approached through their web page. All the participating cats were client owned cats that were recruited as either potential sound study subjects or potential study objects with naturally occurring osteoarthritis.

Table 4. *Demographic data for the participating cats in paper I-IV.*

Paper	Number & diagnosis	DSH/ DLS	Purebred	Age (years)	Weight (kg)	BCS/5	BCS/9	Sex (F/M)
I	46 Sound	74%	26%	5.0 ± 2.7	4.5 ± 1.2	3.4 ± 0.6	-	27F/ 31M
II	10 OA	70%	30%	9.5 ± 1.8	5.1 ± 0.9	3.8 ± 0.4	6.6 ± 0.8	4F/ 6M
	15 Sound	60%	40%	5.9 ± 3.3	4.8 ± 0.9	3.7 ± 0.5	6.5 ± 0.9	6F/ 9M
III	122 (22 OA)*	68%	32%	6.8 ± 3.6	5.2 ± 0.9	3.6 ± 0.7	6.2 ± 1.4	54F/ 68M
IV	6 OA	50%	50%	10.8 ± 2.0	6.0 ± 2.4	4.0 ± 0.6	6.8 ± 1.3	2F/ 4M

Osteoarthritis (OA); Domestic shorthair (DSH); Domestic Longhair (DLH); Kilogram (kg); Body condition score (BCS); Female (F); Male (M). Data presented as mean ± standard deviation. *For detailed diagnostic groups see paper III.

4.3 Methods

4.3.1 Pressure mat technique and collection of kinetic data (paper I-IV)

The kinetic data were collected using a pressure sensitive walkway (Walkway High Resolution HRV4; Tekscan, South Boston, Massachusetts, USA). The portable mat measures 1.95 x 0.45 m and consists of a low profile floor mat (0.57 cm thick) with 4 sensels/cm^2. The walkway was connected to a laptop computer (Siemens Fujitsu Lifebook, Hewlett Packard EliteBook) and data were analysed using specific software provided by the manufacturer (Walkway 7.02). The mat was placed against a wall and transparent plexiglas screens, each 1.0 m long, were placed along the other side of the mat. The walkway was covered with a 1.0 mm thick plastic mat to avoid the slick surface, extending 0.3 m on either side of the end-/starting points for the sensors. The actual end-points of the walkway were demarcated with white tape. Prior to commencing data acquisition the walkway sensors were equilibrated and calibrated as recommended by the manufacturer. The data acquisition parameter was set to a frequency of 60Hz, and each data movie was accompanied by a simultaneous video capture of the pass.

The gait analysis was performed in a quiet room designed for small animal gait analyses, with a maximum of three researchers and the cat owner/-s present. The cat was weighed using an electronic scale in the same room as the gait analysis was performed. The cat was allowed to acclimatize to the settings for

5-10 minutes before walking on the mat. The cat was encouraged to walk on the mat by being called on, using toys or treats, or by placing the transport carrier at the end of the mat. Data collection continued until at least five valid trials were attained. A trial was considered valid when the cat walked in a straight line, at a visually even pace and with the head facing straight forward. The jump was performed from a 1.0 m high examination table. The following data was collected: number of paw strikes for each trial, gait time/distance/velocity, stance/swing/stride time, stride length/velocity/acceleration, VI and PVF. Symmetry ratios (SR) front/hind and left/right was calculated by the software for the previous parameters. A summary of information regarding number of cats and methods used is presented in Table 5.

4.3.2 Owner assessment questionnaires (papers II-IV)

The questionnaires used were "the Feline Musculoskeletal Pain Index" (FMPI) (Gruen *et al.*, 2015; Gruen *et al.*, 2014; Benito *et al.*, 2013a; Benito *et al.*, 2013b; Zamprogno *et al.*, 2010), "the Owner Behaviour Watch" (OBW) (Sul *et al.*, 2014; Bennett & Morton, 2009), "the Zamprogno Question Bank" (ZQB) (Zamprogno *et al.*, 2010) and "the Feline Physical Function Formula" (FPFF) (Stadig & Bergh, 2011).

The FMPI consists of 17 specific questions where the owner rates the cat´s ability to perform various tasks, on a Likert scale. It also contains three comprehensive questions regarding the cat's level of pain and general quality of life. Each question is scored from -1 to 4 and the total maximum score is 80 (Appendix 1). The OBW consists of four questions regarding the domains: general activity, mobility, temperament and grooming and one comprehensive question regarding the cat´s overall ability. The owner is asked to rate the cat´s change in each domain, compared to a normal cat, from 0 - 10 for each question. A total score of zero indicates a normal ability, and 50 is the maximum total score (Appendix 2). The original set of questions used by Zamprogno *et al*. (2010) the ZQB, which consists of 18 questions was also evaluated. The answers were scored on a Likert scale from 0 – 4, with a total maximum score of 72 (Appendix 4). The design of the FPFF was based on the OBW instrument. It consists of 16 questions, requiring binary answers with a total maximum score of 12 (Appendix 3). For further details on each questionnaires, see Appendix 1 – 4 and the individual publications.

The questionnaires that were originally published in English (all but the FPFF) were translated from English to Swedish and back-translated by an official translation company. The forward and backward translations were made by different translators. The final version was then reviewed by a third

independent official translator that made a statement regarding the consistency of the translation.

The owners filled out the questionnaires in the same room as the gait analysis and the physical and orthopaedic examinations were performed, a quiet examination room designed for small animal gait analyses. The owners were presented with paper copies of the questionnaires. The owners were instructed verbally and shown on each questionnaires how to fill it out. The written instruction for the FMPI was read to the owner prior to completion. The owners had access to qualified staff at all times that could answer any questions regarding the questionnaires. To test reliability, paper copies of the CMIs were later posted in pre payed envelopes to the cat owners. The owners were asked to fill out the CMIs again provided that the cat's state of health or disease had not changed.

4.3.3 Physical examination (papers I-IV)

After the pressure mat data collection a complete physical examination was carried out on each cat. The examination comprised the axial and appendicular skeleton, including evaluation of muscle symmetry. Each appendicular joint was evaluated for crepitus, range of motion, effusion, periarticular thickening and pain. Findings, apart from pain, were graded as normal (0), mild (1), moderate (2) or severe (3). It was performed by the same veterinarian (S.S.), who also evaluated the cat´s body condition score (BSC) according to a 5-point system (German & Martin, 2008) and a 9-point system (Laflamme, 1997). The BCS evaluation was made by palpating the ribs, lumbar vertebra and abdominal fat pad according to the written instructions for each scoring system. The cat was also visually inspected from above and from the side to evaluate its contour and absence or presence of a waist. The cats were screened for neurological conditions that could cause pain, gait abnormalities or other symptoms

Pain reactions during the orthopaedic evaluation of the appendicular skeleton were graded according to Zamprogno and co-authors (Zamprogno *et al.*, 2010). The pain response for each joint was graded as follows: 0 = no resentment; 1 = mild withdrawal, mild resistance to manipulation; 2 = moderate withdrawal, body tenses, may orient to site, may vocalize or increase vocalization; 3 = orients to site, forcible withdrawal from manipulation, may vocalize, hiss, or bite; and 4 = tries to escape or prevent manipulation, bites or hisses, marked guarding of site. The highest pain response that was elicited in a single joint during the orthopaedic examination, was given as an overall grading of behavioural response to pain in each cat.

4.3.4 Blood sample & radiography (paper II-IV)

After the gait analysis and the physical and orthopaedic examinations were concluded, a blood sample was collected. Cats that had creatinine, blood urea nitrogen, alanine aminotransferase, alkaline phosphatase, albumin and haemoglobin values within the normal reference range were sedated. The cats were sedated with a combination of medetomidine (50 μg/kg; Sedator vet, 1 mg/ml; Dechra Veterinary Products) and butorphanol (0.4 mg/kg; Dolorex vet, 10 mg/ml; Intervet). The appendicular joint/-s that were found to be affected on the orthopaedic examination was/were radiographed. The radiographs were examined by a board certified radiologist. Sedation was reversed with atipamezole (125 μg/kg; Atipam vet, 5 mg/ml; Dechra Veterinary Products).

Table 5. *Number of cats, assessment methods and questionnaires used for the respective papers I-IV.*

Paper	Total number of cats	Pressure mat	Physical exam.	Blood sample	Radio-graphy	Q: FPFF	Q: OBW	Q: FMPI	Q: ZQB
I	46	46	46	0	0	46	22	0	0
II	25	25	25	10	10	25	25	0	0
III	122	109	122	60	29	120	88	59	91
IV	6	6	6	6	6	6	6	6	6

Questionnaire (Q); Feline Physical Function Formula (FPFF); Owner Behaviour Watch (OBW); Feline Musculoskeletal Pain Index (FMPI); Zamprogno Question Bank (ZQB)

4.3.5 Statistical methods (papers I-IV)

All data were entered into a database (Microsoft Excel) and the statistical analyses were made using the statistical software R (R Core Team, 2017; R Core Team, 2013). All data were evaluated for normal distribution using normal probability plots for the residuals. ANOVA was used to compare inter-cat variability. When analysing the distribution of the vertical forces within a paw, measurements of PVF (%BW) and VI (%BW*sec) were obtained by dividing the paw print into four equally sized areas: craniolateral, craniomedial, caudolateral and caudomedial. The level of significance was set at $P < 0.05$

Paper I: The analyses were based on mixed linear models with random effects for every cat. ICC was used to investigate the accuracy of gait parameters, and the correlation between the parameters sex, age, weight and BCS.

Paper II: Data was log-transformed in some cases where skewness was detected from residual plots. Difference in gait parameters was investigated using R mixed linear models, with health status as fixed factor and cat as random

factor. Difference in The Owner Behaviour Watch was tested using Mann–Whitney's test.

Paper III: Statistical comparison between three groups of cats regarding the descriptive parameters was made using Kruskal-Wallis and Fischer's exact test. Pearson´s correlation coefficient was calculated to describe the reliability between the test results over time. ANOVA test of the difference between the diagnosis for each cat and the total score on the CMI was calculated, as an estimate of the instruments discriminatory ability. Receiver-operating characteristic (ROC) curves were plotted in order to calculate the area under the curve (AUC). AUC was used partly to estimate the instruments discriminatory ability, partly to provide cut-off values. Cronbach's α was analysed as a measurement of the questionnaires internal consistency.

Paper IV: The data were evaluated for normal distribution using normal probability plots for the residuals. The analyses (using R) were based on mixed linear models with fixed effect treatment and time, and random effects for every cat, and pairwise comparison with least square means.

5 Main results

5.1 Pressure mat technique

In sound cats, gait variables from the pressure mat were obtained from two valid trails for each of the included 46 cats, walking at a mean velocity of 0.68 ± 0.17 m/s (I). On average the analysis was performed on a mean of 11.2 ± 2.1 strikes per cat. The variables stance, swing and stride time had moderate agreement, the stride length and VI (%BW*sec) strong agreement, and PVF (%BW) had almost perfect agreement. The symmetry indices (left/right) for stride length, time and velocity, stance time and velocity, and PVF was approximately 1. The symmetry index for PVF front/hind was 1.26 ± 0.18.

Distribution of the vertical forces within the paws were analysed for thirty-nine sound cats, based on two step cycles. During the strike, the main weight was transferred from the caudal part of the paw towards the craniomedial part.

In the same study of sound cats, measurement error due to a “non-centered head position during walk” based on 12 trials from 10 cats were studied. The PVF (% BW) of the front limb to which side the head was positioned, increased by a factor of 1.73 ($P < 0.001$).

Thirteen sound cats contributed with data jumping from a 1.0 m high table. The cats landed with the front paws simultaneously and the hind paws simultaneously in 65 % of the jumps. The time difference between the front and the hind paws hitting the ground was 0.12 ± 0.02 seconds. The symmetry index for the PVF front/hind paws was 1.68 ± 0.57, and the symmetry index for the PVF for the left/right paws was 1.04 ± 0.30.

The OA cats (with previous CCL injury) had a mean velocity of 0.66 (±0.16) m/s, compared to sound cats with a mean velocity of 0.68 (±0.16) m/s (paper II). On average 11.4 (±2.8) strikes from the CCL cats were analysed, and on average 10.9 (±2.0) strikes from the sound cats. The front/hind symmetry index for PVF

(%BW) was 1.4 (±0.1) for the CCL cats and 1.2 (±0.1) for the sound cats (P = 0.001). The symmetry index for the same variable calculated for the limb pair on the opposite the side of the affected hind limb was 1.68 (±0.29). The results indicate that cats with a previous CCL injury put less weight on the affected hind limb, but for a longer time. The nine OA cats showed a different pressure distribution within the paws compared to sound cats. One cat was excluded due to polydactyly.

Of the six cats in the clinical pilot study, five contributed with pressure mat data. One cat was excluded due to polydactyly. There were significant differences in VI, comparing meloxicam treatment to baseline (-0.50 kg*sec, P = 0.025) and robenacoxib to baseline (-0.64 kg*sec, P = 0.005). Regarding the analysis of the pressure distribution under the paws the results showed no significant difference after treatment with neither meloxicam nor robenacoxib.

5.2 Owner assessment questionnaires

In paper II the OBWs total score was compared for OA cats (with previous CCL injury) and sound cats. There was a significantly higher questionnaire score (indicating pain and physical dysfunction) for the OA cats (with previous CCL injury) (9.9 ± 8.7) compared to sound cats (1.1 ± 2.5) (P < 0.031). The osteoarthritic cats were significantly older (9.5 ± 1.8 years) than the sound cats (5.9 ± 3.3 years) (P = 0.006).

Of the 122 cats contributing to paper III, 74 were diagnosed as sound, 26 as uncertain and 22 as osteoarthritic, based on orthopaedic examination and radiography. There was a significant difference in the variables age and weight between the groups sound (5.0 ± 2.8 years; 4.7 ± 1.3 kg), and uncertain (9.0 ± 3.0 years; 6.0 ± 2.1 kg) and osteoarthritis (10.0 ± 2.4 years; 6.0 ± 2.0 kg), respectively (P = 0.0004; 0.002). The cats´ behaviour in the home environment, which was assessed by the owner, was significantly different between sound cats, cats with an uncertain diagnosis and osteoarthritic cats, respectively.

The CMIs used in study III, the FMPI, the ZQB, the OBW, and the FPFF, were filled out by 122 cat owners, at two separate occasions. The FMPI, FPFF and ZQB instruments were filled out correctly in more than 97.8 % of the cases. The OBW instrument was filled out correctly by 58.0 % of the cat owners. Evaluating the results for the two separate answering occasions, the FPFF showed moderate positive linear relationship (0.66), and the other CMIs strong positive linear relationship (>0.70). The diagnostic accuracy, for all four CMIs, estimated with AUC ranged from 0.79 – 0.87, which is considered sound. Cronbach´s α was analysed for internal consistency and all CMIs scored well,

but the FPFF scored lowest. The cut-off values were 3 for FMPI, 1 for OBW, 4 for ZQB, and 2 for FPFF.

In study IV, there were significant differences in the total score of the CMIs FMPI (-2.8, P = 0.041) and OBW (-3.5, P = 0.047) between cats receiving meloxicam compared to baseline, respectively. There were no significant differences in any of the other two CMIs, the ZQB and the FPFF.

5.3 Physical examination

All participating cats were examined with a physical and orthopaedic examination. Of the 58 cats participating in the first paper, all of the cats were deemed sound on the physical and orthopaedic examination.

In the second paper the ten osteoarthritic cats (with previous CCL injury) were significantly older than the fifteen body weight matched sound control cats. All of the cats with OA had palpable periarticular thickening of the affected stifle joint. A decreased range of motion (8/10), and muscle atrophy proximally of the affected stifle joint (8/10), were common findings on clinical examination. Few cats had joint crepitus (1/10) or palpable joint effusion (2/10). Most of the cats showed signs of pain on manipulation of the affected stifle joint, either on palpation of the actual joint (3/10) or at the extremes of the range of motion (8/10).

In the third paper 17 cats were excluded based on the results from the orthopaedic examination (seven cats due to luxated coxofemoral joint, three cats due to neurological disease, one cat due to congenital malformation of the spinal column, and six cats due to insufficient cooperative abilities). The cats that were excluded due to orthopaedic conditions in the musculoskeletal system, had their diagnosis confirmed radiographically. Of the remaining cats, only cats that had findings on the orthopaedic examination *and* normal blood work were radiographed. This resulted in 29 cats being radiographed (Table 6.). On the orthopaedic examination of theses 29 cats 93 (20.0 %) joints out of 464 examined joints had pathological findings. Of the 93 radiographed joints, 41 (44.1 %) had radiographic findings of OA. 21 (22.6 %) of the joints had other findings (categorized as uncertain) and 31 (33.3%) were radiographically normal. Twelve of the 29 radiographed cats (41.4%) were lame on visual gait examination. The clinical characteristics of the 122 cats that contributed with data showed that the osteoarthritic cats were significantly older, heavier and had an increased behavioural response to pain during orthopaedic examination, compared to the sound cats. Results from the orthopaedic examination showed a significant difference in the behavioural response to pain, which was scored according to Zamprogno, *et al.*, 2010, between the three groups respectively.

Table 6. *Illustrating agreement between findings from orthopaedic examination and radiographic findings from 29 radiographed cats in paper III.*

Cat number	R shoulder	L shoulder	R elbow	L elbow	R antebrachio-carpal	L antebrachio-carpal	R front distal	L front distal	R coxofemoral	L coxofemoral	R stifle	L stifle
1									☐	U	☐	
2			OA				U		OA	☐		
3									U	☐	OA	U
4			OA	OA					OA	OA		
5											OA	OA
6											☐	U
7											☐	OA
8											OA	OA
9			OA				☐	☐	OA	OA		
10				☐					OA	☐		
11									☐	OA	U	U
12											U	☐
13			☐						OA	OA	OA	OA
14									OA	☐	OA	U
15			OA	OA								
16			☐						OA	OA		
17			☐	U					OA	☐		
18			U	U								
19									OA	OA		
20			☐	☐					☐	☐		
21		U		OA					☐	☐	U	
22									OA	OA		
23									☐	OA		
24												OA
25											☐	OA
26		U	U	U		OA			☐	☐		
27									☐	U		
28											☐	U
29	☐	☐	U	U	OA	OA			OA	OA		

$\square$: Radiographed joint with findings on orthopaedic examination, but normal appearance on radiography; $\boxed{OA}$: radiographic findings consistent with OA; $\boxed{U}$: uncertain radiographic findings. The tarsocrural joints and the joints distal to them did not have any findings at orthopaedic exam and where therefore not radiographed. Right (R); left (L).

In the clinical pilot study with the six osteoarthritic cats a total orthopaedic score was created by adding the findings from the orthopaedic examination together, including the behavioural response to pain. There was a significant difference in the scores from the physical examination between cats receiving meloxicam compared to baseline values (-2.8 $p = 0.050$). There was no significant difference in physical examination score between robenacoxib and baseline values, or between meloxicam and robenacoxib values. After the treatment period with meloxicam and robenacoxib the cat owner was asked verbally whether their cat´s condition was unchanged, improved or had deteriorated. When the cats received robenacoxib, the cat owners scored four cats as unaltered, one cat as deteriorated and one cat as improved. When they received meloxicam, four cats were considered to be unaltered, zero deteriorated and two improved.

6 Discussion

6.1 Pressure mat technique

The challenges presented by the feline nature and the discordance between findings from orthopaedic examination and radiography creates a need for objective tools to analyse gait, affected by various orthopaedic diseases. Objective tools for gait analysis are also important as gold standard to evaluate subjective assessment tools against. Another advantage of using objective gait analysis is that it is possible to standardize gait analysis in a way that is not possible with VGA. In order to utilize the pressure mat for gait analysis in cats with orthopaedic disease, reference values for sound cats have to be established.

The aim of the first paper was to define parameters for pressure mat analyses during walk and jump, and to define reference values for gait parameters in sound cats. 46/58 (79%) of the participating cats contributed with gait data. To ascertain high quality pressure mat data, the cats must walk at an even pace in a straight line facing forwards. The participating cats were not trained and 9/12 cats did not contribute with any valid registrations because they trotted rather than walked. The actual registrations were facilitated by having Plexiglas on the other side of the pressure mat, not facing the wall. It was checked statistically that the actual gait analysis (left/right symmetry) was not affected by on which side the cat had the wall and the Plexiglas screen. Such details and also preventing the cat from deviating from the straight track it is intended to walk on should be avoided. Having a surface cover on the pressure mat that extends beyond the actual pressure mat and having the area before and after the actual pressure mat free from things that could tempt the cat to turn to early is preferable. Simultaneous video recordings are necessary to ascertain things like the cat walking straight ahead and not looking to the sides. In our study we

analysed data from ten cats that looked to the side and the PVF of the front limb on the same side increased significantly with a factor x1.7.

Collection of reliable data from the pressure mat requires standardized velocity and preferably no acceleration/deceleration. Velocity, BW and body size has previously been shown to affect GRF in dogs (Kim *et al.*, 2011a; Voss *et al.*, 2010). Our results showed that allowing cats to walk at their own preferred velocity and having five registrations across the pressure mat, provided us with at least two valid registrations with an acceptable velocity (0.68 ± 0.17 m/s) and at least eight strikes to analyse. This is in line with previous publications on sound cats. Lascelles an co-author's had a velocity of 0.6 ± 0.1 m/s in the 15 sound cats they studied (Lascelles *et al*., 2007b) and Verdugo and co-authors had a velocity in the range of 0.54 – 0.74 m/s in the 18 sound cats they studied (Verdugo *et al.*, 2013). Verdugo and co-authors also established that male cats had an increased stride length compared to female cats, a gender difference that has been shown in humans as well. The increased body size of male cats did however not affect temporospatial or kinetic variables (Verdugo *et al.*, 2013).

Pressure mat data from cats jumping down from a height could provide information on the time delay between the front limbs and the hind limbs ground contact. A hypothesis was that cats with hind limb OA could have a delay in this time span compared to sound cats[2]. Only 16 (57%) of the 28 sound cats that jumped from 1.0 m height contributed with data. The SI for the front paws was 1.4 ± 0.2 and a fairly large amount of the cats did not land with either the front- or the hind paws simultaneously. Lascelles and co-authors showed no significant difference between the left and the right front limb during landing after jump (Lascelles *et al.*, 2007b) This may indicate that we need to standardize the jumping procedure more before it can be investigated further.

The pressure distribution within the paw was analysed in sound cats, it has been shown in dogs that paw pressure distribution is affected by orthopaedic disease (Souza *et al*., 2014). In dogs the analysis has been performed differently due to the larger surface contact area of the paws. The individual pads have been analysed separately, and major weight bearing pads have been identified. In cats the analysis of pressure distribution under the paw was made by dividing the paw into four equally large quadrants. This makes the results from dogs difficult to compare with cats. Using a pressure mat with higher resolution could overcome this problem, since a more detailed analysis of the cat's paw could be made. The sound cats initiated the ground contact with the caudal part of the paw, then transferring the force craniomedially before lifting the paw off the ground. The cat data on pressure distribution within the paw is likely representative for sound cats. Regarding the pressure distribution under the paws

2. Personal communication B.D.X. Lascelles, 2013.

in cats with OA (with previous CCL injury) the results showed that the pressure distribution under the hindlimb paws differed from the sound cats. This finding indicates that this is something that should be researched further. More information on large samples of cats with uniform orthopaedic disease is however required in order make deductions on the effect the pressure distribution.

The first paper provided reference ranges for sound cats and identified that PVF and VI were reliable parameters to analyse, similar to what has been shown in dogs. In the second paper we compared osteoarthritic cats (with a previous CCL injury) with a control group of sound BW matched cats. The cats with OA and a CCL injury had a front/hind asymmetry for PVF of 1.4 ± 0.1 compared to the sound control cats that had a PVF front/hind asymmetry of 1.2 ± 0.1. The OA cats did not differ significantly in VI. The OA cats had a decreased PVF and VI on the affected limb, compared to the unaffected hind limb. They also had a significantly lower PVF and a longer duration of stance phase, compared to sound cats. The phenomenon of putting less force on the limb, yet with prolonged stance phase has previously been described in horses, which could explain the lack of changes in VI (Weishaupt, 2008). This is most likely the effect of chronic pain, but mechanical instability can also be a contributing factor. The fourth paper where the pressure mat was used to evaluate treatment efficacy of meloxicam and robenacoxib showed a significant difference in VI after treatment compared to before treatment. PVF showed no significant difference, this can possibly be explained by 5/6 cats having mild clinical signs and multiple limb and joints affected.

6.2 Owner assessment questionnaires

Assessing the cat´s behaviour and physical ability to perform various activities as an effect of chronic pain in the home environment has several advantages. However, knowing what to assess and what is affected by chronic pain is important.

The cat owners answered the four disease specific CMIs with the aim to evaluate the validity and reliability of the instruments. In the second paper we established that there was a significant difference in the total score from the OBW instrument when the sound cats and the osteoarthritic cats (with previous CCL injury) were compared. In the third paper we showed that all four CMIs had sound reliability, discriminatory ability and internal consistency. The OBW had room for improvement regarding the readability and The FPFF needs modification in order to improve retest reliability and internal consistency. The conclusion was to recommend the FMPI as the instrument to use in a clinical

setting. The clinical pilot study showed that the FMPI and the OBW were able to detect analgesic efficacy of meloxicam, but not from robenacoxib. This could be explained by one or several of the following reasons. It was a small heterogenous group of cats, where some cats had mild OA, the questionnaires did not manage to pick up small improvements or the cat did not have enough pain from the start to benefit from the treatment.

Overall the FMPI is the instrument that has performed well and has a preferable layout. A possible disadvantage is the somewhat long format of the FMPI at present, and the time it takes to summarize the total score. Perhaps in the future it can be presented in a digital version that will summarize the total score rapidly, saving time in a busy clinical situation.

The advantages of using the CMIs is that it contributes with an assessment of the cat in a home setting where it is not subjected to the stress frequently appearing at the clinic. It is a cost effective and easy tool to use in a clinical setting. Limitations using the CMIs in evaluation of treatment efficacy is that the owners can be subjected to a placebo effect, wanting the cat to have pain relief from the treatment performed. Regarding disease specific instruments for cats, the availability of instruments that are validity and reliability tested is a limitation.

6.3 Physical examination

Physical examination is one of the clinician's most fundamental tools to diagnose disease. The advantage of physical examination as an assessment technique is that it requires little equipment or facilities. The disadvantage is that there are limitations regarding what can be found. Feline OA, accompanied by chronic pain and physical dysfunction, cannot be diagnosed with certainty merely using physical examination.

The majority of the cats studied were comfortable dealing with physical and orthopaedic examination. However, individual adaptations such as examining the cat on the floor were frequent. Overall, visual gait analysis was made of all the participating cats (paper I-IV). Visual gait analysis is valuable when investigating orthopaedic disease, yet has several limitations. One limitation is low agreement amongst observers assessing mild to moderate degrees of lameness. Few pet cats are used to walking on a leash and cats are known for being hard to direct to walk on a straight line at a certain pace. Less than 1/5 cats show lameness as a clinical sign of OA (Slingerland *et al.*, 2011; Clarke *et al*., 2005; Godfrey, 2005; Hardie *et al*., 2002).

The OA cats (with previous CCL injury) in paper II were defined as having clinical findings from the stifle joint affected by the previous CCL injury, that

were more significant than any other finding from the orthopaedic examination. This is a limitation since it cannot be completely excluded that the other, minor findings from the orthopaedic examination, influenced the pressure mat data.

Of the 122 cats contributing with data to paper III, six were excluded due to difficulties in cooperation and eleven due to other orthopaedic disease than OA. In this paper, 29 cats were radiographed due to findings from the orthopaedic examination. 20% of the joints examined had findings on the orthopaedic examination, yet only 44 % of the radiographed joints had findings of OA. This discordance between findings from orthopaedic examination and radiographic findings corroborates previous studies (Lascelles *et al.,* 2007a; Clarke & Bennett, 2006; Budsberg, 1997). In this paper, there was also a fairly large group of cats that were categorized as "uncertain diagnosis". The most common cause for this was abnormal blood work. Since normal blood work was required for sedation and radiography, only cats with pathological findings on the orthopaedic examination that also had normal blood work were radiographed. This is a complicating factor that could create a bias. Results from the orthopaedic examination showed a significant difference in the behavioural response to pain, between the sound cats, the OA cats and the cats with an uncertain diagnosis. This difference is probably caused by peripheral and central sensitisation in cats with OA. It could be interpreted as the osteoarthritic cats having a poorer mood than the sound cats. In humans, it is well recognized that chronic pain has a negative impact on mood (Kuffler, 2017; Ataoglu *et al.*, 2013).

In the clinical pilot study with NSAIDs there was a fairly large variation in the cats' clinical signs of OA. This was illustrated in the variation of the total orthopaedic score for each cat, which may have affected the results. More obvious results and increases in significant differences in a clinical study can probably be achieved with a more homogenous group of cats with more severe uniform clinical signs.

7. Conclusions

The first conclusion was that sound cats have a symmetrical gait, a front/hind limb asymmetry and that the gait parameters PVF and VI are reliable parameters to study (paper I).

The second conclusion regarding osteoarthritic cats (with previous CCL injury) was that they had more asymmetrical front/hind symmetry indices for PVF and VI, decreased PVF and VI on the affected hind limb compared to the unaffected hind limb, a different way of distributing the pressure under the paws and different behaviour in the home environment, compared to sound control cats (paper II).

The third conclusion concerning evaluation of the owner assessment questionnaires in sound cats and cats with OA revealed that neither sound nor osteoarthritic cats displayed a difference in the outcome of the four questionnaires when retested, provided that the cats state of health or disease was unaltered, the questionnaires could discriminate between sound and osteoarthritic cats, cut-off values were established with sound sensitivity and specificity and all four questionnaires had satisfying internal consistency (paper III).

The final conclusion was that treatment with NSAIDs decreased the osteoarthritic cats' pain when measured objectively with the pressure mat and subjectively with the owner assessment questionnaires (paper IV).

8. Future perspectives

The many cats suffering from chronic pain and physical disability caused by OA can hopefully be identified and receive pain relieving treatment in the future. Assessing physical dysfunction as an outcome of chronic pain, using pressure mat technique and questionnaires, shows promising results. The pressure mat needs further investigation with larger groups of cats with different types of orthopaedic conditions of different grades of severity to investigate the way cats compensate for lameness. The pressure distribution under the paws in cats with orthopaedic disease is also something that needs to be investigated further in larger groups with different orthopaedic conditions.

Based on the results in the present study the FMPI is the questionnaire that seems most promising. It has been shown to have sound discriminatory validity and reliability. To be able to evaluate an alteration in the cats prevailing condition, future research establishing cut off values for clinically relevant levels of improvement have to be established. This can then be used to evaluate treatment at home or treatment as part of a clinical trial as efficacious or not. Osteoarthritic cats' increased behavioural response to pain can be interpreted as a deterioration in mood. It is likely that the cats' quality of life is affected by chronic pain and physical dysfunction. This is something that needs to be researched further.

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Popular science summary

Osteoarthritis (OA) is a common cause of chronic pain and physical dysfunction in cats. Signs of disease are often vague and the cats are rarely lame. The most obvious signs are behavioural and life style changes. These changes are frequently interpreted as part of normal aging. The cats are often stressed at the veterinary clinic and are also experts at hiding signs of disease, which complicates the veterinarian's physical examination. The veterinarian diagnoses OA based on what the cat owner tells, physical examination and x-rays. The findings from the physical exam do not always correspond to the findings from the x-rays. This is a challenge, since it makes it hard to know which joints are painful due to OA. Therefore improved methods to diagnose OA and evaluate pain relieving treatment are needed.

There are currently no methods to measure chronic pain caused by OA in cats. By measuring physical dysfunction in the cat, we can however, make an estimation of the cats' difficulties caused by OA. We have used a pressure mat, which measures the load on the cat's limbs and a questionnaire that the cat owner fills out regarding the cat's ability at home. We have compared these two methods with the physical examination that the veterinarian performs.

The goal with the thesis was to show how healthy cats put load on their limbs. Because very little research has been done on this, and in order to show what is not normal, we must first show what is normal. The cats put more load on their front limbs, than the hind limbs – just like dogs. When we compared cats with OA in the stifle joint, we could show that they walk differently, on the pressure mat, compared to healthy cats. They also behaved differently in their home environment compared to healthy cats. The four questionnaire that we evaluated were all trustworthy. The osteoarthritic cats had an increase behavioural response to pain when we examined them physically, compared to healthy cats. This could be interpreted as a mood deterioration caused by chronic pain. Chronic pain has shown to be associated with deteriorated mood in humans. A pilot study with osteoarthritic cats were treated with pain relieving drugs. Using

the pressure mat and the questionnaires the results showed that the cats had beneficial effect of the treatment.

The thesis contributes with knowledge on how to evaluate physical dysfunction in cats caused by OA, using pressure mat technique and owner assessment questionnaires. This makes it easier to diagnose cats with OA and also to evaluate if the pain relieving treatment was effective. This will in the long run, contribute to improved welfare in cats.

Populärvetenskaplig sammanfattning

Artros är en vanlig orsak till kronisk smärta och funktionsnedsättning hos katt. Symtomen är ofta vaga och katterna är sällan halta. De huvudsakliga symptomen består av gradvisa förändringar i kattens beteende och livsstil. Ofta tolkas dessa förändringar som ett normalt åldrande. Katten blir ofta stressad hos veterinären och är dessutom expert på att dölja symptom på sjukdom, vilket försvårar veterinärens undersökning. Veterinären ställer diagnosen artros baserat på information från kattägaren, klinisk undersökning av katten och röntgen. Fynden från den kliniska undersökningen överensstämmer inte alltid med fynden från röntgenundersökningen, vilket är en utmaning, för att kunna bedöma vilka leder som är smärtsamma på grund av artros. Förbättrade metoder behövs för att kunna diagnosticera artros hos katt och för att kunna utvärdera effekten av smärtlindrande behandling.

Det finns inga metoder för att mäta kronisk smärta på grund av artros hos katt. Vi kan däremot mäta den funktionsnedsättning som artros leder till. Genom att mäta kattens funktionsnedsättning med olika metoder kan vi få en uppfattning om kattens besvär och smärta. Vi har använt oss av en tryckmätningsmatta som mäter hur katten belastar tassarna när den går och även av ett frågeformulär som kattägaren får fylla i. Detta har vi jämfört med veterinärens kliniska undersökning. Frågeformuläret ställer frågor om hur katten fungerar hemma och vad den kan och inte kan göra.

Målen med avhandlingen var att visa hur friska katter belastar tassarna när de går på tryckmattan. Eftersom det endast finns knapphändig information om hur friska katter belastar tassarna. För att visa hur sjuka katter belastar tassarna måste vi först ha ett referensmaterial för friska katter. Ett annat mål var att visa hur katter med artros skiljer sig i sitt sätt att belasta tassarna, att testa hur tillförlitliga fyra olika frågeformulär var och att mäta effekten av smärtlindrande läkemedel som katterna fått, med tryckmattan och frågeformulären.

Vi kunde visa hur friska katter går och även vilka faktorer som man bör analysera från tryckmattan. Vi kunde också visa att katter lägger mer vikt på

frambenen, precis som hundar. När vi jämförde katter med artros och tidigare korsbandsskada, så kunde vi visa att de gick på ett annorlunda sätt på mattan och uppförde sig på ett annat sätt i hemmiljön. De fyra frågeformulären som vi testade var alla tillförlitliga. Katter med artros reagerade med ett kraftigare avvärjande beteende än friska katter när man undersökte dem. Detta kan tolkas som att katter med artros har sämre humör på grund av kronisk smärta. Kronisk smärta har visat sig ha ett samband med försämrat humör hos människor. När vi behandlade katter med artros med smärtlindrande medicin, gick det att visa en klar skillnad efter behandlingen.

Avhandlingen bidrar till att utvärdera fysisk nedsättning hos katter med artros genom att använda tryckmatta och frågeformulär för kattägaren. Detta leder till förbättrade metoder för att diagnosticera och behandla artros hos katt, och i förlängningen förbättrad välfärd för katter.

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Appendix 1

Bilaga 1

Instruktioner som lästes för ägarna varje gång FMPI-formuläret fylldes i:

Vår bedömning utgår ifrån detta frågeformulär.
Där får du besvara frågor om din katts förmåga att utföra olika aktiviteter, i jämförelse med din uppfattning om en normal katts förmåga.
Läs frågorna noggrant och sätt ett kryss i lämplig ruta.
"Normal" ligger här, och sedan finns olika grader av "abnormalitet". Om aktiviteten inte är relevant, kryssar du i rutan längst till höger.
Om du anser att din katts förmåga är bättre än normalt, kryssar du i rutan längst till vänster.

Frågeformulär – FMPI

Vad kan din katt göra jämfört med en normal katt?

Kryssa i den ruta som bäst beskriver hur väl din katt kan göra följande:

1) Gå och/eller röra sig normalt och utan besvär

bättre än normalt	normalt	inte helt normalt	lite sämre än normalt	knappt, eller med stor ansträngning	inte alls	jag vet inte, eller inte relevant
☐	☐	☐	☐	☐	☐	☐

2) Springa

bättre än normalt	normalt	inte helt normalt	lite sämre än normalt	knappt, eller med stor ansträngning	inte alls	jag vet inte, eller inte relevant
☐	☐	☐	☐	☐	☐	☐

3) Hoppa upp

bättre än normalt	normalt	inte helt normalt	lite sämre än normalt	knappt, eller med stor ansträngning	inte alls	jag vet inte, eller inte relevant
☐	☐	☐	☐	☐	☐	☐

4) Hoppa upp till en höjd motsvarande en köksbänk, i ett försök

bättre än normalt	normalt	inte helt normalt	lite sämre än normalt	knappt, eller med stor ansträngning	inte alls	jag vet inte, eller inte relevant
☐	☐	☐	☐	☐	☐	☐

5) Hoppa ned (hur väl och hur besvärsfritt)

bättre än normalt	normalt	inte helt normalt	lite sämre än normalt	knappt, eller med stor ansträngning	inte alls	jag vet inte, eller inte relevant
☐	☐	☐	☐	☐	☐	☐

6) Gå upp för trappor

bättre än normalt	normalt	inte helt normalt	lite sämre än normalt	knappt, eller med stor ansträngning	inte alls	jag vet inte, eller inte relevant
☐	☐	☐	☐	☐	☐	☐

7) Gå ned för trappor

bättre än normalt	normalt	inte helt normalt	lite sämre än normalt	knappt, eller med stor ansträngning	inte alls	jag vet inte, eller inte relevant
☐	☐	☐	☐	☐	☐	☐

8) Leka med leksaker och/eller jaga efter föremål

bättre än normalt	normalt	inte helt normalt	lite sämre än normalt	knappt, eller med stor ansträngning	inte alls	jag vet inte, eller inte relevant
☐	☐	☐	☐	☐	☐	☐

Vad kan din katt göra jämfört med en normal katt? (fortsättning)

Kryssa i den ruta som bäst beskriver hur väl din katt kan göra följande:

9) Leka och samverka med andra husdjur

bättre än normalt	normalt	inte helt normalt	lite sämre än normalt	knappt, eller med stor ansträngning	inte alls	jag vet inte, eller inte relevant
☐	☐	☐	☐	☐	☐	☐

10) Resa sig från viloposition

bättre än normalt	normalt	inte helt normalt	lite sämre än normalt	knappt, eller med stor ansträngning	inte alls	jag vet inte, eller inte relevant
☐	☐	☐	☐	☐	☐	☐

11) Ligga och/eller sitta ned

bättre än normalt	normalt	inte helt normalt	lite sämre än normalt	knappt, eller med stor ansträngning	inte alls	jag vet inte, eller inte relevant
☐	☐	☐	☐	☐	☐	☐

12) Sträcka på sig

bättre än normalt	normalt	inte helt normalt	lite sämre än normalt	knappt, eller med stor ansträngning	inte alls	jag vet inte, eller inte relevant
☐	☐	☐	☐	☐	☐	☐

13) Tvätta och trimma sig själv

bättre än normalt	normalt	inte helt normalt	lite sämre än normalt	knappt, eller med stor ansträngning	inte alls	jag vet inte, eller inte relevant
☐	☐	☐	☐	☐	☐	☐

14) Samverka med dig och övriga familjemedlemmar

bättre än normalt	normalt	inte helt normalt	lite sämre än normalt	knappt, eller med stor ansträngning	inte alls	jag vet inte, eller inte relevant
☐	☐	☐	☐	☐	☐	☐

15) Bli berörd, buren och/eller hållen

bättre än normalt	normalt	inte helt normalt	lite sämre än normalt	knappt, eller med stor ansträngning	inte alls	jag vet inte, eller inte relevant
☐	☐	☐	☐	☐	☐	☐

Vad kan din katt göra jämfört med en normal katt? (fortsättning)

Kryssa i den ruta som bäst beskriver hur väl din katt kan göra följande:

16) Äta

bättre än normalt	normalt	inte helt normalt	lite sämre än normalt	knappt, eller med stor ansträngning	inte alls	jag vet inte, eller inte relevant
☐	☐	☐	☐	☐	☐	☐

17) Gå på lådan (stiga i och ur, sitta på huk och täcka över avföringen)

bättre än normalt	normalt	inte helt normalt	lite sämre än normalt	knappt, eller med stor ansträngning	inte alls	jag vet inte, eller inte relevant
☐	☐	☐	☐	☐	☐	☐

Hur aktiv är din katt generellt sett?

mer aktiv än normalt	normalt aktiv	inte helt normalt	lite mindre aktiv än normalt	knappast aktiv	inte aktiv alls	jag vet inte, eller inte relevant
☐	☐	☐	☐	☐	☐	☐

Hur ont har din katt?

Kryssa i den ruta som bäst beskriver din katts smärtnivå under den senaste veckan.

ingen smärta	lite smärta	mild smärta	medelsvår (måttlig) smärta	mycket svår (allvarlig) smärta
☐	☐	☐	☐	☐

Kryssa i den ruta som bäst beskriver din katts smärtnivå idag.

ingen smärta	lite smärta	mild smärta	medelsvår (måttlig) smärta	mycket svår (allvarlig) smärta
☐	☐	☐	☐	☐

Betygsätt din katts allmänna livskvalitet. (Hur väl kan katten utföra sina favoritaktiviteter, äta och röra sig i sin omgivning?)

utmärkt	bra	skaplig	dålig
☐	☐	☐	☐

Vad kan din katt göra jämfört med en normal katt? (fortsättning)

Kryssa i den ruta som bäst beskriver hur väl din katt kan göra följande:

16) Äta

bättre än normalt	normalt	inte helt normalt	lite sämre än normalt	knappt, eller med stor ansträngning	inte alls	jag vet inte, eller inte relevant
☐	☐	☐	☐	☐	☐	☐

17) Gå på lådan (stiga i och ur, sitta på huk och täcka över avföringen)

bättre än normalt	normalt	inte helt normalt	lite sämre än normalt	knappt, eller med stor ansträngning	inte alls	jag vet inte, eller inte relevant
☐	☐	☐	☐	☐	☐	☐

Hur aktiv är din katt generellt sett?

mer aktiv än normalt	normalt aktiv	inte helt normalt	lite mindre aktiv än normalt	knappast aktiv	inte aktiv alls	jag vet inte, eller inte relevant
☐	☐	☐	☐	☐	☐	☐

Hur ont har din katt?

Kryssa i den ruta som bäst beskriver din katts smärtnivå under den senaste veckan.

ingen smärta	lite smärta	mild smärta	medelsvår (måttlig) smärta	mycket svår (allvarlig) smärta
☐	☐	☐	☐	☐

Kryssa i den ruta som bäst beskriver din katts smärtnivå idag.

ingen smärta	lite smärta	mild smärta	medelsvår (måttlig) smärta	mycket svår (allvarlig) smärta
☐	☐	☐	☐	☐

Betygsätt din katts allmänna livskvalitet. (Hur väl kan katten utföra sina favoritaktiviteter, äta och röra sig i sin omgivning?)

utmärkt	bra	skaplig	dålig
☐	☐	☐	☐

Appendix 2

Owner behaviour watch

Kattens namn_____ Datum_____

Kattägarens namn_____

Beteende	*Generell bedömning*		*Grad av förändring 1(lindrig)-10(mycket kraftig)*
	Normal	*Onormal*	
1. Rörlighet			
2. Aktivitetsnivå			
3. Vård av päls och klor			
4. Temperament och humör			
5. Total grad av problem från 1 (lindriga) till 10 (mycket kraftiga)			

Beteendebedömning: Tänk på hur din katt brukade vara och jämför det med hur han/hon är nu. Använd de olika aktiviteterna i listan nedan som en guide, och gradera hur stor förändringen är mellan 1-10.

Rörlighet	Hopp upp och ned	Vägrar eller tvekar att hoppa UPP eller NED Mindre smidig i trappor Försöker inte längre nå högt belägna platser
	Storlek/höjd på hopp upp och ned	Tar mindre hopp, t. ex. tar flera steg för att nå högt belägna platser Frekvens av hopp, t. ex. hoppar till högt belägna platser mer sällan än tidigare
	Smidighet	Rörelser ser mindre smidiga ut än tidigare Har blivit stelare
	Förändringar i toalettbeteende	Förändrad lokalisation, t. ex. tvekar/vägrar gå ut eller tvekar/vägrar använda kattlådan. Svårigheter att använda kattlådan, t. ex. missar kattlådan ibland/ofta
Aktivitets-nivå	Sovvanor	Sover eller vilar mer Ligger på samma plats under lång tid, byter inte plats ofta Förändrad viloplats
	Lek	Leker mindre Initierar inte längre till lek Svårare att locka till lek
	Jakt	Jagar mindre än tidigare
Vård av päls och klor	Pälskondition	Matt eller tovig/skivig päls, generellt eller på ett visst område Observeras tvätt av pälsen mindre ofta eller med kortare duration Överdrivet tvättande av vissa områden
	Klösbeteende	Vässar klorna mindre ofta Förändrad plats/höjd där katten vässar klorna Klorna är förväxta eller fastnar i mattor eller klickar mot hårda golv
Temperament och humör	Tolerans mot ägare och andra djur	Mindre intresserad av att umgås Sur vid kontakt med andra katter Sur vid kontakt med andra djur samt ägaren
	Generell attityd	Tystare Spenderar mer tid ensam Söker inte /undviker kontakt med andra katter eller andra djur Söker inte /undviker kontakt med ägaren

1

Appendix 3

Feline physical function formula

Stadig, 2011

Datum……..

Kattens namn……...

Kattens ras……

Hane/hona…….

Kastrerad……..

Född…….

Vikt……

Löpnummer……

Ägarens namn……...

Adress……

Telefonnummer……

Markera med en ring kring svaret, tack eller skriv på raden.

1. Är katten

Innekatt Både ute och innekatt. Utekatt.

2. Vad äter katten för foder?.....

3. Äter katten någon form av kosttillskott?

JA NEJ

Om JA, vad:……..

4. Äter katten någon medicin?

JA NEJ

Om Ja, vad……..

1

5. Verkar katten frisk?

JA NEJ

Om NEJ, beskriv:……

6. Har katten några symptom från rörelseapparaten såsom till exempel hälta?

JA NEJ

Om JA, beskriv……

7. Hoppar katten *lika ofta* upp eller ner, t ex från möbler som tidigare?

JA NEJ

Om NEJ, beskriv:……

8. Hoppar katten *lika högt* upp och ner som tidigare?

JA NEJ

Om NEJ, beskriv:……

9. Har katten samma toalettvanor som tidigare?

JA NEJ

Om NEJ, beskriv:……

10. Har katten samma sovvanor som tidigare?

JA NEJ

Om NEJ, beskriv:……

11. Har katten samma jaktvanor som tidigare?

JA NEJ

Om NEJ,
beskriv:……

12. Leker katten på samma sätt/lika mycket som tidigare?

JA NEJ

Om NEJ, beskriv:……

13. Pälsvård: tvättar sig katten på samma sätt/lika mycket som tidigare?

JA NEJ

Om NEJ, beskriv:……

14. Vässar katten klorna/klöser lika mycket/på samma sätt som tidigare?

JA NEJ

Om NEJ, beskriv:……

15. Temperament/humör: interagerar/umgås katten likadant med ägaren eller andra djur som tidigare?

JA NEJ

Om NEJ, beskriv:……..

16. Allmänt: är katten lika mycket med familjen/andra djur i hushållet som tidigare eller är den mer stillsam eller drar sig undan?

JA NEJ

Om NEJ, beskriv:……

2011-01-10/Sarah Stadig

Appendix 4

Zamprogno question bank

Djurägares namn: Datum:
Telefonnummer:

Kattens namn:

Aktivitet	Grad av påverkan på aktiviteten till följd av smärta					
	Ej relevant	Påverkar aldrig	Påverkar sällan	Påverkar ibland	Påverkar ofta	Påverkar alltid
Gång						
Springer						
Förmåga att hoppa upp						
Förmåga att hoppa ned						
Gå upp för trappor						
Gå ned för trappor						
Lek med andra husdjur						
Reser sig från liggande						
Pälsvård						
Jakt						
Förmåga att sträcka på sig						
Ätbeteende						
Höjd på hopp upp						
Höjd på hopp ned						
Sovvanor						
Lek med leksaker						
Täcker över urinavföring med sand						
Sömnlängd						

Djurägares namn: Datum:
Telefonnummer:

Kattens namn:

Livskvalitet

Lista de fem aktiviteter som är viktigast för att din katt ska ha bra livskvalitet. Bedöm (i procent) hur viktig varje aktivitet är för din katts livskvalitet, den totala bedömningspoängen för alla fem aktiviteter ska bli 100.

Bedöm sedan hur stor förmåga din katt har att utföra varje aktivitet genom att sätta ett kryss på skalan nedan, där 0 betyder att aktiviteten inte kan utföras alls och 100 innebär att katten har full förmåga att utföra aktiviteten.

Aktivitet	Viktning (0-100%)	Förmåga (0-100)
1.		0_____100
2.		0_____100
3.		0_____100
4.		0_____100
5.		0_____100