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On diabetes mellitus

The cat, the owner, and the choices we make

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On diabetes mellitus. The cat, the owner, and the choices we make

Abstract

Diabetes mellitus (DM) is a common endocrine diseases in cats. Although treatment may offer a favourable prognosis and a potential for remission, disease management often encompasses challenges. The overall aim of this thesis was to broaden the understanding of DM in cats and contribute to an improved clinical management, including aspects related to the cat, the owner, and to the veterinarian.

A questionnaire sent to owners of cats with DM contributed with information on clinical outcomes and owner experiences. Eating predominantly a commercially available wet diet increased odds of remission, and remission was associated with a better quality of life of the cat. Difficulties and worries associated with DM management were common among owners. Interviews demonstrated that both owners and veterinarians considered the cat's quality of life as central, and this, together with a strong sense of responsibility, guided reasoning around the cat's DM and treatment. Clinical decision-making was influenced by the human-cat relationship, moral values, veterinary-owner communication and other contextual factors. Finally, hair cortisol concentration (HCC) was evaluated as a biomarker of long-term hypothalamic–pituitary–adrenal (HPA) axis activity and stress. Cats with chronic disease, including DM, had higher HCC than healthy cats, suggesting that disease and disease management affect HPA-axis activity. Combing demonstrated potential as a low-stress method for hair sampling.

Together, the four studies provide new insights into the clinical, emotional, and ethical dimensions of DM in cats, and highlight the importance of integrating the lived experiences of owners, cats and veterinarians in DM management.

Keywords: Cat, diabetes, wet diet, owner, veterinary, remission, quality of life, non-invasive, stress, chronic disease

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Om diabetes mellitus. Katten, ägaren, och de beslut vi fattar.

Abstract

Diabetes mellitus (DM) är en vanlig endokrin sjukdom hos katter. Vid behandling kan prognosen vara gynnsam och med möjlighet till remission, men sjukdomen kan också innebära utmaningar. Det övergripande syftet med avhandlingen var att bidra till en djupare förståelse av hanteringen av DM hos katt och förbättra den kliniska hanteringen, inkluderande aspekter relaterade till katten, ägaren och veterinären.

En enkät skickad till ägare av katter med DM undersökte sjukdomsutfall och ägarnas upplevelser. Katter som främst åt kommersiellt tillgänglig blötmat hade högre odds för remission, och remission var kopplad till bättre livskvalitet hos katten. Det var vanligt för ägare att uppleva svårigheter och oro kopplade till sjukdomen och behandlingen. Intervjuer visade hur både ägare och veterinärer betraktade kattens livskvalitet som central, och detta tillsammans med en stark ansvarskänsla styrde resonemang kring kattens behandling. Kliniska beslut påverkades av relationen mellan människa och katt, moraliska värderingar, kommunikation mellan veterinär och ägare och andra kontextuella faktorer. Slutligen utvärderades hårkortisolkoncentration (HCC) som en biomarkör för långvarig aktivitet över hypotalamus-hypofys-binjureaxeln (HPA-axeln) och stress. Katter med kronisk sjukdom, inklusive DM, hade högre HCC än friska katter, vilket kan innebära att sjukdom i sig och behandling påverkar aktiviteten över HPA-axeln. Kamning visade potential som en lågstressmetod för hårprovtagning.

Tillsammans ger de fyra studierna nya insikter i kliniska, känslomässiga och etiska dimensioner av DM hos katt och belyser vikten av att integrera perspektiv från både ägare, katt och veterinär i den kliniska hanteringen.

Nyckelord: Katt, diabetes, blötmat, ägare, veterinär, remission, livskvalitet, icke-invasiv, stress, kronisk sjukdom

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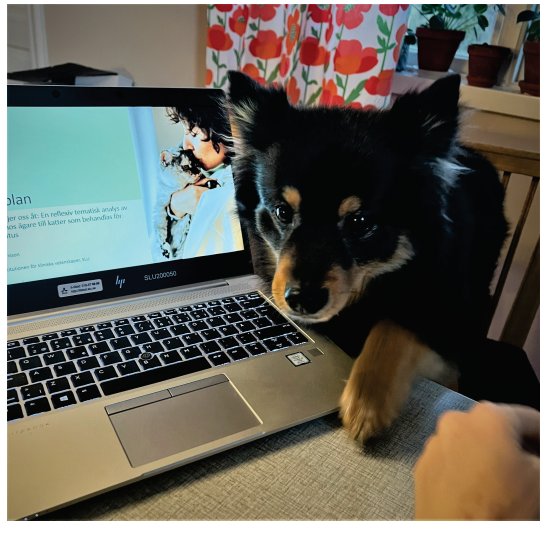
Dedication

To Alexander, my forever rock and berth in the ether.

Saga, you would have loved walking on my laptop while I was writing this thesis. Luckily, Pelle stepped up.



“I meant," said Ipslore bitterly, "what is there in this world that truly makes living worthwhile?"

Death thought about it.

CATS, he said eventually. CATS ARE NICE.”

— Terry Pratchett, Sourcery

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. Rothlin-Zachrisson N, Öhlund M, Röcklinsberg H, Ström Holst B. (2023). Survival, remission, and quality of life in diabetic cats. J Vet Intern Med., 37(1), 58-69.

II. Rothlin-Zachrisson N, Ström Holst B, Öhlund M, Leksell J, Röcklinsberg H. (2025). In sickness and health: Owners' experiences and considerations in the initiation and continuation of treatment for cats with diabetes mellitus. (submitted)

III. Rothlin-Zachrisson N, Ström Holst B, Öhlund M, Leksell J, Röcklinsberg H. (2025). To treat or not to treat: Experiences and considerations of veterinarians managing cats with diabetes mellitus. (submitted)

IV. Rothlin-Zachrisson N, Röcklinsberg H, Jettel E, Bergqvist Johansson F, Stadig S, Öhlund M, Mariti C, Ström Holst B. (2024). Hair cortisol concentrations in clipped and combed hair and associations with characteristics, health status and stress in domestic cats. Scientific Reports 14(1): 21846.

Papers I and IV are reproduced with the permission of the publishers.

The contribution of Ninni Rothlin Zachrisson to the papers included in this thesis was as follows:

I. Malin Öhlund, Agneta Egenvall, Tove Fall, Helene Hansson-Hemlin, Helena Röcklinsberg, and Bodil Ström Holst contributed to the design of the study. Malin Öhlund created the questionnaire and collected the data. Ninni Rothlin Zachrisson compiled the results, performed the statistical analyses and drafted the manuscript. All authors contributed to interpretations of the results and revision of the final manuscript.

II. Ninni Rothlin Zachrisson, Bodil-Ström Holst, Helena Röcklinsberg, and Malin Öhlund contributed to the design of the study. Ninni Rothlin Zachrisson collected the data, performed data analysis and drafted the manuscript. All authors contributed to the development of the interview guide, to interpretations of the data and the results, and revision of the final manuscript.

III. Ninni Rothlin Zachrisson, Bodil-Ström Holst, Helena Röcklinsberg, and Malin Öhlund contributed to the design of the study. Ninni Rothlin Zachrisson collected the data, performed data analysis and drafted the manuscript. All authors contributed to the development of the interview guide, to interpretations of the data and the results, and revision of the final manuscript.

IV. Ninni Rothlin Zachrisson, Emma Jettel, Felicia Johansson Bergqvist, and Sarah Stadig collected the data. Ninni Rothlin Zachrisson, Emma Jettel, and Felicia Johansson Bergqvist performed laboratory analyses and created the questionnaire. Ninni Rothlin Zachrisson analysed the data and drafted the manuscript. All authors contributed to interpretations of the results and revision of the final manuscript.

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Abbreviations

AIC	Akaike information criterion
BA	Bland-Altman
BG	Blood glucose
CI	Confidence interval
CKD	Chronic kidney disease
DM	Diabetes mellitus
ELISA	Enzyme-linked immunosorbent assay
HBGM	Home blood glucose monitoring
HPA	Hypothalamic-pituitary-adrenal
HT	Hyperthyroidism
LOA	Limit of agreement
OR	Odds ratio
RTA	Reflexive thematic analysis
SLU	Swedish University of Agricultural Sciences
QoL	Quality of life

1. Introduction

Cats have been an important part of human life for thousands of years (Clutton-Brock, 2002, Driscoll et al., 2007). Initially their presence was primarily in the form of vermin control, but as domestication proceeded they shifted from outdoor life to sharing the home and lifestyle of humans. In 2024, is was estimated that every fifth household in Sweden shelters at least one cat, a number that had increased compared to previous estimates (SKK, 2024). Domestic cats can reach high ages, reflected in the age of insured cats (Egenvall et al., 2009, Bonnett and Egenvall, 2010) and cats attending veterinary practices (O'Neill et al., 2015). Suggested reasons for this includes the advances of veterinary medicine and the acceptance and willingness of owners to engage in medical care for their cat (Egenvall et al., 2009, Ray et al., 2021). With risk factors including higher age (Prahl et al., 2007, Öhlund et al., 2015, O'Neill et al., 2016) obesity and a sedentary lifestyle (Prahl et al., 2007, Slingerland et al., 2009, Sallander et al., 2012, Öhlund et al., 2017), diabetes mellitus is emerging as one of the most common endocrine diseases in cats, with disease prevalence varying from 0.25% to 1 % in studied populations (Panciera et al., 1990, McCann et al., 2007, Prahl et al., 2007, Lederer et al., 2009, Waite et al., 2025). Management of diabetes mellitus may entail challenges for both owner and cat, as well as for veterinary professionals.

1.1 Aetiology and risk factors for diabetes mellitus

Diabetes mellitus (DM) is a syndrome of glucose dysregulation. It is characterised by persistent hyperglycaemia caused by either impaired insulin secretion by pancreatic β-cells, inadequate insulin action on target tissues, or a combination of both (American Diabetes Association, 2013).

In cats, DM has a heterogeneous aetiology. Even though the exact cause remains unknown, various factors are believed to contribute to disease development, leading to a progressive loss of β-cell function and secretion of adequate insulin to maintain euglycaemia (Appleton et al., 2001, American Diabetes Association, 2013, Gostelow and Hazuchova, 2023). Glucotoxicity, referring to the detrimental effect of persistent hyperglycaemia on β-cells and their function, is believed to contribute to disease progression in cats, as it does in humans (Zini et al., 2009, Bensellam et al., 2012, Link et al., 2013). An aetiologic classification of causes related to β-cell function and target organ function has been proposed (Niessen, 2022), rather than the umbrella term of feline type 2 DM, recognising the diversity in causes of DM in cats. Co-morbidities like hypersomatotropism and hyperadrenocorticism have been linked to DM development, and the former seems far more common than the latter, although it is often overlooked in the clinical setting (Blois et al., 2010, Niessen et al., 2015, Guse et al., 2024). Pancreatitis and DM may coexist in cats (Saunders et al., 2002, Zini et al., 2015), but the direction of the effect one has on the other has yet to be established (Zini et al., 2009, Davison, 2015).

Risk factors for DM development include modifiable factors such as body condition, activity level, and the cat receiving certain drugs; and non-modifiable factors such as increased age, sex, breed, and genetic susceptibility. The function of pancreatic β-cells and their ability to adapt insulin secretion to meet and compensate for increasing peripheral demands seem to be central in DM development (O'Brien et al., 1986, Appleton et al., 2001), and not all cats that have risk factors for the disease develop DM.

A major contributor to decreased insulin sensitivity in target organs (Hoenig et al., 2013), overweight and obesity are perhaps the most recognised risk factors for DM (Scarlett and Donoghue, 1998, Scott-Moncrieff, 2010, Öhlund et al., 2017), with a four-fold increased risk of DM development in overweight cats (Scarlett and Donoghue, 1998). Regarding the role of diet, findings are conflicting (Slingerland et al., 2009, Verbrugghe and Hesta, 2017, Öhlund et al., 2017), and further research is needed to elucidate the effect of macronutrients and food intake on glucose metabolism and DM development. An association between dry food diet and an increased risk of DM in normal-weight cats was seen, suggesting a higher susceptibility for long-term post-prandial hyperglycaemia and following β-cell exhaustion in these cats (Öhlund et al., 2017). However, other

associations between diet and DM development may instead be linked to overweight and obesity as a result of dietary composition and feeding habits (Scarlett and Donoghue, 1998, Rand et al., 2004, Slingerland et al., 2009, Öhlund et al., 2018). Other modifiable risk factors include eating behaviour (Lederer et al., 2003, Öhlund et al., 2017), lifestyle factors (Slingerland et al., 2009, Öhlund et al., 2017), and the administration of drugs with diabetogenic properties (Lederer et al., 2003, McCann et al., 2007, Lowe et al., 2009, Slingerland et al., 2009, Nerhagen et al., 2021).

Most cats are middle-aged when diagnosed (Panciera et al., 1990, Prahl et al., 2007, Öhlund et al., 2015, Guse et al., 2025), and neutered male cats have an increased risk of DM (McCann et al., 2007, Öhlund et al., 2017, Waite et al., 2025). This may possibly be related to a predisposition to obesity (Lund et al., 2005, Öhlund et al., 2018), increased glucose resistance as compared to female cats (Appleton et al., 2001), or an increased likelihood of hypersomatotropism (Niessen et al., 2015). Neutered cats are more likely to develop DM compared to intact cats, likely an effect of the decrease in energy requirements and increase in food intake following gonadectomy (Hoenig and Ferguson, 2002, Prahl et al., 2007). Some breeds, including Burmese, Russian Blue and Norwegian Forest Cats, seem predisposed to DM (Prahl et al., 2007, Lederer et al., 2009, Öhlund et al., 2015, Öhlund et al., 2017), and in one study, domestic cats had a slightly higher risk of DM compared to pedigree cats (Öhlund et al., 2017).

1.2 Clinical features and diagnosis

Classical clinical signs of DM are a result of persistent hyperglycaemia and following glucosuria, and are thus by themselves not indicative of the cause of DM. The severity of clinical signs depends on disease progress, and while polyuria, polydipsia, weight loss and lethargy are commonly reported by owners (Schaer, 1977, Crenshaw and Peterson, 1996), excessive weakness, decreased appetite and gastrointestinal signs are examples of clinical signs associated with more longstanding or severe disease stages and diabetic ketoacidosis (Cooper et al., 2015).

For DM diagnosis, confirmation of hyperglycaemia is usually combined with the presence of clinical signs (Sparkes et al., 2015, Behrend et al., 2018). Glucose can be measured in blood, interstitial fluid and urine. As a response to stress, cats can develop a rapid short-term elevation in blood glucose (BG)

concentrations, known as ‘stress hyperglycaemia’ (Rand et al., 2002). This may complicate the establishment of a DM diagnosis. Therefore, confirmation of persistent hyperglycaemia or glucosuria is recommended (Crenshaw et al., 1996, Niessen et al., 2022), to lower the risk of wrongly diagnosing DM based on transient stress-induced hyperglycaemia. One common approach is to measure serum fructosamine, a glycated serum protein considered representative of the average BG concentration during the preceding weeks of the test (Crenshaw et al., 1996, Link and Rand, 2008).

In cases of elevated BG without clinical signs of DM, alterations in glycated proteins, or glucosuria, DM can be classified as subclinical if stress-induced hyperglycaemia has been ruled out (Niessen et al., 2022). To date, no validated test exists to determine whether cats are at risk of developing DM (Gostelow and Hazuchova, 2023).

1.3 Disease management

DM management is heavily dependent on the active participation of the owner and includes administration of hypoglycaemic agents, dietary modifications, lifestyle interventions and at-home assessment. In addition, other diseases and conditions that affect glycaemic homeostasis should be appropriately addressed, and DM management should be adjusted accordingly. Examples of concurrent diseases include chronic pancreatitis, hyperthyroidism (HT), hypersomatotropism, and various medical conditions requiring corticosteroid therapy (Crenshaw and Peterson, 1996, Goossens et al., 1998, Scott-Moncrieff, 2010, Niessen et al., 2013).

DM management aims to minimise clinical signs and prevent complications associated with the disease and its treatment, such as diabetic ketoacidosis or hypoglycaemic episodes due to insulin overdose (Sparkes et al., 2015, Behrend et al., 2018, Niessen, 2022). Additionally, the quality of life (QoL) of both the cat and the owner is increasingly recognised as a key consideration (Niessen et al., 2010, Sparkes et al., 2015, Hazuchova et al., 2018), emphasising the owner's role in disease management. When determining an appropriate treatment strategy, the benefits of tight glycaemic control must be weighed against the demands placed on the owner, short and long-term, and the risk of complications. Owners’ capabilities, engagement, and perceptions of good animal husbandry may shape treatment goals and influence the management plan considered appropriate for each individual

owner (Sparkes et al., 2015). Customised owner education and proper involvement of the veterinary team is important for owner compliance and confidence (Albuquerque et al., 2019). Although detailed management advice exists (Sparkes et al., 2015, Behrend et al., 2018), all care plans must be adapted to the individual cat and owner. Allowing owners to choose between different care options, taking into account both their own circumstances and the cat's needs, is a key aspect of management.

1.3.1 Insulin treatment and disease monitoring

Due to its impact on glucose homeostasis, exogenous insulin treatment is considered an effective and widely accepted treatment for glycaemic control. Insulin is usually administered subcutaneously twice daily using insulin pens or multi-dose vials and syringes, and longer-acting preparations like insulin glargine, insulin detemir, and protamine zinc insulin are recommended (Behrend et al., 2018). In monitoring a cat with DM, an important aspect to consider is the presence or absence of clinical signs (Bennett, 2002). Keeping a diary that records general demeanour, water intake, appetite, urination, and weight can be helpful, especially if combined with information on insulin administration and glucose measurements.

Home blood glucose monitoring (HBGM) may serve as an important part of successful management (Roomp and Rand, 2009, Roomp and Rand, 2012). Even if representing a technical and financial challenge, especially initially (Hazuchova et al., 2018), being able to perform HBGM may enhance the owner's sense of control and, consequently, positively affect their QoL (Niessen et al., 2010). Because of substantial day-to-day variation (Reusch et al., 2006, Alt et al., 2007), single BG measurements should not be used to evaluate treatment response, but rather to detect hypoglycaemia, establish nadir (the lowest point in BG concentrations), and prevent unnecessary insulin administration. Commonly, BG is measured at home using a handheld glucometer and test strips, along with fine needles, such as insulin syringes or lancets (Figure 1). Capillary blood is typically sampled from the ear veins, but the paw pads can also be pricked.

For owners who cannot or do not wish to use a glucometer, or for cats who do not tolerate this type of handling, continuous glucose monitoring systems may offer an alternative method (Del Baldo et al., 2021, Re et al., 2023).

Figure 1. Blood glucose measurement by handheld glucometer and subcutaneous insulin injection in a cat with diabetes mellitus. Photo: Raymond Engmark

Although representing a more blunt measurement and not an adequate indicator of glycaemic control (Aldridge et al., 2020), urine testing can be more convenient and less expensive to use to detect trends in BG, including indications of diabetic remission.

1.3.2 Diet and lifestyle interventions

Diet plays a major role in management of DM in cats. Goals of dietary intervention include achieving an optimal body condition to reduce insulin resistance and optimising nutrient composition to support glycaemic control (Sparkes et al., 2015, Behrend et al., 2018) . Although weight loss is a consequence of untreated DM, the common weight problem in cats diagnosed with DM is overweight or obesity. As obesity is linked to insulin resistance (Hoenig et al., 2013), the nutritional profile of DM diets should ideally also be suitable for obesity management. If concomitant diseases that profit from nutritional management are present, alternative feeding plans may be required (Villaverde and Hervera, 2025).

Considering the deteriorating effects of chronic hyperglycaemia on β-cell function (Zini et al., 2009), it is important to efficiently manage glucotoxicity. As obligate carnivores, cats naturally predominantly consume prey (e.g., small mammals or birds), and their metabolic and digestive physiology reflects evolutionary adaptation to a protein-rich, low-carbohydrate diet (Plantinga et al., 2011). Although capable of digesting carbohydrates, cats metabolise them less efficiently than other species, with both carbohydrate type and quantity influencing postprandial BG (Appleton

et al., 2004, de-Oliveira et al., 2008). Compared to dogs, cats exhibit slower plasma glucose clearance after carbohydrate ingestion (Hewson-Hughes et al., 2011), and carbohydrate-rich diets results in higher postprandial glucose concentrations in healthy cats compared to diets high in protein or fat (Farrow 2013). In addition to species-specific metabolism, slower gastric emptying may contribute to prolonged glucose clearance after meals or glucose loads (Coradini et al., 2015). Current feeding recommendations suggest a carbohydrate intake of ≤12% of metabolisable energy (ME) or 3g/100 kcal (Sparkes et al., 2015, Behrend et al., 2018), and some advocate for even lower levels (Gottlieb and Rand, 2013). High dietary protein is also recommended to maintain muscle mass and enhance satiety (Laflamme and Hannah, 2005, Behrend et al., 2018).

Wet or canned food may be preferable to dry kibble, as its higher water content can improve satiety and dilute caloric intake (Wei et al., 2011), and it generally contains less carbohydrates. However, not all cats tolerate dietary changes, and individual food preferences must be considered. Owner non-adherence to prescribed feeding protocols has been reported as a perceived compliance issue by veterinarians (Niessen et al., 2017), and treat restriction may be perceived by owners as negatively affecting the human–animal bond (Nielson et al., 2024). Alongside nutritional adjustments intended to optimise body condition, increased physical activity is typically encouraged (German, 2006).

1.3.3 Oral hypoglycaemic drugs

Oral hypoglycaemic agents have been explored as a treatment option for cats with DM. Glipizide, a second generation sulfonylureas, stimulates pancreatic insulin release, an action that requires sufficient functional capacity of β-cells (Palm and Feldman, 2013). It has been used successfully in some cats with DM (Nelson et al., 1993, Feldman et al., 1997); however, since it cannot be ruled out that treatment may contribute to deterioration of β-cell function through amyloid deposition (Hoenig et al., 2000), its use is mostly restricted to cases where insulin therapy is not feasible (Sparkes et al., 2015). In Sweden, the marketing authorization for glipizide was withdrawn in 2021.

Sodium-glucose cotransporter 2 (SGLT-2) inhibitors are novel agents for treatment of hyperglycaemia in cats with non–insulin-dependent DM, exerting their effect by promoting renal glucose excretion (Hoenig et al., 2018). The SGLT-2 inhibitor velagliflozin was approved in Sweden in 2023,

i.e., after data collection for the studies included in this thesis had been completed and is therefore not discussed further here.

Biguanides (metformin) increases insulin sensitivity in peripheral tissues and inhibits hepatic glucose production and is widely used in treatment of DM in humans, but seem to be of limited use in cats (Nelson et al., 2004). Other oral drugs, including those targeting insulin sensitivity and lipid metabolism (Clark et al., 2014) and metabolic pathways of BG regulation (Riederer et al., 2016) either lack efficacy in cats or have not yet been sufficiently studied.

1.4 Disease outcomes

1.4.1 Diabetic remission

If pancreatic β-cells regain their ability to secrete insulin and sustain glucose homeostasis, alongside resolution of peripheral insulin resistance, diabetic remission may occur (Scott-Moncrieff, 2010). For the individual cat, this means a periodic or life-long recovery from clinical signs of DM, without requiring exogenous hypoglycaemic treatment to maintain glycaemic homeostasis. For the owner, remission can considerably reduce the burden of daily DM management, allowing for less rigid routines and a freer, more flexible lifestyle. As a result of reported high proportions of cats achieving an insulin-independent state of DM, and because of the great benefits for both cats and owners, remission is nowadays considered a treatment goal in itself by many, especially in newly diagnosed cats (Gottlieb and Rand, 2018).

Remission rates have typically been reported to vary between 15–60% (Boari et al., 2008, Hall et al., 2009, Marshall et al., 2009, Roomp and Rand, 2009, Hoelmkjaer et al., 2015, Zini et al., 2018, Gottlieb et al., 2024), with even higher rates in small sub-groups of cats using an intensive treatment protocol (Marshall et al., 2009, Roomp and Rand, 2009). Previous treatment with corticosteroids (Roomp and Rand, 2009, Gottlieb et al., 2024), early institution of glycaemic control, and older cat age have been positively associated with remission, whereas factors related to disease progress and poor glycaemic control have been associated with decreased remission rates (Roomp and Rand, 2009, Zini et al., 2009, Zini et al., 2010). Cat characteristics, specifics of DM, and the efficacy of different management protocols, have been studied in relation to remission (Nelson et al., 2001,

Mazzaferro et al., 2003, Bennett et al., 2006, Weaver et al., 2006, Marshall et al., 2009, Roomp and Rand, 2009, Roomp and Rand, 2012). However, considerate differences between studies, including study design and varying criteria for DM diagnosis and remission, makes it difficult to establish factors that may predict remission (Gostelow et al., 2014).

Because reversal of glucotoxicity is thought to be one of the main attributes behind diabetic remission in cats (Zini et al., 2010), it is generally recommended that hypoglycaemic treatment is promptly initiated following DM diagnosis. Even after achieving remission, many cats have an impaired glucose tolerance compared to healthy cats (Gottlieb et al., 2015), and to avoid relapse from remission it is recommended to keep the cat on a DM-appropriate diet, maintain healthy body condition and avoid glucocorticoid treatment. Relapse occurs in about 25–40%, resulting in overt DM that requires resumed hypoglycaemic treatment (Nelson et al., 1999, Bennett et al., 2006, Zini et al., 2010, Gottlieb et al., 2015, Gottlieb et al., 2024). Though not well studied, a second remission seems uncommon, although not impossible (Roomp and Rand, 2009).

For cats that do not achieve remission, or in most cats that relapse from remission, hypoglycaemic treatment is lifelong. As prognostic factors remain uncertain, it is difficult to predict whether a cat will achieve remission. Upon DM diagnosis, the owner must therefore consider whether a potentially lifelong insulin treatment and the associated lifestyle adjustments are feasible and acceptable.

Not all management strategies are suitable for every cat–owner pair, and the risk of insulin-induced hypoglycaemia should not be overlooked in more intensive treatment protocols that aim for tighter glycaemic control (Roomp and Rand, 2009).

1.4.2 Survival time and mortality

Reported median survival times for diabetic cats vary widely across studies, reflecting differences in study populations, management strategies, and follow-up periods. Older studies report median survival times of 17–29 months (Kraus et al., 1997, Goossens et al., 1998, Callegari et al., 2013), and more recently, 26 months (Gottlieb et al., 2024). Survival times have also been reported as approximately 60%–80% of cats still alive more than 1 year, 30%–40% still alive more than 3 years and 10% more than 5 years after diagnosis. Presence of concurrent diseases, remission and glycaemic control

have been associated with survival time (Goossens et al., 1998, Callegari et al., 2013, Gottlieb et al., 2024).
About 6%–17% of cats are euthanised shortly after a DM diagnosis and 35%–40% are euthanised within the first year (Kraus et al., 1997, Goossens et al., 1998, Callegari et al., 2013, Niessen et al., 2017, Gottlieb et al., 2024). These outcomes have been linked to the disease itself, its complications, or to concurrent conditions (Callegari et al., 2013, Niessen et al., 2017, Gottlieb et al., 2024), but the specific reasons for euthanasia among owners have not been extensively studied. In one study, veterinarians estimated that owners chose to euthanise their cat at the time of diagnosis or discontinued treatment in approximately one out of ten cases. Contributing factors included concurrent diseases, perceived treatment failure, the age of the cat, and financial constraints. Demographic and contextual factors, such as practice type and owner perceptions, were also reported to influence the proportion of euthanasia cases (Niessen et al., 2017).

In addition, several aspects of how medical treatment and management negatively affect owner QoL have been identified, mostly including items with an impact on the owner's lifestyle (Niessen et al., 2010), and it is possible that these factors also influence decisions regarding euthanasia.

1.4.3 Cat and owner wellbeing

There is a growing recognition of the need to move beyond purely clinical measures when assessing disease outcomes. This may be related to the medical advances and the on-going discussion of ethical medical care in veterinary medicine (Rollin, 2007, Moore, 2011, Mullan, 2012, Grimm et al., 2018). A more comprehensive understanding of health and medical care that also incorporates the lived experiences of the animal is encouraged (Niessen, 2011), and concepts such as QoL, emotional wellbeing, happiness, and the relational aspects of care are gaining attention in research and clinical decision-making (McMillan, 2000, Belshaw, 2018, Britton et al., 2018). Although commonly used and widely understood in general terms, there is no single agreed-upon definition of QoL in animals. As a concept, QoL encompasses not only physical health but also other broader, subjective, and often contextual-dependent aspects of life (McMillan, 2000).

Within feline medicine, QoL is increasingly being included in assessment of the benefits and burdens of medical interventions (Tzannes et al., 2008, Niessen et al., 2010, Reynolds et al., 2010, Zamprogno et al., 2010, Freeman

et al., 2012, Bijsmans et al., 2016, Noble et al., 2019, Noli, 2019). Regarding DM in cats, recognising the impact of the disease and its treatment on the owner, the cat, and the bond between the two is essential for successful disease management (Niessen et al., 2010). As it is ultimately the owner who makes decisions regarding their cat's care, satisfaction with the chosen treatment and its compatibility with the owner's lifestyle are important considerations. The perceived challenges and a sense of being overwhelmed by DM management may be substantial, possibly reflected in a recent study where nearly two-thirds of cats euthanised within three days of diagnosis had not received any treatment (Waite et al., 2025).

Owners are concerned about the pet's QoL, and their perceptions of QoL are important in decisions regarding treatment initiation and euthanasia (Slater et al., 1996, Christiansen et al., 2015). Regarding DM, the QoL of the animal was the most important aspect considered for both owners and veterinary clinicians, according to veterinarians (Niessen et al., 2017). Other studies have shown that owners are willing to trade longevity for preserved QoL in cats with cardiac disease (Reynolds et al., 2010), and that owners' satisfaction with lymphoma treatment is closely linked to perceived cat wellbeing during therapy, with key indicators for QoL including appetite, gastrointestinal health, and playfulness (Tzannes et al., 2008).

Recognising the interrelationship between owner and cat, a specific tool has been designed to evaluate the impact of DM on the QoL of cats and their owners (Niessen et al., 2010), allowing for more specific monitoring of both. Many owners of diabetic cats reported that the factors most strongly associated with a negative impact on their QoL were related to the demands placed on them, rather than to concerns about the cat. These included lifestyle restrictions imposed by treatment, such as difficulty finding suitable caregivers during holidays, and disruptions to social and family life. This was also reflected in how owners perceived insulin administration, where the negative impact was more often attributed to the ongoing commitment required than to practical or cat-related challenges. Including the owner's experience of how QoL is affected is important, as veterinarians may hold differing views on the main challenges of treatment (Niessen et al., 2017).

1.5 Assessment of the cat

Although the disease itself and the demands of ongoing management may affect the emotional and physical state of the cat, information on how DM affects wellbeing and the lived experience of the cat is limited. Poor glycaemic control can cause discomfort; and repeated veterinary visits, dietary modifications, and procedures such as blood sampling may be perceived as aversive. Additionally, disruptions to established routines, including increased owner attentiveness or altered interactions with other household cats, may influence the cat–owner relationship and contribute to inter-cat conflict (Amat et al., 2016, Ramos, 2019).

One built-in problem with assessment of welfare in companion animals, including QoL, is that assessments rely on interpretations of certain behaviours and clinical features, with foremost owners, but also veterinarians, acting as proxy informants for the individual cat (Kessler and Turner, 1997, Belshaw, 2018). Proxies may differ in their perceptions of wellbeing, in what they consider to be priorities or concerns, and in their tolerance for interventions (Bijsmans et al., 2016). Many owners form strong bonds with their cats and commonly ascribe them human emotions, such as behavioural responses and cognitive abilities (Morris et al., 2008). Although it has been argued that anthropomorphism may be central to the formation of relationships between humans and companion animals (Serpell, 2002), this tendency to attribute human characteristics to animals have been raised as a concern, as it contribute to owners inaccurately reporting their cat's QoL (Bradshaw and Casey, 2007). Over- or under-estimating the animal's experiences and abilities could lead to a discrepancy between a third party's assessment of an animal's QoL and the factors that are truly meaningful or impactful for the cat (Sands et al., 2004, Thornton et al., 2018).

1.5.1 Stress as an indicator of reduced cat wellbeing

Stress commonly refers to the physiological and behavioural responses caused by aversive or unpleasant stimuli, and through its association with anxiety, pain, fear, and other states of affective discomfort, stress can be an important part of an animal's wellbeing (Moberg, 2000). In the context of health and disease, stress can be defined by the presence of different events that activate a stress response, or the stress response system (Möstl and Palme, 2002). Stress is a normal part of life, and necessary for survival and health. When non-threatening, stress responses can be positive for the

individual and a normal part of development. However, if the animal lacks the ability to predict, cope, or control a stressful situation, the stress response is negative and may affect wellbeing (Koolhaas et al., 1999, McMillan, 2000). Stress can be differentiated as acute or chronic, depending on its duration (Moberg, 2000). The response may have an additive effect, with the overall stress response increasing with the number of stressors (Schreck, 2000), and sustained, or chronic, exposure to a stressor can lead to an increased sensitivity to other novel stressors (Sakellaris and Verniklos-Daneillis, 1975).

Cats may experience stress due to a variety of causes, including environmental changes, department from established routines, approach by unfamiliar humans or other animals, and unpredictability in human handling (Carlstead et al., 1993, Stella et al., 2013, Mariti et al., 2016, Quimby et al., 2017). A key factor influencing their response to an adverse stimulus appears to be the extent to which that stimulus is perceived as predictable and controllable (Carlstead et al., 1993, Koolhaas et al., 2011), and unpredictability or a reduced ability to cope may contribute to chronic stress (Griffin, 2011). How the individual cat responds to stress depends on its temperament and prior socialisation and experiences (Kessler and Turner, 1997, Amat et al., 2016).

The stress response

The stress response system is complex, and activation encompasses a coordinated response including various body systems, with changes in physiology, behaviour, and the neuroendocrine system.

The main physiological mechanisms involve the hypothalamic-pituitary-adrenocortical (HPA) axis and the sympatho-adreno-medullary system. Activation of these systems triggers a cascade of hormonal responses that have physiological and adaptive effects; the latter system including catecholamine release and immediate changes in cardiovascular function, respiration, and blood pressure, commonly known as the fight-or-flight response (Sjaastad et al., 2010). In the HPA axis, also known as the stress axis, the main active hormone in cats is cortisol, a corticosteroid secreted by the adrenal cortex by a hormonal signalling pathway originating from the hypothalamus. Cortisol mediates a negative feedback control, inhibiting axis activity on several levels (Mormède et al., 2007). See Figure 2 for a schematic overview of the HPA axis. Glucocorticoids exerts their activity by a number of mechanisms, affecting metabolism, reproductive function, and

immunological responses. One preeminent effect is to mobilise energy substrates and increase circulating BG concentrations, ensuring that skeletal muscles and the brain get the energy they need to cope with the perceived threat (Sapolsky et al., 2000). The activity of the HPA axis varies both between and within species and different biological, genetic, and environmental factors contribute to this variability (Moberg, 1987, Mormède et al., 2007).

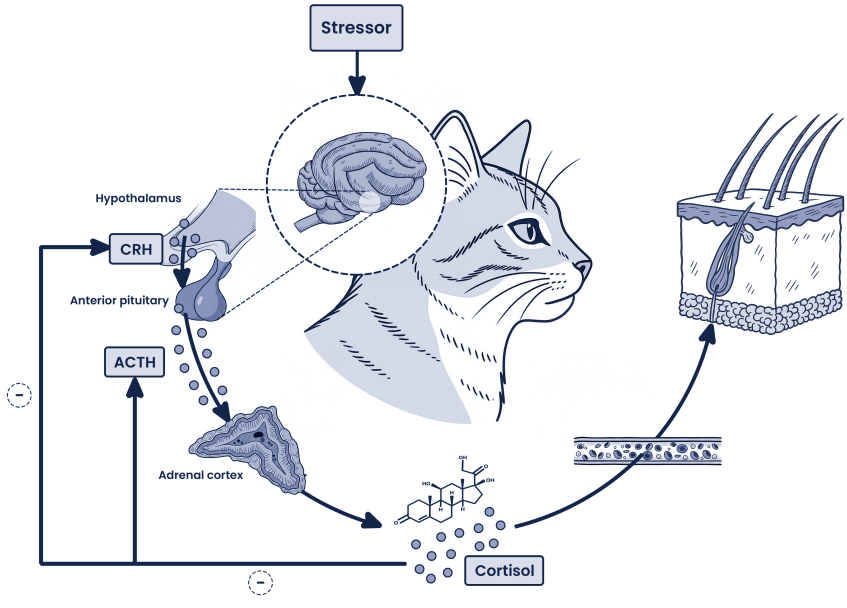

Figure 2. Schematic overview of the HPA axis and incorporation of cortisol into the growing hair. Illustration: Alexander Flodin.

Behavioural changes may serve as coping strategies to reduce the adverse impact of a stressor or may result from hormonal alterations triggered by activation of the stress response system (Carr, 2002, Rochlitz, 2013). These changes include withdrawal or hiding, attempts to avoid the stressor through escape, reduced playfulness, altered interaction patterns with humans or other animals, or displays of aggressive behaviour (Armstrong and Blanchard, 2009, Rochlitz, 2013) and development of compulsive behaviours (Luescher, 2003). However, behavioural changes may be challenging for owners to recognise, particularly when the cat exhibits inhibitory responses such as withdrawal or reduced activity (Amat et al.,

2016) or displays behaviours that owners may interpret as typical for the species, such as avoiding other animals, given the common perception of cats as non-social (Mariti et al., 2017).

Measurement of stress

Although measuring stress holds great potential for assessing animal wellbeing (Moberg, 1987), the complex nature of the stress response entails that no single tool for evaluating all aspects of stress exists. It has been suggested that the best assessment is made indirectly, by using both behavioural and physiological data (McCobb et al., 2005). As the HPA axis is central in stressor responses, studies on circulating cortisol concentrations represent a common approach to assessment of the stress response system. In cats, studies assessing cortisol concentrations and behavioural valuation of stress show conflicting results. Behavioural assessment of stress have been reported to correlate with urinary cortisol concentrations (Carlstead et al., 1993, Rochlitz et al., 1998), whereas other studies assessing stress linked behaviours and urinary cortisol (McCobb et al., 2005) and serum cortisol (Stella et al., 2013) failed to demonstrate such an association. These discrepancies may reflect differences in environmental conditions, individual coping mechanisms, and methodological aspects.

Cortisol can be quantified from various biological material, differing in cortisol metabolism, sampling requirements, and the time span reflected. For measurements of momentary circulating cortisol, serum or plasma is suitable, although the effects of temporary fluctuations due to sample-associated handling and stress must be considered (Carlstead et al., 1993). For more long-term and peak-less assessments, urine or faeces can be used (Carlstead et al., 1993, Schatz and Palme, 2001). As a higher proportion of cortisol is excreted in faeces than in urine, and considering the less invasive nature of sample collection, faecal cortisol concentrations may be more suitable than urine for assessment of circulating cortisol concentrations in the preceding approximate 24 hours. For a long-term assessment, cortisol quantified from hair represents a non-invasive method that has been increasingly studied and applied for HPA axis assessment over the last two decades (Koren et al., 2002, Davenport et al., 2006, Accorsi et al., 2008, Meyer et al., 2014).

Hair cortisol concentrations

During active hair growth, cortisol is continuously incorporated into the shaft, likely via passive diffusion from the bloodstream (Figure 2), although the exact mechanism remains unclear (Meyer and Novak, 2012). As incorporation occurs throughout the growth period, hair cortisol concentrations (HCC) reflect integrated systemic levels over weeks to months (Stalder et al., 2012), reducing the influence of short-term fluctuations and sampling-induced changes.

Our understanding of HCC has limitations, and recognising them is essential, particularly when evaluating animal welfare and stress. It is not yet clear whether hair cortisol derives solely from systemic circulation or is partly produced locally in the follicle (Ito et al., 2005, Stalder and Kirschbaum, 2012, Sergiel et al., 2020), and whether external contaminations from sweat or sebum may influence results (Salaberger et al., 2016). Further, HCC are thought to be influenced by factors related to both hair physiology and growth patterns, including body region (Terwissen, 2013, Burnard et al., 2017), hair colour (Yamanashi and Misato; Suzuki, 2013, Burnett et al., 2014), and season of the year (Bacci et al., 2014, Roth et al., 2016). Alterations in HCC have also been reported with younger age, pregnancy, and lactation, while the effects of sex appear to be inconsistent. Species-specific variations in behaviour, shedding cycles and environmental conditions point to the need to study HCC in each species (Heimbürge et al., 2019). HCC have been associated with a wide array or stressors and medical disorders in various species (Davenport et al., 2006, Comin et al., 2013, Cattet, 2014, Burnett et al., 2015, Qin et al., 2015, Stubsjøen et al., 2015, Roth et al., 2016).

Until recently, HCC in domestic cats has primarily been investigated in free-roaming and shelter populations, using varying hair sampling methods (Accorsi et al., 2008, Finkler and Terkel, 2010, Galuppi et al., 2013). In these populations, neutering status, social dominance, and behaviour were linked to HCC. More recently, studies in owned domestic cats have linked increased HCC to behaviours typically associated with stress, such as elimination outside the litterbox and owner-directed aggression (Contreras et al., 2021, Wojtaś, 2023). Regarding disease, higher HCC have been reported in shelter cats with dermatophyte infections (Galuppi et al., 2013), and in owned cats in later stages of chronic kidney disease (CKD) (Kim et al., 2025). While HCC was initially associated with owner-reported chronic disease (Contreras

et al., 2021), this association was no longer significant after adjustment for additional variables, perhaps reflecting the complexity of the relationship between the feline stress response and behaviour. However, poor coat condition was associated with elevated HCC, and as coat condition has been linked to stress (Arhant, 2015) and to chronic disorders such as HT and DM (Greco, 2001, Carney et al., 2016, Vogelnest, 2017), this may reflect the influence of illness on feline behaviour and overall wellbeing.

1.6 Clinical decisions and their implications

Successful management of DM depends on the owner's ability and willingness to carry out treatment and sustain it over time, and few other diseases entail such a degree of responsibility on the owner in their own home. Cats often occupy a central place in human households and are frequently regarded as family members (Endenburg and Vorstenbosch, 1992, McConnell et al., 2019, Bouma et al., 2021). The strong bond owners may form with their cats can lead to considerable emotional investment if the cat becomes ill. Veterinary practice has evolved alongside this human–animal bond, and the changed view of companion animals has been suggested as partly responsible for owners' willingness to pursue extensive measures for their animals' health (Knesl et al., 2016). Owners with a stronger bond to their pet have been shown to be more likely to seek higher levels of veterinary care compared to owners with a weaker bond (Lue et al., 2008).

According to Swedish law (SFS 2018:1192), animals are legal properties of the owner, and it is the owner´s responsibility to save the animal from unnecessary harm. Within the limits of legislation, it is the owner who makes the decision on treatment initiation or continuation and euthanasia. Caring for a pet with DM may bring positive aspects, such as increased interactions and a perceived strengthening of the relationship (Niessen et al., 2010, Aptekmann et al., 2014). However, distress and challenges, emotional, practical and financial, are also reported by owners of chronically ill animals, where impaired psychosocial functioning, reduced QoL, depression and anxiety are increasingly recognised in the concept of caregiver burden (Spitznagel et al., 2017). Recognising this, alongside aspects of protecting cat welfare, veterinary care takes place within a complex relationship between the veterinarian, the owner, and the cat (Rosoff et al., 2018). Although the veterinary profession is focused on the wellbeing and care of

the animal, the owner is also deeply integrated in veterinary responsibilities (Rollin, 2006, Morgan and McDonald, 2007).

One important cause of friction is that owners and veterinarians may hold differing fundamental beliefs about our responsibilities toward animals, including the moral importance of animals, and what is believed to be in the animals' best interest (Endenburg and Vorstenbosch, 1992, Morgan and McDonald, 2007). Consequently, what one sees as appropriate care or action may not align with another's view. Differing views on what constitutes the best way forward in the clinical situation, and balancing the responsibilities of many, has been described as one of the greatest challenges in veterinary medicine (Rollin, 2013). Commonly encountered ethical issues in small animal practice include euthanasia due to financial inability or unwillingness to continue treatment, situations where care is compromised by limited owner finances leading to the need for empirical therapeutic trials instead of diagnostics (Kipperman et al., 2018), and cases where the owner wishes to pursue treatment despite it being in conflict with the welfare of the animal (Morgan, 2009, Batchelor and McKeegan, 2012). When not resolved satisfactorily, such challenges may contribute to moral stress, and concerns have been raised about their role in poor veterinary mental health (Cohen, 2007, Rollin, 2011, Batchelor and McKeegan, 2012, Kipperman et al., 2018).

Communication between veterinarians and owners is a key aspect of clinical practice. How information is delivered, and how owners are engaged in the process, shapes their participation in decision-making and their capacity to manage the animal's condition (Cornell and Kopcha, 2007). Communication styles are largely determined by how the relationship between the veterinary practitioner and the owner is conceptualised, and approaches have been shown to vary between consultations. In a paternalistic approach, the veterinarian takes the active role, making decisions based on medical judgment and assuming that moral values align with those of the owner (Shaw et al., 2006). A shared model is more collaborative, with veterinarian and owner contributing equally to decisions, balancing medical recommendations with the owner's preferences and circumstances (Charles et al., 1999), whereas in the informed approach, the veterinarian acts as a teacher, providing requested information, while the owner decides independently (Cornell and Kopcha, 2007). Although the paternalistic model remains prevalent (Bard et al., 2017), there is an expressed wish to move

away from hierarchical approaches towards more relationship-centred models of communication (Board, 2015).

2. Aims

Diabetes mellitus (DM) is a common endocrine disease in cats, and the complexity in its management provides an outlet for different aspects related to clinical outcomes, disease management, and ethical considerations. By including aspects related to the cat, the owner, and the veterinarian, the overall aim of this thesis is to broaden the understanding of DM in cats and contribute to improved clinical management.

The specific objectives are:

- Investigate disease outcome for cats with DM, and the impact that DM has on the life situation of owner and cat;
- Explore owner experiences of initiating and sustaining DM treatment;
- Explore veterinary considerations in managing cats with DM;
- Evaluate a low-stress sampling method for assessment of cortisol concentrations in cat hair, and relate hair cortisol concentrations to cat characteristics, health status, and stress.

3. Comments on materials and methods

In this section, an overview of the materials and methods used in the included four papers are presented. For more detailed information, see respective papers. All statistical analyses were performed using the statistical software-program R Studio (2022).

3.1 Evaluation of disease outcomes (Paper I)

In this cross-sectional retrospective questionnaire study, we investigated disease outcomes in cats diagnosed with DM.

3.1.1 Study sample and questionnaire

Data were obtained from the Agria Pet Insurance database. All insured cats with a DM diagnosis during a five year period (2009–2013) were included (n =1369). At the time the study was conducted, approximately a third (36%) of all cats in Sweden were insured. The Agria Pet Insurance was market-leading and validated for research purposes (Egenvall et al., 1998).

The questionnaire was digitally available for participating owners though an online provider (Netigate). It included questions on the cat and its characteristics, and vaccination status as an indicator for the level of care provided by the owner. The cat's age at diagnosis and at death was standardised to January 1st of the respective years. Initial survival was defined as the cat living more than four weeks post-diagnosis. Survival time was estimated from December 31st of the DM diagnosis year to January 1st of the year of death. Treatment-related questions included whether the cat received insulin, use of oral glucose-lowering medication, special diet, hospitalisation, or no specific treatment. Additional results from the questionnaire are reported elsewhere (Öhlund et al., 2017).

3.1.2 Disease outcomes and data analysis

The disease outcomes examined included initial survival (defined as survival beyond four weeks following DM diagnosis); survival time (expressed in years as a minimum estimate); achievement of remission, with or without subsequent relapse; and the cat's QoL. Four logistic regression models were applied for categorical outcomes, while one linear regression model was used to assess survival time as a continuous variable. Final model selection was based on a backward elimination approach, guided by a reduced Akaike Information Criterion (AIC), to help determine the best-fitting model. To quantify the strength between variables and disease outcomes in the final regression models, odds ratios (OR) were calculated. Potential interactions between variables were examined and included where relevant. Possible confounders were identified and controlled for within each regression model

3.2 Qualitative exploration of individuals' experiences and perceptions (Papers II and III)

In Papers II and III, the experiences and considerations of owners to cats treated for DM, and veterinarians who manage cats with DM, were explored using a qualitative research approach with in-depth interviews.

3.2.1 Participants and interviews

Individual qualitative interviews were chosen for data collection, as they are appropriate for exploring lived experiences and understanding social issues (Dicicco-Bloom and Crabtree, 2006). Due to its flexibility in questioning and follow-up, a semi-structured approach was applied, gaining deeper insight into participants' reasoning and the opportunity to request clarifications or examples of specific situations (Kvale and Brinkmann, 2009). The interviews followed a pre-determined interview guide, and were conducted in Swedish, the majority through a digital video conference program (Zoom). They were recorded to enable later transcription.

Participants were recruited through a combination of purposive and convenience sampling. Invitations were distributed in one Facebook group targeting cat owners and two Facebook groups targeting veterinarians. Some individuals were approached directly. Selection criteria for cat owners included residency in Sweden, and current or past ownership of one or more cats diagnosed with DM; and for veterinarians, having experience of cats

diagnosed with DM. The inclusion criteria were intentionally kept broad (Kristensen and Ravn, 2015).

Two pilot interviews were conducted in each group, and reviewed to assess question clarity, relevance, and participant engagement with the topic. The interview guide was adjusted accordingly. To determine and evaluate the number of interviews needed, data collection and the information obtained were assessed continuously and prospectively. This process was determined by the research questions of the studies, and was guided by the concept of information power (Malterud K, 2016) and Braun and Clarke's reflections on data collection within reflexive thematic analysis (RTA) (Braun and Clarke, 2021). In both Paper II and III, an initial set of interviews was conducted consecutively. During these, field notes were taken to review the quality of the data and the variety of participants' experiences and subsequent interviews were determined in relation to these, which helped inform the decision on participant selection and when to conclude data collection. To reduce the risk of earlier data influencing later interviews, transcription and coding were postponed until all interviews were completed. When the data was assessed as sufficiently rich, two additional owner interviews and one veterinarian interview were conducted to reduce the risk of stopping data collection too early. Data collection was concluded after twelve interviews with owners and ten interviews with veterinarians.

3.2.2 Theoretical framework and analytical process

Thematic analysis is a method used within the qualitative research paradigm to systematically identify and interpret patterns within a dataset. A reflexive approach to TA acknowledges the researcher's subjectivity as a valuable resource and recognises the influence of the researcher on both data collection and analysis (Braun and Clarke, 2019, Braun and Clarke, 2022a), thereby enriching and deepening the analytical process (Finlay, 2021). Considering the research questions and aiming to incorporate the experiences and knowledge of the author into the process, RTA was chosen as the analytical method.

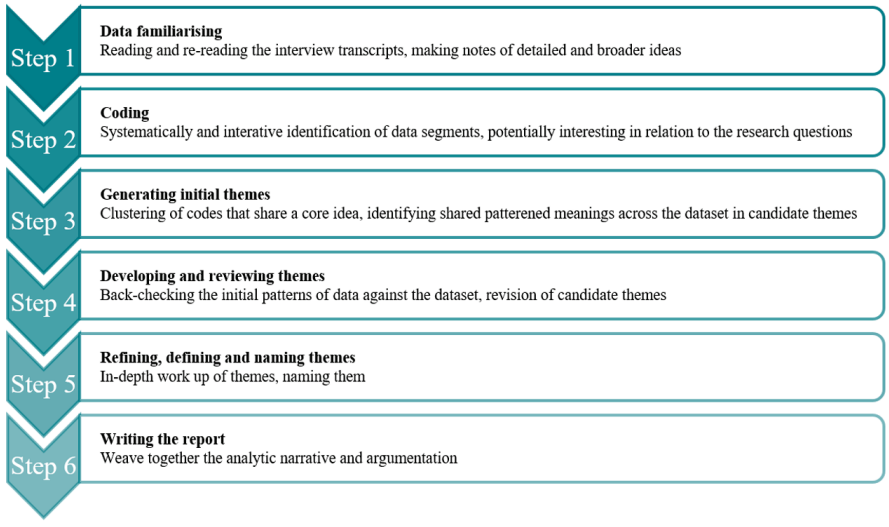

Figure 3. Overview of the analytical process of reflexive thematic analysis. Note that the process is not strictly linear, and that former steps are continuously revisited during the analytical process.

The analytical processes were underpinned by constructionist theoretical framework with an experiential approach. This means that the researcher explores how people interpret and give meaning to their experiences, acknowledging that these meanings are shaped by their social and personal contexts (Braun and Clarke, 2022b). Following Braun & Clarke (Braun and Clarke, 2006, Braun and Clarke, 2019), a six-phase RTA process was undertaken. First, the transcripts were reviewed in depth, followed by an iterative coding process at both semantic and interpretive levels. Candidate themes were developed by clustering related and meaning-sharing codes and were continuously refined through comparison with original data to ensure accurate representation. Theme construction was consultative with regular discussions in the research group to discuss interpretations and findings. See Figure 3 for an overview of the analytical process.

3.3 Assessment of HPA axis activity (Paper IV)

This study investigated cortisol concentrations in hair (HCC), and evaluated the use of HCC in assessment of long-term stress in healthy cats and cats

with chronic disease. In addition, it investigated a minimally invasive method of hair sampling for HCC analysis.

3.3.1 Study sample and questionnaire

Privately owned cats were recruited either through personal contacts or during visits to one of four small animal veterinary clinics, including two referral clinics and two smaller general practices. Based on previous research on effects of sex and reproductive activity on measured cortisol in cats (Finkler and Terkel, 2010, Franchini et al., 2019, Alekseeva et al., 2020), the study strived to include both neutered and intact cats of both sexes. In Sweden, most cats are neutered at a young age unless intended for breeding. Consequently, the subset of intact cats was sampled at the time of neutering, and younger compared to the cats with chronic diseases.

A questionnaire was developed based on existing literature on feline stress and owner involvement in assessment (Carlstead et al., 1993, Heath, 2007, Amat, 2009, Amat et al., 2016, Deborah L. Duffy, 2017, Mariti et al., 2017). Most questions were retrospective, related to 2–16 weeks before hair sampling. Comprehensibility was pilot-tested with four cat owners not involved in the study, and revisions were made accordingly. The final questionnaire was distributed digitally, by e-mail, or by post when email addresses were unavailable. Questions included the cat's sex, age at hair sampling, and hair characteristics (e.g., coat colour). Stress assessment was based on owner-reported exposure to potential stressors and observed behavioural signs. For cats with chronic disease, clinical signs were recorded to evaluate disease impact. Cats receiving corticosteroid treatment were excluded from the study.

3.3.2 Hair sampling

Hair was sampled once per cat during June 2020 and November 2022. Each cat provided at least one hair sample, collected by either mechanical clipping (dorsal front leg or caudoventral abdomen) or combing (dorsal and lateral body using a fine-toothed clean comb). Combing was included as a novel non-invasive sampling procedure with potential to further reduce stress during sampling. Sampling was performed during veterinary visits or by owners at home (combing only). Clipping sites were chosen based on routine clinical procedures to avoid unnecessary shaving. For sampling locations and methods, see Figure 4. After collection, all hair samples were wrapped in

aluminium foil and stored at room temperature in a dark, dry environment at a maximum time of seven months, until cortisol analysis.

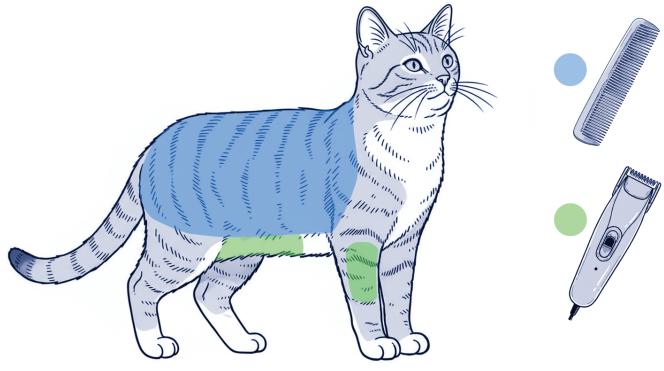

Figure 4. Hair sampling locations and sampling methods (comb or mechanical clippers) for analysis of HCC. Illustration: Alexander Flodin.

3.3.3 Hair preparation and cortisol extraction

Based on previously reported hair growth rates in domestic cats (Baker, 1974, Hendriks et al., 1997), longer hair samples were trimmed to approximately 40 mm in length when possible, roughly corresponding to 16 weeks of growth and thereby representing the retrospective time period of interest. Cortisol extraction from hair was performed using a protocol partly adapted from Meyer et al. (Meyer et al., 2014).

Hair cortisol was quantified using a commercial competitive high-sensitivity ELISA kit (Salimetrics® Salivary Cortisol Enzyme Immunoassay Kit, LCC 2021), and converted to pg/mg hair (Meyer et al., 2014). To evaluate assay performance, mean within-assay and between-assay coefficients of variation (CV) were calculated, based on instructions from the manufacturer. To evaluate assay accuracy, linearity and recovery upon dilution was performed.

3.3.4 Data analysis

Prior to data analysis, cat age at sampling was standardised to January 1st of each year. Sex was categorised as neutered or intact (male/female), with a separate category for females that had experienced pregnancy or oestrus

within 2–16 weeks prior to sampling. Stress was classified into three groups based on owner assessment. Regardless of owner stress assessment, cats with recent pregnancy or oestrus were included in the group displaying stress. Cats in owner-reported diabetic remission were categorised as healthy.

We assessed and compared measured HCC across the three hair sampling locations and methods using Spearman's rank correlation and Bland–Altman (BA) plots. With BA analysis, differences between two paired measurements of the same variable (HCC) were compared for agreement and the variation was quantified. Analysis included graphical interpretation, including clinically interpreting the relevance of the given discrepancy, and calculation of mean differences (bias) between paired values. Limits of agreement (LOA) were defined as bias ±1.96 standard deviations of the paired differences. Outliers were identified as measurements of HCC falling outside LOA.

Associations between HCC and owner-reported cat characteristics, stress, and health status were assessed with two multiple linear regression models; one for HCC from clipped front leg samples, and one for combed samples, both using log-transformed HCC to improve model fit. Variables with $p < 0.2$ in univariable analysis were included in the models, alongside key variables (health status, presence of other animals, stressors, and stress signs) informed by previous studies (Galuppi et al., 2013, Contreras et al., 2021). Final models were refined via backward elimination, guided by AIC and exclusion of variables with $p \geq 0.05$. Residuals were assessed for normality using QQ plots.

4. Results

In this section, the most important results are included. For more results and details, see Papers I–IV.

4.1 Evaluation of disease outcomes (Paper I)

In total, 1369 cats diagnosed with DM were identified from the Agria Pet Insurance register. Of these cats' owners, 484 completed the questionnaire, corresponding to a 35% response rate. Seven incomplete or inconclusive questionnaires were excluded, leaving 477 questionnaires for analysis. About two thirds of the cats (333/477, 70%) were not alive at the time when their owners answered the questionnaire. Mean cat age at DM diagnosis was 10.7 years (±3.1), and most cats were neutered (474/477, 99.9%), of male sex (337/477, 71%), and were domestic cats (365/477, 77%). The most commonly represented pedigrees were Norwegian Forest Cat (38/477, 8%) and Burmese (18/477, 4%). Thirty-five cats (7%) were reported to suffer from another chronic disease.

The majority (85%) of cat owners were females, and the owners' median age at cat diagnosis was 46–55 years (range 16–90 years).

4.1.1 Initial survival and factors associated with early euthanasia

Of the 477 cats, 15% (72/477) were euthanised within 4 weeks of DM diagnosis. The most commonly stated reasons were related to the cat, including not wanting the cat to suffer (53%), poor prognosis (32%), or because of concurrent disease (21%). Thirteen percent of owners stated that euthanasia was performed because treatment was too difficult.

The cat surviving ≥4 weeks after diagnosis was associated with owner perceived lifestyle limitations and worries about complications of DM, e.g.,

hypoglycaemia. Increased cat age at the time of diagnosis was associated with reduced odds of surviving beyond four weeks, with the odds decreasing by 0.13 for each additional year (p =0.04). When owners reported experiencing external expectations to euthanise their cat, the odds of survival beyond four weeks decreased by one third per year (p =0.01), with this negative association being the most pronounced in cats aged approximately 15 years or older. Among cats whose owners expressed concerns about the costs associated with DM, younger individuals exhibited lower odds of initial survival, particularly those under approximately 10 years of age. In this sub-group, the odds of surviving beyond four weeks increased by 52% for each additional year of age (p =0.05).

4.1.2 Treatment and survival time

The initial survival rate was 85% (405/477). Ninety-three percent of the owners of these cats implemented dietary adjustments (378/405), and 89% administered insulin injections (360/405). Among owners administering insulin, 50% performed HBGM, 12% urine glucose monitoring, 6% practiced both methods, and 31% did not monitor glucose levels at home. Of the 45 cats (11%) that did not receive insulin, 27 did not receive any hypoglycaemic medication, and all but one cat had dietary adjustments implemented.

Table 1. Survival time of cats diagnosed with DM that were still alive ≥4 weeks after DM diagnosis (n=405).

Survival time of 405 cats that survived ≥4 weeks after diagnosis	**n**	**Median survival time (years)**	**IQR**	**Range (years)**
Dead at time of questionnaire	261	1	3	0–14
Alive at time of the questionnaire	144	2	2	-

IQR = interquartile range

Across all 405 cats, the most commonly provided diet was a dry veterinary prescription formulation for the management of DM (253/405, 62%), offered either as the primary diet or in combination with other diets. Eleven percent were predominantly fed a commercially available (CA) wet diet, which was generally reported to be low in carbohydrates, and 7% (27/405) received a

weight management prescription diet. Other diets (102/405, 25%) included wild prey, CA dry food, and dry food labelled as being low in carbohydrates.

Survival varied widely, particularly among deceased cats, see Table 1. Almost two-thirds of cats (299/477) survived for more than one year after diagnosis, with a smaller proportion surviving more than three (118/477), five (47/477), and eight years (7/477). See Figure 5.

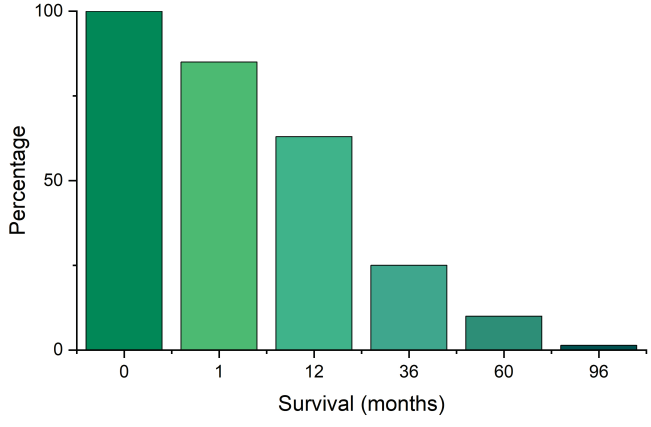

Figure 5. Minimum survival time (months) after DM diagnosis (n=477), showing the proportion of cats surviving at least the specified duration.

Cats with a QoL perceived as better or same as before DM diagnosis survived 0.6 years longer compared to cats with a worse QoL ($p = 0.01$). Survival time was 0.6 years shorter in cats whose owners worried about medication related issues ($p = 0.002$); and in cats who received insulin treatment, survival time decreased by 0.25 years for each additional year of age ($p < 0.001$).

4.1.3 Factors associated with other disease outcomes

Remission rate and life-long management

The remission rate was 29% (118/405), and in almost two thirds of these cats (73/118, 62%) no relapse was reported. For the 118 cats, time to remission was relatively evenly distributed across the first year following diagnosis, with a comparable proportion of cases achieving remission in each time interval; 22% within 0–3 months, 29% within 4–6 months, 19% within 7–12 months, and 25% after ≥12 months of treatment. In 71% of cats (287/405), remission was not achieved.

Cats that predominantly received a CA wet diet had three-fold higher odds of achieving remission, compared to cats that were fed a dry or a combination of dry and wet veterinary prescription DM diet (p =0.01). Furthermore, cats fed a CA wet diet had higher odds of achieving remission without relapse (OR 14.8, p =0.01).

4.1.4 Owner perceptions of management and cat QoL

Reasons for euthanasia within four weeks of DM diagnosis

The most common reasons for euthanising the cat ≤4 weeks after DM diagnosis was a wish not to let the cat suffer (53%), poor prognosis (32%), and concurrent diseases (21%). Less commonly reported reasons were treatment failure (15%), treatment being too difficult (13%), and insufficient veterinary support (4%). In 25% of euthanised cats, DM treatment had been initiated. No owners indicated financial costs as a reason for euthanasia.

Quality of life of the cat

Of the cats alive at the time of the questionnaire (144/477), current QoL was assessed as excellent in 46%, good in 51%, and poor in 2% of cats. Compared to before DM diagnosis, QoL was assessed as unchanged in 67%, better in 16%, and worse in 10% of cats. Among the cats that were deceased at the time of the questionnaire (333/477), 44% of owners (148/333) assessed QoL as worse than before diagnosis, 36% as unchanged, and 4% as better.

Both remission (p <0.001) and remission without relapse (p =0.002) were positively associated with QoL. See Figure 6 for an overview of owner-assessed change in QoL in cats achieving remission or not. Assessing QoL as worse was associated with owner concerns regarding both DM limiting the cat's life and the cat's medication.

Perceptions related to DM and disease management

Difficulties and worries related to DM and disease management was reported in 80% of owners of all cats surviving ≥4 weeks (329/405). For these owners, the most common experience, regardless of whether the cat achieved remission, was that the cat's DM imposed limitations on their daily life, such as difficulties travelling and finding a cat sitter (51%). Other sources of concern for owners included worries about complications related to the cat's DM (45%), the cat's medication (29%), difficulties measuring BG (21%),

and costs (15%). Thirteen percent of the owners were concerned about DM-related limitations to the cat's life.

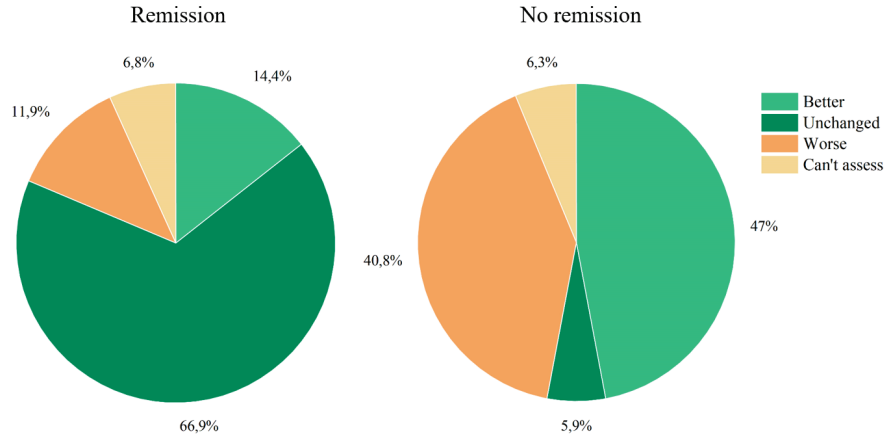

Figure 6. Owner-assessed change of quality of life in cats that did (n =118) and did not (n =287) achieve diabetic remission, compared to before the cat got DM. All cats survived ≥4 weeks after DM diagnosis.

4.2 Qualitative exploration of owners' experiences and perceptions (Paper II)

4.2.1 Characteristics of participants

Twelve owners participated, 11 of whom were female. Three lived in rural areas and nine in towns, representing diverse regions of Sweden. Each interview focused on one cat with DM; all cats had received insulin treatment, and three had achieved remission. At the time of interview, three cats had died; two from DM and one from unrelated causes. Four owners had prior experience with DM, either in humans (n =3) or cats (n =1).

4.2.2 Thematic structure

One overarching theme, *it's for life—defining cat ownership*, was generated as the conceptual anchor for three themes. *In sickness and health* reflected owners' considerations when initiating treatment for cats with DM, emphasising the cat as a family member and the evolving human–animal relationship. *The cat—opportunities and responsibilities* came from owners'

rationalizations regarding treatment, focusing on QoL and compromises regarding medical care. *Who decides about life?* addressed euthanasia decisions, highlighting responsibility, inner conflict, and attempts to simplify the process. An overview of the analytical structure is provided in Figure 7.

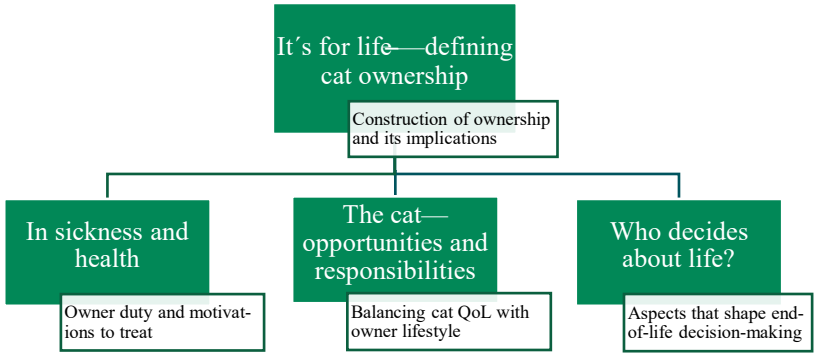

Figure 7. Thematic structure and summaries of themes in owners' experiences of treating DM in cats.

Overarching theme: It´s for life—defining cat ownership

Although owners struggled to communicate a clear underlying rationale for deciding to treat their cat upon DM diagnosis, they framed the decision as an expression of responsibility, and less as a response to cat-specific factors. As one participant explained: "*I think that when you choose to become a cat owner, or animal owner, you do it for life.*" (Julia). Such perspectives positioned treatment as a self-evident responsibility, shaped by views of ownership and obligation rather than by the specific context of DM. Fulfilling an enduring commitment to the care of the cat was expressed, consciously or not, as implicitly included when acquiring an animal. Owners defined their view of ownership by contrasting it with the opposing perspective:

> *"But when it's about it [medical treatment] being an inconvenience only for the owner that only causes like...Like, you have to engage daily with your animal. I think that you sign up for that when you take care of an animal."* (Anna)

By evoking owner responsibility as a moral imperative rather than a choice subject to external factors, owners' sense-making of ownership formed a

foundation for further reasoning about the human–cat relationship, DM management, and the justification of euthanasia.

Theme 1: In sickness and health

The relationship with their cat was described in terms beyond companionship, likening it to family-related or parenting. Viewing the human–cat relationship through an anthropomorphic lens seemed to intensify both the perceived bond and the moral commitment, rendering medical care a non-negotiable aspect of fulfilling owner obligations:

> *"She is my responsibility, like a child. If she had needed insulin every morning and evening, I would have solved it."* (Hanna).

Ascribing the cat the role of a family member, distinct from more functional forms of ownership, such as keeping a barn cat for pest control (as described by one owner), suggests that the value owners attach to the cat, and the type of relationship they seek, shape their decisions and their perceived duty.

Furthermore, the articulated strength and uniqueness of the bond with the cat influenced owners' reasoning, considering both the duration and the distinct properties of an interspecies bond. Long-term, close relationships seemed to reinforce commitment to treatment, and weaker or more recent bonds made euthanasia seem more acceptable:

> *"[…] If I'd had her since she was a kitten, I would have felt differently. […] If I'd been allowed to decide for myself, I'd probably have put her down there and then."* (Ingrid)

The absence of prolonged attachment and shared experience may lead owners to perceive treatment obligations as less immediate or compelling, allowing other factors, such as convenience, financial considerations, or the cat's current health and wellbeing, to play a greater role in decision-making. Ingrid's account further illustrates how perceptions of duty may be shaped within a social context, where differing emotional attachments and levels of commitment among family members can influence interpretations of duty and generate tension. Other accounts spoke of the complexity of household

decision-making in terms of differing views on the cat's QoL and the extent of medical care.

Theme 2: The cat—opportunities and responsibilities

Across accounts, cat wellbeing and QoL functioned as a guiding principle in decisions, with owners aiming to ensure that medical care served the cat's best interests. As per definitions on what was included in the concept of QoL, owners listed appetite, the cat being able to live their desired lifestyle, and preserved interactions with humans. While simultaneously safeguarding the cat's wellbeing, owners discussed their willingness to make changes to the recommended regimen to enable them to proceed with treatment:

> *"If I had had to measure her blood sugar twice a day, it would not have worked. Not for her, or for me."* (Mia)

> *"So, you have to be able to slack a bit, like an hour here or there. You can't be too hard on yourself, especially when you work and have small children."* (Eva)

Reframing the desired management protocols as negotiable, i.e., pursuing regimens that protected QoL while remaining feasible, operated as adaptations that reduced owner and cat stress and sustained treatment adherence. As perceived by owners, cats permitted such pragmatic flexibility, and given that no treatment effectively narrows options for euthanasia, these adjustments constituted a morally justifiable middle path that preserved cat welfare.

However, the constant awareness of the cat's dependence carried an emotional weight, often characterised by guilt, frustration, and a sense of restriction. Owners described how the properties of DM management place responsibility squarely on the caregiver, and that this intensified stress, particularly for those without social support:

> *"If I choose to do something else one evening, like stay longer at a friend's house for dinner, I immediately feel guilty for not giving him his insulin."* (Julia)

Strategies to manage risk during unavoidable absences, such as work commitments or night shifts, were also reported, including withholding

scheduled insulin injections or reducing the insulin dose to prevent hypoglycaemic crises. Owners also described care as strengthening the relationship, building trust, and providing a sense of fulfilment: "*It's a big achievement to turn things around, and I'm very proud of it…knowing you've helped someone feel better again*" (Anna). Yet alongside this sense of fulfilment, reflections frequently turned to the difficult questions of how long treatment should continue and when euthanasia might represent the best decision.

Theme 3: Who decides about life?

The decision over life and death brought out deeper moral questions on who has the right to end a life, and under what conditions. Euthanasia was framed as permissible only once a threshold had been crossed, loosely defined in terms of the cat's welfare and QoL. Owners often explicitly rejected convenience or financial motives as legitimate grounds. In practice, this required continual assessment of the cat's behaviour and response to treatment, weighing the 'relief' of death against the harm of suffering, with co-existing diseases complicating the evaluation. A slow deterioration of the cat and the lack of a clear-cut endpoint made this evaluation emotionally taxing and constantly present in their lives. Even when deterioration in DM was evident, owners could experience the decision as a moral breach:

> *"It feels a bit like a betrayal that I didn't keep fighting, but at the same time...It felt like we had been trying for so long, and he wasn't getting any better. […] We had reached the end of the road."* (Hanna)

This conflict was especially acute after sustained efforts to treat; the very history of caregiving intensified guilt by raising the subjective threshold for stopping. Here, responsibility was constructed as perseverance, and choosing euthanasia risked being read as giving up. Thus, tension lies between two competing moral imperatives: minimising suffering (the cat's welfare) and honouring a sustained duty of care (the owner's commitment).

To manage the ethical and emotional conflict of actively choosing to end their cat's life, hope for a peaceful, unassisted death was expressed: *"It would just be better if we came home one day, and she wasn't alive"* (Julia). Others sought decisive guidance from the veterinarian. These strategies seemed to help redistribute moral responsibility: a natural death removed the owner

from the active role, while clear clinical guidance enabled shared or clinician-led judgment. Both approaches allowed owners to maintain their moral position as responsible, non-abandoning guardians.

4.3 Qualitative exploration of veterinarians' experiences and perceptions (Paper III)

4.3.1 Characteristics of participants

Ten veterinarians were interviewed, nine female and one male, aged approximately 30–65 with 5–40 years since graduation. They represented diverse geographic regions of Sweden and predominantly worked in small animal practice, with professional backgrounds spanning various clinic types and sizes, including both primary care and referral practices.

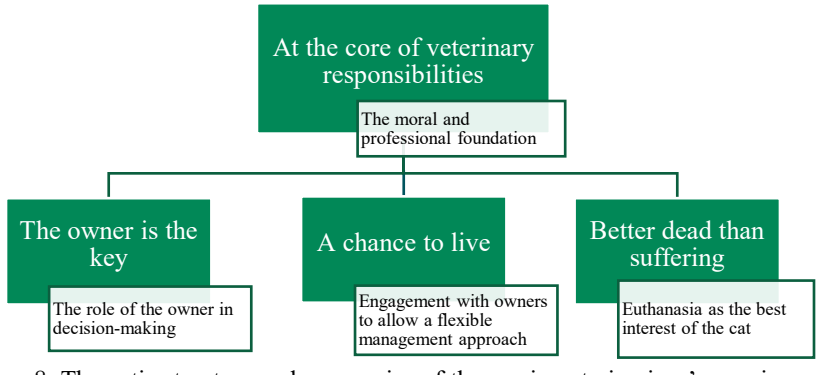

Figure 8. Thematic structure and summaries of themes in veterinarians' experiences of managing DM in cats and their owners.

4.3.2 Thematic structure

One overarching theme that relates to veterinary prioritisation of the cat's wellbeing tied together three themes constructed from the data. The first theme, *the owner is the key*, explored the narrative of how veterinarians approach the role of the owner in decision-making regarding DM. The second theme discusses how veterinarians balance medical ideals with practical realities; *a chance to live*. The third theme, *better dead than suffering*, concerns the perception of euthanasia as means of ensuring that no unnecessary suffering is caused, and how veterinarians navigate the

associated professional and emotional challenges. See Figure 8 for a thematic overview.

Overarching theme: At the core of veterinary responsibilities

Participants consistently framed the cat as the centre of veterinary care and cat welfare and QoL as the primary veterinary obligation, inherent to the veterinary role. This laid the foundation for further reasoning. At the same time, veterinarians described a dual responsibility, recognising the owner's wellbeing as being inseparable from that of the cat.

> *"If you have a healthy cat, you have a healthy owner. I often think it goes together."* (Carolina)

Describing animal and human welfare in relation to one another suggests that veterinary care encompasses a responsibility in which priorities, as reported by some veterinarians, appeared to shift depending on circumstances. In the treatment of DM, this becomes especially relevant, given the continuous involvement required of the owner.

Theme 1: The owner is the key

The first theme explored how veterinarians considered DM management in relation to the owner's willingness and their ability to engage in care. While regarding themselves as stewards of the cat's welfare, there was an acknowledgement that this obligation could only be realised through the owner. As Karl articulated, "*the owners need to trust us and be happy with what we do; otherwise, we won't be able to provide the care the animals truly need."* This rather pragmatic view suggests a reality in which veterinarians are constrained by the owner's consent, reflecting how owners hold final authority over treatment and euthanasia decisions upon DM diagnosis. In this sense, collaboration with owners can be seen not as a diversion from the cat's best interests, but as a prerequisite for achieving them. One strategy for enabling such collaboration was careful attention to the owner's perspective. Veterinarians described acknowledging the weight of decision-making, validating feelings of overwhelm, and recognising a potential disconnect between professional familiarity with procedures and owners' lived experiences:

> *"I think it's important to acknowledge that it's a big decision [to choose medical treatment], that a serious illness [diabetes mellitus] is something that will require significant effort. You need to show the owner that you see them, that you understand them in this situation."* (Emelie)

This sensitivity framed the owner not merely as a gatekeeper to treatment initiation, but as a partner whose confidence, trust, and emotional wellbeing may directly shape the cat's outcome. The importance of 'de-dramatising' DM was expressed, and participants described sharing their experiences of DM as a manageable disease with the possibility of successful care. Others focused on providing detailed, transparent information about the disease, treatment demands, and lifestyle changes, thus supporting informed decision-making. Both approaches may reflect distinct commitments: the former prioritising reassurance and beneficence, the latter emphasising respect for owner autonomy and moral agency. Across these strategies, the underlying reasoning remained consistent: access to the cat's wellbeing is mediated through the owner.

Theme 2: A chance to live

The second theme conceptualises veterinarians' accounts of engaging closely with owners to avoid euthanasia and make treatment feasible in cats deemed to have a reasonable chance of responding well to treatment. A key to this approach was that not only one optimal treatment regimen exists. Participants described how previous experiences of successful clinical outcomes served as motivation: if some cats thrive under treatment, withholding that opportunity from others may feel unjustified. Employing incremental strategies were common:

> *"I'm not very strict, so to speak. Rather, I feel that if you can just get things started and everything flows smoothly, then you can become stricter later if needed, once they [the owners] are on track."* (Susanne)

By implementing tailored strategies, participants aimed to enhance owner compliance and engagement while still fulfilling their perceived obligations to the cat. Strategies included initiating dietary changes prior to insulin therapy or simplifying DM monitoring. The veterinarian could implement

these adaptations even when owners had not explicitly expressed limitations or hesitation.

Treatment plans were also adapted to accommodate the owner's needs and capabilities rather than to serve as motivators to commit to care. Although there was generally a high level of acceptance for various owner reasons to compromise, financial constraint was often viewed as particularly frustrating:

> *"You try to make something out of nothing, by finding something that might not be gold standard, or even silver standard, but at least a bronze standard."* (Emma)

In accounts describing this, frustration appeared to arise not toward the owner, but from the tension created by financial constraints, which limited the owner's willingness to treat, the quality of care the cat received, and the veterinarian's professional duty, leaving veterinarians feeling insufficient. Modifications described included reducing veterinary visits, accepting less stringent disease control to lower the risk of insulin overdose, or relying solely on a low-carbohydrate, high-protein diet despite the potential added benefit of insulin.

Theme 3: Better dead than suffering

The third theme focuses on the veterinarian's reasoning surrounding euthanasia. Euthanasia was conceptualised as an ultimate responsibility to prevent suffering when satisfactory care could not be assured, whether due to the cat's condition or the circumstances related to the owner's willingness and ability to ensure adequate medical care. Accounts gave the sense that euthanasia was perceived not as a failure, but as prioritising the cat and as fulfilment of the veterinarian's professional obligations:

> *"Above all, perhaps, when it comes to recommending euthanasia...When I think that this is not okay, we can't do this...That is from the cat's perspective."* (Lotta)

Within this framing of the animal´s lived experience, different pathways were evident. In some accounts, euthanasia was presented as a response to insurmountable owner limitations, such as severe illness, where even the

most basic treatment could not be provided. Others described an uncompromising stance, in which full owner commitment to insulin protocols, HBGM, and regular visits was considered a prerequisite for initiating treatment: "*if you feel that you don't have the ability, for whatever reason, […] then we shouldn't start, then it's better to just leave it.*" (Karin). When owners choose euthanasia despite available treatment, veterinarians' described this as a responsible exercise of ownership. Still, simultaneously their accounts spoke of moral loss:

> *"It's not for everyone, and they're taking responsibility as owners by not letting it [the cat] go untreated or simply ignoring it, but it still hurts the heart. […]It's a shame that this cat didn't get that chance."* (Helen)

In this context, euthanasia can be framed as a 'second-best' option. While not ideal, since the cat might have lived well under different circumstances, under non-ideal conditions, euthanasia may be reframed as the most responsible course of action. In addition to fulfilling obligations toward the cat, these accounts also suggest an acknowledgment of the structural limits of veterinary care, including owner capacity, financial constraints, and the broader social context.

4.4 Assessment of HPA axis activity (Paper IV)

Cat characteristics and sampled hair

Complete questionnaires from 167 cats were included in analysis. From these cats, 255 hair samples were analysed for HCC; 109 clipped front leg samples, 26 clipped abdominal samples, and 120 combed samples. Not all cats were sampled from all three locations. Of the cats, 103 were reported as healthy and 64 as chronically ill. The most common types of chronic illness were DM (n =28), HT (n =19), and CKD (n =14).

Agreement between sampling methods

Twenty-three cats had paired hair samples from both the front leg and abdomen, with a Spearman's ρ of 0.72 (CI 0.39–0.89). BA analysis indicated a mean difference of 0.38pg/mg (LOA: –6.74 to 7.50), with one value falling

outside the limits. Agreement was stronger at lower HCC levels (≤5.6pg/mg), see Figure 9.

Sixty-two cats had hair sampled from both the front leg and by combing, with a Spearman's ρ of 0.61 (CI 0.41–0.76). After removal of three outliers (n =59), BA analysis showed a mean difference of –5.51pg/mg (LOA: –28.05 to 17.02), with three values falling outside the limits. As with abdominal samples, agreement was greatest at lower concentrations (≤10pg/mg) and declined with increasing HCC, see Figure 9.

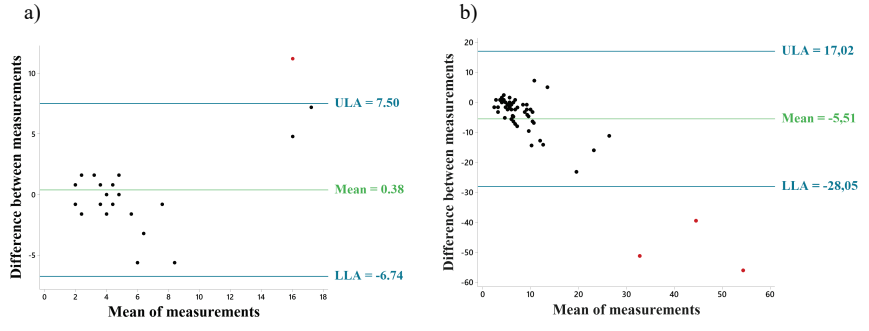

Figure 9. Bland-Altman plots of agreement between hair cortisol concentrations (pg/mg) in hair from a) the dorsal area of the front leg and the abdomen (n=23), b) the dorsal area of the front leg and combed samples (n=59).

Associations between cat characteristics and HCC

In clipped front leg hair samples (n =109), back-transformed predictions of HCC were associated with reproductive history, with higher values in females that had experienced oestrus or pregnancy compared to spayed females (p =0.008). Higher HCC was also associated with living in a multi-cat household (p =0.042), regardless of whether owners observed inter-cat conflict.

In combed hair samples (n =120), back-transformed predictions of HCC were associated with sex, with intact males showing higher values than spayed females (p =0.013). Higher HCC was also associated with the presence of chronic disease (p =0.025), independent of whether clinical signs were reported.

Factors not associated with HCC in either regression model included age, primary hair colour, coat pattern, hair length, household location, presence of other animals or children (<18 years), indoor or outdoor access, and age

at household introduction. Neither exposure to potential stressors nor the display of stress-related behaviours predicted HCC.

5. Discussion

DM is a complex disease, and management involves the owner, the cat and the veterinary clinician. This thesis aimed to broaden the understanding of DM management in cats by integrating perspectives from clinical practise, owners, and veterinarians. The work assessed disease outcomes and their impact on both cats and owners, examined the practical, emotional, and ethical challenges faced by owners in providing treatment, and analysed veterinarians' reasoning and experiences balancing perceived responsibilities with contextual constraints. Hair cortisol concentrations (HCC) were evaluated, including a low-stress hair sampling method, with results related to cat characteristics and presence of chronic disease. Collectively, the results contribute to an understanding of DM in cats as both a clinical condition and a lived reality, shaped by treatment outcomes, human–animal relationships, and professional responsibilities.

5.1 Disease outcomes (Paper I)

This study provides information on the clinical reality of cats with DM and their owners, and informs later discussions on owners' and veterinarians' experiences.

5.1.1 Mortality and survival time

Of the 477 cats, 15% were euthanised within 4 weeks of receiving their DM diagnosis, which is in accordance with previous studies (Kraus et al., 1997, Goossens et al., 1998, Callegari et al., 2013, Niessen et al., 2017). Reasons for this included a reluctance to let the cat suffer and a stated poor prognosis, which suggests an owner's concern over their cat´s QoL guides euthanasia decisions. For younger cats, the prospect of long-term therapy or a more

complex disease course may have discouraged owners from initiating treatment, explaining the interaction between cat age and a worry about DM-related costs on early euthanasia. For older cats, especially those over 15 years of age, reduced survival among owners anticipating euthanasia may reflect limited acceptance of DM in advanced age, and a perception that treatment is less justified late in life. The presence of comorbidities may affect initial survival in newly diagnosed cats (Kraus et al., 1997, Niessen et al., 2017, Gottlieb et al., 2024) and overall survival time (Callegari et al., 2013). In our study, no association between the presence of concurrent disease and initial survival or survival time was seen, and a low proportion of reported concurrent or recurrent diseases (7%, 35/477 cats) may have contributed to the lack of association. However, 21% of owners of cats not surviving more than four weeks after diagnosis reported presence of concurrent diseases as a contributing reason, suggesting influence of newly emerging or diagnosed co-occurring diseases.

Variations in study design and reporting may limit comparisons of survival time (Kraus et al., 1997, Goossens et al., 1998, Callegari et al., 2013, Niessen et al., 2017, Gottlieb et al., 2024, Waite et al., 2025), and more precise data on the interval between DM diagnosis and death in the present study would have facilitated such comparisons. Nonetheless, our ≥1, 3 and 5-year survival rates are consistent with earlier findings (Kraus et al., 1997, Goossens et al., 1998), although survival here was calculated as the shortest possible time after diagnosis, indicating that many cats likely lived longer. A recent study reported a median time to death of only 68 days (Waite et al., 2025), but such discrepancies may reflect differences in study populations, disease course, and the variables included in survival analyses.

The observed association between longer survival, absence of perceived owner worries about medication, and better cat QoL may indicate a more favourable disease course with improved glycaemic control and greater treatment stability. It may also suggest that cat QoL improved after an initial treatment period, reflecting the time required to establish glycaemic control and adapt to management routines (Albuquerque et al., 2019). Conversely, shorter survival may be linked to unstable disease control and reduced QoL, potentially reinforced by owner stress and difficulties in maintaining treatment routines.

5.1.2 Remission

Remission is a highly desirable outcome for cats with DM and their owners. It is believed to occur through reversal of glucotoxicity (Zini et al., 2009), supported by promptly initiated hypoglycaemic treatment (Marshall et al., 2009). Remission rates have been shown to vary widely between different studies, study designs and treatment protocols (Bennett et al., 2006, Hall et al., 2009, Marshall et al., 2009, Roomp and Rand, 2009, Zini et al., 2010, Gottlieb et al., 2024). Of the 29% of cats that achieved remission in this study, more than a third experienced relapse, which is in line with what has been previously recorded (Roomp and Rand, 2009, Zini et al., 2010, Gottlieb et al., 2024). No association between remission and hypoglycaemic treatment or home glucose monitoring were seen, however, 91% of the cats were treated with insulin. As no information on disease course, type of insulin and monitoring protocols, or glycaemic control, were available, it is possible that the effect of these factors on the odds of remission is underestimated. Noteworthy, in the European Union, protamine zinc insulin was approved for use in cats in 2013, making it more probable that the insulin administered to the cats in this study being medium-acting (lente insulin, Caninsulin), or, although perhaps less probable at the time, other long-acting formulas approved for use in humans (e.g., glargine insulin).

Interestingly, in this study, a similar proportion of cats achieved remission 6-9 or ≥12 months after receiving their DM diagnosis compared to a few months after DM diagnosis. Again, detailed information on treatment protocols was not available, and factors that could potentially explain these later occurrences of remission are progressive weight loss, lowering insulin resistance, later treatment of other co-morbidities that facilitate insulin resistance, or that hypoglycaemic treatment may preserve enough β-cell function to facilitate a later remission. Previously, remission has most commonly been reported in the months following DM diagnosis, but it cannot be excluded that shorter follow-up time affected the reported remission rates in some studies (Bennett et al., 2006, Boari et al., 2008, Hall et al., 2009, Riederer et al., 2016). Information on the possibility of a late remission might serve as encouragement for owners, who might lose hope and wish for treatment discontinuation if remission is not promptly achieved in their cat. Because of the study design, information on how DM diagnosis and remission was confirmed was lacking. Thus, the inclusion of wrongly diagnosed DM cases, e.g. stress-induced hyperglycaemia cases, cannot be

excluded (Niessen et al., 2022), which could have influenced the reported remission rate. However, this seems unlikely as such misclassifications would result in a high proportion of early remissions.

The role of the diet in treatment of DM is well established, although more research is needed to evaluate its role in promoting remission (Gostelow et al., 2014). The association between CA wet food and increased odds of remission seen in this study can be explained by low carbohydrate contents (Singh et al., 2015) or by the weight loss properties of wet diets (Wei et al., 2011) and nutritional contents (de-Oliveira et al., 2008), facilitating reversal of insulin resistance, or a combination of both. There are many factors contributing to insulin resistance (Scott-Moncrieff, 2010) and while some cats may achieve remission even when fed a higher-carbohydrate diet (Bennett et al., 2006, Hall et al., 2009, Gottlieb et al., 2024), for others dietary management alone can be crucial. Further studies are needed that more clearly compare the properties of different diets. Commercially available diets are easily accessible to owners and may lower the initial barrier to treatment by making the process feel less daunting.

Cats in remission show metabolic abnormalities regarding β-cell capacity and cell sensitivity to insulin (Gottlieb et al., 2020), and lowering the demands of insulin-producing cells seem reasonable (Gostelow and Hazuchova, 2023). The association between CA wet diet and staying in remission emphasises the current recommendations of continuing wet, low-carbohydrate diets after remission (Behrend et al., 2018). However, information on whether owners kept their cats on the chosen diet was not available and some owners may have changed their cat's diet after achieving remission.

5.1.3 Impact of DM on cat and owner

Remission was associated with an increased QoL of the cat. A disease state independent of hypoglycaemic treatment and the cat being able to maintain euglycaemia may seem obviously preferable to the opposite. However, among owners of cats that were alive at the time of the survey, a majority assessed their cat´s overall QoL at that time as excellent or good, independent of remission. This suggests that although owner perceived QoL of the cat may be better in cats achieving remission, owners can still judge QoL as satisfactory even when remission is not achieved. This emphasises QoL as a disease outcome in and of itself and other disease outcomes and treatment

protocols should be assessed in relation to this. In this study, QoL was subjectively assessed by owners, and which properties they ascribed to the concept were not known. Using a validated DM specific QoL tool could have improved assessment and made results more comparable with other studies.

Experiencing challenges and difficulties associated with DM management was common, and included both concerns about perceived limitations in owners' lifestyle and worries over DM-related concepts, similar to what has been reported elsewhere (Niessen et al., 2010, Aptekmann et al., 2014, Hazuchova et al., 2018, Albuquerque et al., 2019). About half of the owners reported lifestyle limitations and over a third expressed concern about complications, yet neither were linked to decreased odds of the cat surviving the first four weeks. This may reflect that such challenges emerge mostly after treatment has begun, as only 13% of owners of cats that did not survive more than four weeks cited treatment difficulty as the reason.

5.2 Experiences of owners and veterinarians

While Study I provided insights into clinical management of DM in cats, Studies II and III explored the reasoning, motivations, and emotional responses that underlie treatment decisions, and how these interpretations shape day-to-day management practices.

5.2.1 Perceived responsibilities of care

Both owner and veterinarian perspectives placed 'responsibility' at the centre of reasoning, although each group framed it differently. For owners, while rationales for initiating treatment were often vaguely articulated, the primary justification was strikingly consistent and embedded in a moral understanding of ownership as an enduring obligation. Owners perceived their responsibility as a duty that was created when they acquired their cat. In this sense, owner responsibilities are obligatory once the cat enters the human system of created dependency (Cooke, 2011). With the cat living in a world in which humans set the boundaries, owners assuming that this duty extends to include advanced medical treatment signals a perception of owner responsibility that clearly goes beyond the cat´s lawful status as mere property (Glanville et al., 2020). In the interviews, it became clear that these boundaries were not to be defined by factors related to finances or

convenience, and owners' view of responsible ownership was incompatible with not doing what could be done for the cat. In this context, euthanising the cat upon DM diagnosis challenges the societal norms that allow euthanasia based on owner convenience (Sanders, 1995, Batchelor and McKeegan, 2012).

That owners described their cats as "a child" or "family member", in contrast to, e.g., terms of function ("a barn cat"), reflects an anthropomorphic view of the relationship between human and cat. Owners' perceptions of their relationship with their cat have been linked to owner behaviours, including protective behaviour and the quality of care provided (Bouma et al., 2021). It is reasonable to believe that how owners articulate their relationship with the cat and their desired form of relationship also affects decisions in the context of veterinary care and DM. In addition to considering the cat a part of the family, dimensions of affinity also included the special properties of the inter-species bond, implying that the cat is valued both for its intrinsic being and because the owner perceives the relationship as unique, an example of how humans can construct meaning around their relationships with animals (Beverland et al., 2008). In the interviews, affinity was also understood in terms of both duration and social context, where the length and perceived strength of the relationship and the ways in which care was negotiated within household dynamics became central. The cat has been appreciated for its independence, for providing support and company (Zasloff, 1996), and is valued for strong attributes such as 'love' or 'personality' (Hoffmann et al., 2018), and how the bond with the cat is experienced is shaped by the individual and their needs within the relationship (Stammbach and Turner, 1999). Differing needs and levels of attachment among family members and weaker or newer bonds, lacking reciprocity (Ines et al., 2021), may therefore influence interpretations of responsibility. Together, these accounts demonstrate that decisions regarding DM treatment are actively negotiated within a social and emotional context, where varying acceptance of DM management and perceptions of owner responsibilities co-exist.

For veterinarians, the concept of responsibility primarily centred on duties regarding the welfare of the cat, which aligns with professional and normative obligations and the ethos of veterinary care (Morgan and McDonald, 2007, Weich and Grimm, 2018, Springer et al., 2019). These responsibilities extended beyond providing medical treatment to encompass,

most importantly, the cat's QoL. By emphasising this, QoL was positioned as an essential outcome in its own right, requiring attention not only to clinical parameters but also to the broader biopsychosocial context in which treatment is delivered, as highlighted in both human DM management (McMillan et al., 2004) and in cats (Niessen et al., 2010). However, care for the cat cannot be exercised in isolation. Veterinarians, to varying degrees, also framed their responsibilities as extending to the owner, reflecting a more holistic approach to practice. Incorporating the owner within veterinary responsibilities encapsulates the moral and professional foundation of veterinary care: advocating for the cat's best interests and ensuring its wellbeing while simultaneously recognising the interconnected relationship between animal and owner (Tannenbaum, 1985). Still, this dual responsibility carries an inherent conflict, as it requires negotiation between prioritising the cat's welfare and acknowledging the owner's needs.

5.2.2 The role of the owner

Not surprisingly, owner ability is recognised as important and as a factor that must be taken into consideration in veterinary decision-making regarding ill animals (Grimm et al., 2018, Deelen et al., 2023b). This was also evident in veterinarians' interviews, where safeguarding the cat's welfare was articulated as being inseparable from the owner's capability and willingness to provide or decline medical care. Recognising that cat QoL ultimately depended on the owner, this positions the veterinarian–owner relationship not as a secondary concern, but as a necessary condition for fulfilling responsibilities regarding the cat. Veterinarians' accounts of communication with owners at the time of a DM diagnosis included validation of owner concerns and feelings of overwhelm. This demonstrates an awareness of the concerns associated with DM treatment, as has been shown in previous studies (Niessen et al., 2010, Aptekmann et al., 2014, Hazuchova et al., 2018), and as seen in the first study of this thesis.

Some veterinarians fostered trust through encouragement and positive framing of previous treatment outcomes, aiming to reduce owner anxiety and strengthen confidence. For others, the emphasis lay in providing extensive information about the disease and its management, thereby enabling the owner to make an informed decision. These strategies represent different ways of engaging with owners, and both share the goal of fostering trust and building a partnership, an important condition for treatment adherence and,

ultimately, for preserving the cat's QoL (Abood, 2007). This suggests that veterinary communication style not only reflects the dynamic of the relationship with the owner, e.g., a more paternalistic or shared approach (Christiansen et al., 2015), but is also indicative of how they approach the owner as a means of obtaining the outcomes they assess as the most beneficial in guarding the cat's QoL.

5.2.3 Pragmatism in DM treatment

Owners were highly aware of their active role in DM management and in ensuring the QoL of their cat, and cat wellbeing functioned as a guiding principle in treatment-related decisions. However, while some owners were able to integrate the recommended DM management plan into their lifestyle with ease, others found themselves having to adapt treatment protocols to be able to proceed, for reasons related both to themselves and their lifestyle and to the cat. Supporting the rationale for these adaptations was the notion that no treatment would lead to euthanasia, a decision that, proposedly, conflicts with the view owners could have of themselves as responsible cat owners. By ensuring cat QoL, owners could justify making some adjustments to the treatment plan while also taking responsibility for their situation. Creating a regimen that worked for both themselves and their cat thus constituted a morally defensible compromise.

This pragmatic approach was also echoed among veterinarians, recognising that modifying treatment regimens represents a legitimate, and sometimes necessary, strategy to avoid euthanasia and make DM management possible and sustainable for both owner and cat. As with owners, the rationale for this flexibility was grounded in being able to safeguard the cat's QoL. Often, reasoning was framed in terms of offering the cat a chance at treatment and, ultimately, a chance to live. Emphasising medical actions performed in the prospect of a good QoL of the cat may frame euthanasia as undesirable, as it deprives the cat of this possibility, as argued by Yeates (Yeates, 2010). This suggests an attempt to avoid euthanasia in situations where it would not align with the veterinarians' professional role or ethical convictions, e.g., when a disease is treatable and treatment could be initiated, were it not for limitations in owner capacity (Yeates et al., 2011, Ogden et al., 2012). Adaptations in the desired management plan were implemented both proactively, without owners explicitly requesting adjustments, and in direct response to owner´s

expressed wishes and needs. Based on prior experiences of how owners react and perceive DM management, the former strategy may increase the likelihood that owners would initiate treatment. However, framing decisions around what veterinarians deemed feasible may risk blurring the line between supporting and steering the owner, thus limiting the owners' role in decision-making and challenging their autonomy (Christiansen et al., 2015).

In contrast to treatment modifications serving as motivational tools and rational means of sustaining adherence, financial constraints set absolute limits to what could be offered and imposed boundaries that could not be negotiated or modified in the same way as, e.g., lifestyle-related factors. In this context, veterinarians' role was to support owners in maximising the value of limited interventions while upholding the responsibility to prioritise the cat's QoL. As reported in other studies (Batchelor and McKeegan, 2012, Moses et al., 2018), financial obstacles were perceived as very stressful. Although actual costs related to DM management have been reported as lower than predicted after a time of treatment (Albuquerque et al., 2019) it is still a concern for many owners, and costs associated with treatment influence clinical decisions and veterinary ability to provide the desired medical care (Kipperman et al., 2017). However, in interviews, veterinarians emphasised that they did not adjust medical advice based on presumptions of an owner's finances, but rather when owners expressed limited monetary circumstances. This could reflect a response to owners' expectations that the veterinarian will prioritise the animal's wellbeing over cost considerations (Coe et al., 2007), or a prioritisation of care for the cat and respect for the owner by not forming preconceived ideas about them.

In these accounts of both veterinarian and owner perspectives, pragmatism functioned not as an abandonment of responsibility but as a way of upholding it within non-ideal conditions. However, it introduces ethical ambiguity in how far DM management protocols can be adjusted before treatment risks comforting the owner at the cost of the benefit to the cat.

5.2.4 Effects of caregiving and the weight of euthanasia decisions

Considering the specific demands of DM management, including the need for regularity and the extensive responsibility placed on owners in home care, it is perhaps unsurprising that owner accounts of long-term disease management were marked by feelings of guilt, frustration, and concern for the future. However, the extent to which these feelings affected owners and

occupied their life-space was notable. Framing the dependence of the cat on the owner to provide care worked as a central factor for this emotional distress, particularly when caregiver responsibilities conflicted with the owner's wish to prioritise, for example, social life or spontaneity. Although not explicitly addressed in interviews, owner accounts resonate with previously reported caregiver burdens among owners of chronically ill companion animals, including the negative impact of care on perceived stress levels, social life, and feelings of insufficiency related to the care of the animal (Spitznagel and Carlson, 2019). In interviews, this was particularly apparent among owners who identified themselves as the primary caretaker. This suggests that in the context of DM management, the inability to rely on others may contribute to feelings of social isolation and intensify the burden of care, as underlined by previous results here (Paper I) and elsewhere (Niessen et al., 2010).

It has been argued that the active choice of medical care over euthanasia may predispose owners to a more positive caregiving experience, indicating that providing care to an animal in need is associated with positive psychological outcomes, such as increased feelings of being needed and valued (Britton et al., 2018). The insights gained from owner interviews nuance this notion. Even though positive accounts of meaningfulness were present, the perceived responsibility of choosing treatment also contributed to more negative elements of caregiving. This was especially tangible if the cat did not respond as hoped to treatment, if owner struggled with the strain of DM management, or upon an owner doubts about whether the cat really benefits from the treatment.

Considering euthanasia, owners' accounts of having made past commitments to sustain the cat´s life through the course of DM with repeated decisions on treatment continuation can make a euthanasia decision increasingly burdened with guilt. This made the decision harder. Owners typically viewed euthanasia as being justified only when the cat's wellbeing and QoL had irreversibly declined, a prioritisation in line with other studies on important factors in owner end-of-life decisions (Slater et al., 1996, Reynolds et al., 2010, Christiansen et al., 2015, Littlewood et al., 2021). Thus, euthanasia was framed as an act of compassion, bringing relief for the cat. Guilt has been described to be present in owners of companion animals before and after euthanasia (Bussolari et al., 2018, Spitznagel et al., 2020). In owner interviews, guilt was present simultaneously with the owner

believing further intervention was futile and when euthanasia was left as the only reasonable choice, possibly related to the conflict rising from going against one´s self-concept of responsible ownership (Hewson, 2014), but perhaps also reflecting the depth of the owner–cat relationship. Owners' considerations of hoping for a natural death may reflect an attempt to redistribute the moral burden of decision-making while preserving their self-understanding as responsible guardians of the cat's wellbeing. Within this rationale, seeking decisive veterinary guidance, including prognostic information, played an important role for many owners. This could not only reflect a desire to make decisions on the best possible grounds, but also to avoid becoming 'blind' to subtle signs of the cat's declining condition. Systematic discussions of QoL at different life stages may support early recognition of deterioration (Yeates and Main, 2009, Niessen, 2011), offering owners a framework for interpreting changes that might otherwise be difficult to perceive. Importantly, a trusting veterinarian–owner relationship remains critical throughout the entire course of DM management, including the terminal stage.

5.2.5 Euthanasia as being the best interest of the cat

Across veterinarians´ narratives, overlapping but distinct framings of euthanasia were constructed, each reflecting how veterinarians negotiated their responsibilities toward the cat, the owner, and themselves. Reflections included experiences from both when DM was first diagnosed and in later stages of disease management.

Euthanasia was generally understood as an act that was in the cat's best interest, justified in relation to the overall responsibility to protect the cat from suffering. Within this framing, ensuring relief from suffering could be seen as the highest expression of veterinary responsibility (McMillan, 2001), providing a peaceful passing, or a "good death" (Matte et al., 2019). In practice, whether due to an irreversible decline in the cat's condition or because the owner was unable to provide DM care, veterinarians reasoned that euthanasia was the most welfare-oriented choice, blurring the lines between euthanasia categorised as absolute or contextually justified (Yeates et al., 2011). However, veterinarians must handle to interests of both animal and owner, and acting in what is presumed as the cat's best interest does not necessarily require consideration of the owner's interests (Yeates and Main, 2010, Rollin, 2013). By requiring total owner commitment to more rigorous

treatment protocols, allowing no deviations or compromises with what was perceived as optimal treatment for the cat, a strong advocacy for the cat was demonstrated. In this sense of 'all-or-nothing', the cat was safeguarded by protecting it from potential upcoming suffering stemming from inadequate or compromised care, deemed likely to happen if full commitment to veterinary visits, and treatment protocols were lacking. By avoiding harm that could arise from inadequate care, this precautionary approach resembles euthanasia decisions informed by veterinarians' prior negative experiences with the quality of care provided by some owners (Deelen et al., 2023a). This approach may also include consideration for the owner, as initiating a burdensome treatment with a deemed low likelihood of success could be seen as unjustifiable, hand at the cost of owner autonomy (Morgan and McDonald, 2007).

Although veterinarians approached euthanasia with a practical perspective, accounts of where DM treatment was both available and feasible but declined by the owner, were described with a sense of regret. While euthanasia could be framed as a responsible owner decision, the cat was perceived as having lost the chance of a life worth living. Such situations expose the limits of the veterinarian's role as the animal's advocate (Coghlan, 2018), rendering emotional distress. While respecting owner autonomy and meeting owner expectations on the consultation were seen as other parts of the veterinarian's responsibility, participants also expressed grief, frustration, or regret at what might have been possible under different conditions.

5.3 HCC (Paper IV)

Veterinarian and owner reasoning is focused on the cat's wellbeing, with QoL and welfare guiding clinical decision-making. Managing DM involves daily treatment routines and lifestyle adjustments that can contribute to stress in the cat, yet stress is often difficult for owners to assess. Study IV evaluated hair cortisol concentration (HCC) as an objective indicator of long-term HPA axis activity and stress in cats.

5.3.1 Comparison of sampling methods and locations

Traditionally, hair for cortisol analysis has been collected by clipping or shaving an area on the animal. To ensure inclusion of only actively growing

hair, sampling may be performed using the shave–reshave method, which involves an initial shave followed by collection of regrown hair through a second shave. In domestic cats, hair has been predominantly shaved (Accorsi et al., 2008, Kim et al., 2025), or clipped, using mechanical devices (Galuppi et al., 2013, Contreras et al., 2021) or scissors (Finkler and Terkel, 2010, Wojtaś, 2023), and only one study has applied the shave-reshave method (Contreras et al., 2021). Recruitment of animals for clinical studies can be challenging. Common reasons that may influence cat owners' willingness to participate include concerns about potential discomfort to their cat and apprehension regarding transportation required for study involvement (Gruen et al., 2014). Finding ways to facilitate owner inclusion is therefore important. We explored combing as a low-stress hair sampling method with minimally invasive properties that both cat and their owners accept and could easily perform at home.

In comparison, HCC varied both between and within sampling sites and methods, but despite this variability, agreement between methods was observed, particularly at lower HCC levels. Several factors may have contributed to variation. Differences in body location likely reflected variability in hair type, growth rate, follicular activity, and shedding patterns, which are known to differ across the feline coat, and both season and photoperiod can influence hair growth (Baker, 1974, Hendriks et al., 1997). The combing method introduced additional variability, as it samples from a broader, less standardised body area and collects a mix of loose hairs, potentially influenced by individual shedding and grooming behaviours. This likely explains the wider HCC range observed in combed hair samples compared to clipped samples (front leg and abdominal), including very high cortisol concentrations measured in combed samples from a few individuals.

Not all cats were sampled across all methods and locations, and the modest sample size reduced statistical power in comparisons. The importance of repeatability in method comparisons have been accentuated (Bland and Altman, 1999), and should be included in future studies of HCC analysis in combed hair in cats. Nonetheless, there was consistency in paired measurements between methods and locations, and combing represents a less-invasive sampling method that can be performed at home, and is therefore more attractive to owners and, likely, also to cats.

5.3.2 Associations between HCC and cat characteristics, stress and health

Separate regression models were used for assessment of HCC quantified from front leg samples (n =109) and from combed samples (n =120), respectively, in relation to cat characteristics, stress, and health status. The effect of age on HCC has not been studied in juvenile cats, but results from other species have indicated an age-dependent decline in HCC (González-de-la-Vara et al., 2011, Comin et al., 2012). The youngest cats in our study were 6 months old at sampling, with sampled hair possibly representing cortisol concentrations from approximately 12 weeks of age onward. Because of this, and the fact that cats with chronic diseases tend to be of middle age or older, and reproductively active cats are often younger, both regression models controlled for cat age. Age had no effect on HCC in neither clipped or combed hair samples.

In the present study, no association was found between HCC and exposure to potential stressors or the display of stress-related behaviours. Previous studies have reported that HCC in cats was higher when behaviours such as defecating or urinating outside the litterbox or displaying aggression towards family members were reported by owners (Contreras et al., 2021, Wojtaś, 2023). However, in one of these studies, owner-reported stress levels were not significantly correlated with HCC when other factors related to the cat and its home environment were taken into account (Contreras et al., 2021). A potential explanation for the lack of association in the present study could be owners' limited ability to recognise signs of stress in their cats (Mariti et al., 2017), or individual variability in HPA axis activity and response to stressors (Miller et al., 2007, Packer et al., 2019, Stella and Croney, 2019). Furthermore, differences in temperament and personality, which can strongly influence coping strategies and stress responses (McCune, 1995, Amat et al., 2016), were not considered in this study and may have contributed to the absence of significant associations. The questionnaire only included questions on anticipated stress response behaviours, and inquiries about cat behaviours that are indicative of good welfare (Slater et al., 2013) could have provided a more nuanced analysis and interpretation of HPA axis alterations in relation to owners' perceptions of their cat.

In contrast to previous results (Wojtaś, 2023), cats living in multi-cat households had higher HCC compared to cats in single-cat households. A

multi-cat household was defined as the cat sharing a living space with at least one other cat. In multi-cat households, competition over resources may arise, leading to inter-cat aggression and other behaviours associated with stress (Elzerman et al., 2020). Behaviour and stress levels of cats in both single- and multi-cat households are shaped by multiple interacting factors, such as environmental enrichment, resource distribution, and social compatibility among cats (Carlstead et al., 1993, Rochlitz, 2013). These are all factors that could not be controlled for in this study, and no further differentiation regarding the number of cohabiting cats was therefore made. It has been suggested that it is rather these complex factors than the actual number of resident cats that should be considered when evaluating multi-cat household dynamics (Finka and Foreman-Worsley, 2022). This finding invokes attention to the complex relationship between social and environmental factors in HPA axis activity, and further studies would be beneficial for a better understanding of feline stress responses in this context.

Although studies in other species have shown inconclusive results, the finding that HCC was associated with pregnancy or oestrus in clipped hair samples, and with being an intact male in combed samples, is perhaps not surprising. These associations may result from hormonal changes during pregnancy, parturition, increased energetic expenditures, and general maternal efforts post-partum (Alekseeva et al., 2020, Fusi et al., 2021). During pregnancy, cortisol is crucial for foetal development, leading to increased circulating cortisol concentrations until parturition (Bacci et al., 2014). A lower HCC has been reported in spayed free-roaming domestic female cats compared to intact females, possibly influenced by agonistic behaviour or reproductive status (Finkler and Terkel, 2010). The majority of intact females without owner-reported oestrus or pregnancy were at least one year old at the time of hair sampling, suggesting presence of oestrus periods not reported by the owner (Griffin, 2001). In a study of wildcats and feral cats, higher HCC was observed in male cats compared to females, although this difference was not statistically significant, possibly due to a small sample size (Franchini et al., 2019). The association between male sex and HCC should be interpreted with caution, as the limited number of male cats in our sample influenced the results, with an uncertainty highlighted by a wide CI. A larger sample size is necessary for a more comprehensive exploration of HCC and sex in domestic cats. A low proportion of intact

individuals may explain the lack of association between sex and HCC previously reported in owned cats (Contreras et al., 2021, Wojtaś, 2023).

The presence of chronic disease was associated with higher HCC in combed hair samples. Recently, higher HCC was reported in owned cats with later stages of CKD compared to earlier stages (Kim et al., 2025). Previously, elevated HCC levels have been associated with dermatophyte infection in shelter cats (Galuppi et al., 2013). However, the relationship may go both ways as the negative effect of chronic stress on the immune system can increase the risk of infectious disease (Pruett, 2003). A higher urine cortisol–creatinine ratio has been described in cats with HT (De Lange et al., 2004) and in hospitalised cats with various diseases (Henry et al., 1996), as well as in shelter cats with signs of systemic disease (McCobb et al., 2005). Altered activity of the HPA axis may therefore be associated with both the disease process, and with events that are related to, but not directly associated with disease. This may include veterinary visits and transportation of the cat to the clinic (Quimby et al., 2017), animal synchronisation with owner stress, as seen in dogs (Sundman et al., 2019), and daily administration of medications (Reynolds et al., 2010). Although DM, HT, and CKD were the most commonly represented diseases in the studied population, a diverse range of diseases was observed, and the cats exhibited various stages of illness. Further examination of specific diseases could provide deeper insights into the influence of individual diseases and disease states on HCC. Interestingly, the presence of clinical signs reported by owners did not show an association with HCC. This discrepancy could be attributed to factors such as questionnaire design, inaccurate owner reporting, or the owner's ability to recognise clinical signs of disease. Furthermore, HPA axis dysregulation, manifesting as hypocortisolism following a period of chronic HPA axis hyperactivity, might contribute to this observed discrepancy (Packer et al., 2019). Although not included as a variable in our study, a dull coat condition has been linked to variations in HCC (Contreras et al., 2021), to stress (Arhant, 2015), and to chronic diseases such as HT and DM (Greco, 2001, Carney et al., 2016, Vogelnest, 2017), suggesting an interplay between illness, behaviour, and overall wellbeing. The possibility of a disparity between the observable condition of a chronically ill cat and its actual impact, as measured by HCC, warrants additional investigation.

5.4 Limitations and comments on methodologies

In Study I, the main limitation is that all data were owner-reported, with most cats no longer alive at the time of questionnaire completion. This may have introduced recall bias and misinterpretations of medical history, and detailed information on several aspects was lacking. Participating owners may also represent a more motivated subgroup. The definitions of DM and diabetic remission were adapted for owner understanding and did not fully align with internationally accepted definitions (Niessen et al., 2022), which may limit comparability with other studies. Although subjective assessment of the QoL of an animal may add important and more holistic qualitative value (Belshaw, 2018), such an assessment could also be unreliable, and owners may overlook or misinterpret important aspects. Using species-specific health tools offer structured and disease-specific QoL assessments, and inclusion of such tools may have facilitated a more accurate assessment and allowed comparison between studies and populations. Finally, as only insured cats were included in the first study, some findings may not be generalisable to uninsured populations.

In Studies 2 and 3, composition of the two participant groups naturally shaped the analysis and results, and cultural, gender-related, demographic, and other contextual factors likely influenced reasoning (Amiot and Bastian, 2015). Recruitment through social and professional networks was effective; however, a greater proportion of male participants may have been desirable. The predominance of female participants may reflect gendered differences in decision-making among cat owners managing DM. Factors influencing these differences could include the stronger emotional investment in the cat reported among female owners (Lue et al., 2008, Grigg and Kogan, 2019) or a heightened sense of caregiving responsibilities in women (Bouma et al., 2021). This imbalance may also mirror broader structural patterns, such as the feminisation of the veterinary profession, observed both in Sweden (Östensson, 2010) and elsewhere (Federation of Veterinarians of Europe, 2023). As the interviewer was a veterinarian, responses may have been influenced by social desirability or perceived expectations, and the lack of anonymity inherent to interviews could have further shaped how interviewees responded.

The terminology used in Studies 2 and 3 reflects the vocabulary chosen by participants. However, even though the terms ‘welfare’ and ‘QoL’ have been used interchangeably in the literature (McMillan, 2000, Green and

Mellor, 2011), no detailed definition or in-depth discussion of what QoL was understood to entail was included. The subjectivity inherent in this lack of definition may have influenced how veterinarians and owners justified prioritising the cat's QoL above all else, interpreting it as their central responsibility. This ambiguity highlights how QoL could be explored further as a qualitative research topic in its own right.

In Study IV, as an observational study, there was limited control over the included subjects, and potential confounding factors cannot be excluded. The relatively small sample size and sub-groups further restricts the robustness of the findings. As discussed in the first study, reliance on owner-reported information carries a risk of subjectivity, inaccuracies, recall bias, and misinterpretation. No clinical confirmation of the cats' health status was available, and the absence of a validated stress scale or evaluation tool likely constrained the accuracy of stress assessment.

6. Conclusions, clinical implications, and future perspectives

Diabetes mellitus in cats is a chronic disease that affects the lives of both the cat and owner. Its treatment carries both demanding and permissive aspects, which may complicate the clinical situation and management. The four studies in this thesis collectively contribute new insights for an enhanced understanding of DM, with implications for improved clinical management. Here, the most important conclusions are reported.

- The remission rate in treated cats was 29%. Of these cats, an approximate equal proportion achieved remission within the first months of treatment or one year, respectively. Remission was associated with a better QoL of the cat.
- Feeding the cat a commercially available wet diet was associated with a higher odds of remission. Considering the 40% relapse rate, cats in remission should be monitored for re-occurrence of clinical signs of DM.
- Owners experiencing challenges associated with DM management was common, regarding, e.g., perceived lifestyle limitations.
- Owners' experiences were shaped by the human–cat bond and were context-dependent. Thus, individual owner–cat pairs require different management approaches.
- Veterinarians recognised the owner as an inseparable aspect in prioritising the cat's QoL in DM management. Balancing flexibility with the potential consequences of suboptimal care is relevant in veterinarian–owner communication in shaping management plans.

- Combing hair demonstrates a potential for simplified, low-stress sampling method for quantifying HCC in cats. HCC may serve as a component in assessing the impact of chronic disease, but should be interpreted in the context of individual cat characteristics and living conditions.

Some areas warrants further attention. First, as remission is a highly desirable outcome in cats with DM, accentuated by the association with a better QoL, more research on optimal management to achieve this is needed. The reported association between serving the cat a commercially available wet diet and remission could be a result of dietary composition related to both nutritional and moisture contents, although information on other factors like feeding schedules, weight loss, and management of co-morbidities was not available for analysis. The availability of diets in regular supermarkets or convenience stores may help reduce barriers to treatment, which can make management feel more practical and less overwhelming. Further investigation of diets with differing carbohydrate properties are needed, perhaps most appropriately conducted though prospective clinical studies.

The association between QoL and disease outcomes, as well as both veterinarians and owners describing how QoL was the main emphasis, accentuates the importance of integrating QoL assessments in clinical practice and in research. Notably, a majority of owners of cats that were still alive and under treatment assessed their cat's QoL as 'good' or 'excellent', regardless of whether remission had been achieved. QoL should be considered an outcome in its own right, against which other disease outcomes and treatment protocols should be evaluated.

The interviews indicate that future QoL assessments in the clinical setting benefit from including additional aspects. Alongside established quantitative assessment tools, incorporating qualitative elements by asking owners about their individual experiences could make assessments more specific. Participating cat owners stated how caregiving involved difficult emotions, such as guilt and burden, which may persist or change during disease and management progress. Repeated evaluations, not only of the cat's QoL but also of the owner's responsibilities and wellbeing throughout the disease course, could improve support for both cat and owner and contribute to more sustainable care. In addition, veterinary awareness of the owner's lived experience, including the burden and psychosocial distress they may

experience, offers an opportunity to respond, strengthening communication and supporting treatment adherence. Decreasing owner burden could also serve to improve veterinary psychosocial health by reducing the need to compromise between perceived responsibilities toward the cat and the owner.

Our findings suggest that veterinarians' understanding and definitions of cat welfare and QoL are central to how they balance responsibilities toward both cat and owner, and how they frame treatment options. Future research would benefit from exploring how veterinarians in small animal practice conceptualise these definitions. In addition, prospective interview studies with owners who chose euthanasia rather than treatment could provide deeper insights into the rationale behind such decisions and the factors influencing them. Furthermore, exploring perceived challenges in relation to the support available from veterinarians, social networks, or online sources could help to clarify how the veterinary team may better support owners. Including owners and veterinarians from different countries would allow comparisons and enhance transferability, as would including quantitative research to test the findings within broader populations.

The non-invasive nature and simple sampling procedure of combed hair for HCC assessment provide advantages as an indicator of long-term stress in cats. Some variation between hair sampling methods can be expected, and comparison with other biological materials, such as faecal cortisol, could help determine how well HCC from combed hair reflects circulating cortisol concentrations. Future studies should also consider cat personality, stress coping mechanisms, and validated behavioural and QoL assessments. Finally, analysis of HCC in both cats and their owners could provide further insights into how DM affects both.

The introduction of SGLT-2 offers new possibilities for DM care, but the broader implications of this new hypoglycaemic treatment has not yet been studied. Therefore, future studies should investigate their impact not only on clinical outcomes, but also on the QoL of both cat and owner, as well as on the practical and ethical considerations faced by owners and veterinarians.

References

2022. RStudio: Integrated Development Environment for R.

ABOOD, S. K. 2007. Increasing Adherence in Practice: Making Your Clients Partners in Care. *Veterinary Clinics of North America: Small Animal Practice,* 37**,** 151–164.

ACCORSI, P. A., CARLONI, E., VALSECCHI, P., VIGGIANI, R., GAMBERONI, M., TAMANINI, C. & SEREN, E. 2008. Cortisol determination in hair and faeces from domestic cats and dogs. *General and Comparative Endocrinology,* 155**,** 398–402.

ALBUQUERQUE, C. S., BAUMAN, B. L., RZEZNITZECK, J., CANEY, S. M. & GUNN-MOORE, D. A. 2019. Priorities on treatment and monitoring of diabetic cats from the owners' points of view. *J Feline Med Surg***,** 1098612X19858154.

ALDRIDGE, C. F., BEHREND, E. N., SMITH, J. R., WELLES, E. G. & LEE, H. P. 2020. Accuracy of urine dipstick tests and urine glucose-to-creatinine ratios for assessment of glucosuria in dogs and cats. *Journal of the American Veterinary Medical Association,* 257**,** 391–396.

ALEKSEEVA, G. S., LOSHCHAGINA, J. A., EROFEEVA, M. N. & NAIDENKO, S. V. 2020. Stressed by Maternity: Changes of Cortisol Level in Lactating Domestic Cats. *Animals,* 10**,** 903.

ALT, N., KLEY, S., HAESSIG, M. & REUSCH, C. E. 2007. Day-to-day variability of blood glucose concentration curves generated at home in cats with diabetes mellitus. *J Am Vet Med Assoc,* 230**,** 1011–7.

AMAT, M., CAMPS, T. & MANTECA, X. 2016. Stress in owned cats: behavioural changes and welfare implications. *Journal of Feline Medicine and Surgery,* 18**,** 577–586.

AMAT, M., JOSÉ LUÍS RUIZ DE LA TORRE, JAUME FATJÓ, VALENTINA M. MARIOTTI, SOPHIE VAN WIJK, XAVIER MANTECA 2009. Potential risk factors associated with feline behaviour problems. *Applied Animal Behaviour Science,* 121**,** 134–139.

AMERICAN DIABETES ASSOCIATION 2013. Diagnosis and classification of diabetes mellitus. *Diabetes care,* 36**,** S67–S74.

AMIOT, C. E. & BASTIAN, B. 2015. Toward a psychology of human–animal relations. *Psychological bulletin,* 141**,** 6.

APPLETON, D., RAND, J., PRIEST, J., SUNVOLD, G. & VICKERS, J. 2004. Dietary carbohydrate source affects glucose concentrations, insulin secretion, and food intake in overweight cats. *Nutrition Research,* 24**,** 447–467.

APPLETON, D. J., RAND, J. S. & SUNVOLD, G. D. 2001. Insulin Sensitivity Decreases with Obesity, and Lean Cats with Low Insulin Sensitivity are at Greatest Risk of Glucose Intolerance with Weight Gain. *Journal of Feline Medicine and Surgery,* 3**,** 211–228.

APTEKMANN, K. P., ARMSTRONG, J., CORADINI, M. & RAND, J. 2014. Owner experiences in treating dogs and cats diagnosed with diabetes mellitus in the United States. *Journal of the American Animal Hospital Association,* 50**,** 247–53.

ARHANT, C., WOGRITSCH, R., TROXLER, J. 2015. Assessment of behavior and physical condition of shelter cats as animal-based indicators of welfare. *Journal of Veterinary Behavior,* 10**,** 399–406.

ARMSTRONG, P. J. & BLANCHARD, G. 2009. Hepatic Lipidosis in Cats. *Veterinary Clinics of North America: Small Animal Practice,* 39**,** 599–616.

BACCI, M. L., NANNONI, E., GOVONI, N., SCORRANO, F., ZANNONI, A., FORNI, M., MARTELLI, G. & SARDI, L. 2014. Hair cortisol determination in sows in two consecutive reproductive cycles. *Reproductive Biology,* 14**,** 218–223.

BAKER, K. P. 1974. Hair growth and replacement in the cat. *British Veterinary Journal,* 130**,** 327–335.

BARD, A. M., MAIN, D. C. J., HAASE, A. M., WHAY, H. R., ROE, E. J. & REYHER, K. K. 2017. The future of veterinary communication: Partnership or persuasion? A qualitative investigation of veterinary communication in the pursuit of client behaviour change. *PLOS ONE,* 12**,** e0171380.

BATCHELOR, C. E. M. & MCKEEGAN, D. E. F. 2012. Survey of the frequency and perceived stressfulness of ethical dilemmas encountered in UK veterinary practice. *Veterinary Record,* 170**,** 19–19.

BEHREND, E., HOLFORD, A., LATHAN, P., RUCINSKY, R. & SCHULMAN, R. 2018. 2018 AAHA Diabetes Management Guidelines for Dogs and Cats. *Journal of the American Animal Hospital Association,* 54**,** 1–21.

BELSHAW, Z. 2018. Quality of life assessment in companion animals: what, why, who, when and how. *Companion Animal,* 23**,** 264–268.

BENNETT, N. 2002. Monitoring techniques for diabetes mellitus in the dog and the cat. *Clinical techniques in small animal practice,* 17**,** 65–69.

BENNETT, N., GRECO, D. S., PETERSON, M. E., KIRK, C., MATHES, M. & FETTMAN, M. J. 2006. Comparison of a low carbohydrate-low fiber diet and a moderate carbohydrate-high fiber diet in the management of feline diabetes mellitus. *J Feline Med Surg,* 8**,** 73–84.

BENSELLAM, M., LAYBUTT, D. R. & JONAS, J.-C. 2012. The molecular mechanisms of pancreatic β-cell glucotoxicity: recent findings and future research directions. *Molecular and cellular endocrinology,* 364**,** 1–27.

BEVERLAND, M. B., FARRELLY, F. & LIM, E. A. C. 2008. Exploring the dark side of pet ownership: Status-and control-based pet consumption. *Journal of Business Research,* 61**,** 490–496.

BIJSMANS, E. S., JEPSON, R. E., SYME, H. M., ELLIOTT, J. & NIESSEN, S. J. M. 2016. Psychometric Validation of a General Health Quality of Life Tool for Cats Used to Compare Healthy Cats and Cats with Chronic Kidney Disease. *Journal of Veterinary Internal Medicine,* 30**,** 183–191.

BLAND, J. M. & ALTMAN, D. G. 1999. Measuring agreement in method comparison studies. *Statistical Methods in Medical Research,* 8**,** 135–160.

BLOIS, S. L., DICKIE, E. L., KRUTH, S. A. & ALLEN, D. G. 2010. Multiple endocrine diseases in cats: 15 cases (1997–2008). *Journal of feline medicine and surgery,* 12**,** 637–642.

BOARD, V. F. P. 2015. Taking charge of our future: A vision for the veterinary profession for 2030.

BOARI, A., ASTE, G., ROCCONI, F., DALESSANDRI, A. & VITA, S. 2008. Glargine insulin and high-protein-low-carbohydrate diet in cats with diabetes mellitus. *Veterinary Research Communications,* 32**,** 243–245.

BONNETT, B. N. & EGENVALL, A. 2010. Age patterns of disease and death in insured Swedish dogs, cats and horses. *Journal of Comparative Pathology,* 142**,** S33–S38.

BOUMA, E. M. C., REIJGWART, M. L. & DIJKSTRA, A. 2021. Family Member, Best Friend, Child or 'Just' a Pet, Owners' Relationship Perceptions and Consequences for Their Cats. *International Journal of Environmental Research and Public Health,* 19**,** 193.

BRADSHAW, J. W. & CASEY, R. 2007. Anthropomorphism and anthropocentrism as influences in the quality of life of companion animals. *Animal welfare,* 16**,** 149–154.

BRAUN, V. & CLARKE, V. 2006. Using thematic analysis in psychology. *Qualitative Research in Psychology,* 3**,** 77–101.

BRAUN, V. & CLARKE, V. 2019. Reflecting on reflexive thematic analysis. *Qualitative Research in Sport, Exercise and Health,* 11**,** 589–597.

BRAUN, V. & CLARKE, V. 2021. To saturate or not to saturate? Questioning data saturation as a useful concept for thematic analysis and sample-size rationales. *Qualitative Research in Sport, Exercise and Health,* 13**,** 201–216.

BRAUN, V. & CLARKE, V. 2022a. Conceptual and design thinking for thematic analysis. *Qualitative psychology,* 9**,** 3.

BRAUN, V. & CLARKE, V. 2022b. Thematic analysis: A practical guide. Sage London.

BRITTON, K., GALIOTO, R., TREMONT, G., CHAPMAN, K., HOGUE, O., CARLSON, M. D. & SPITZNAGEL, M. B. 2018. Caregiving for a Companion Animal Compared to a Family Member: Burden and Positive Experiences in Caregivers. *Frontiers in Veterinary Science,* 5.

BURNARD, C., RALPH, C., HYND, P., HOCKING EDWARDS, J. & TILBROOK, A. 2017. Hair cortisol and its potential value as a physiological measure of stress response in human and non-human animals. *Animal Production Science,* 57**,** 401–414.

BURNETT, T. A., MADUREIRA, A. M. L., SILPER, B. F., NADALIN, A., TAHMASBI, A., VEIRA, D. M. & CERRI, R. L. A. 2014. Short communication: Factors affecting hair cortisol concentrations in lactating dairy cows. *Journal of Dairy Science,* 97**,** 7685–7690.

BURNETT, T. A., MADUREIRA, A. M. L., SILPER, B. F., TAHMASBI, A., NADALIN, A., VEIRA, D. M. & CERRI, R. L. A. 2015. Relationship of concentrations of cortisol in hair with health, biomarkers in blood, and reproductive status in dairy cows. *Journal of Dairy Science,* 98**,** 4414–4426.

BUSSOLARI, C. J., HABARTH, J., KATZ, R., PHILLIPS, S., CARMACK, B. & PACKMAN, W. 2018. The euthanasia decision-making process: A qualitative exploration of bereaved companion animal owners. *Bereavement Care,* 37**,** 101–108.

CALLEGARI, C., MERCURIALI, E., HAFNER, M., COPPOLA, L. M., GUAZZETTI, S., LUTZ, T. A., REUSCH, C. E. & ZINI, E. 2013. Survival time and prognostic factors in cats with newly diagnosed diabetes mellitus: 114 cases (2000-2009). *Journal of the American Veterinary Medical Association,* 243**,** 91–5.

CARLSTEAD, K., BROWN, J. L. & STRAWN, W. 1993. Behavioral and physiological correlates of stress in laboratory cats. *Applied Animal Behaviour Science,* 38**,** 143–158.

CARNEY, H. C., WARD, C. R., BAILEY, S. J., BRUYETTE, D., DENNIS, S., FERGUSON, D., HINC, A. & RUCINSKY, A. R. 2016. 2016 AAFP Guidelines for the Management of Feline Hyperthyroidism. *Journal of Feline Medicine and Surgery,* 18**,** 400–416.

CARR, J. A. 2002. Stress, neuropeptides, and feeding behavior: a comparative perspective. *Integrative and comparative biology,* 42**,** 582–590.

CATTET, M., MACBETH, B. J., JANZ, D. M., ZEDROSSER, A., SWENSON, J. E., DUMOND, M., STENHOUSE, G. B. 2014. Quantifying long-term stress in brown bears with the hair cortisol concentration: a biomarker that may be confounded by rapid changes in response to capture and handling. *Conservation Physiology,* 2.

CHARLES, C., GAFNI, A. & WHELAN, T. 1999. Decision-making in the physician–patient encounter: revisiting the shared treatment decision-making model. *Social science & medicine,* 49**,** 651–661.

CHRISTIANSEN, S. B., KRISTENSEN, A. T., LASSEN, J. & SANDØE, P. 2015. Veterinarians' role in clients' decision-making regarding seriously ill companion animal patients. *Acta Veterinaria Scandinavica,* 58.

CLARK, M., THOMASETH, K., DIRIKOLU, L., FERGUSON, D. C. & HOENIG, M. 2014. Effects of pioglitazone on insulin sensitivity and serum lipids in obese cats. *J Vet Intern Med,* 28**,** 166–74.

CLUTTON-BROCK, J. 2002. *The British Museum Book of Cats Ancient and Modern,* London British Museum Press.

COE, J. B., ADAMS, C. L. & BONNETT, B. N. 2007. A focus group study of veterinarians' and pet owners' perceptions of the monetary aspects of veterinary care. *Journal of the American Veterinary Medical Association,* 231**,** 1510–1518.

COGHLAN, S. 2018. Strong Patient Advocacy and the Fundamental Ethical Role of Veterinarians. *Journal of Agricultural and Environmental Ethics,* 31**,** 349–367.

COHEN, S. P. 2007. Compassion Fatigue and the Veterinary Health Team. *Veterinary Clinics of North America: Small Animal Practice,* 37**,** 123–134.

COMIN, A., PERIC, T., CORAZZIN, M., VERONESI, M. C., MELONI, T., ZUFFERLI, V., CORNACCHIA, G. & PRANDI, A. 2013. Hair cortisol as a marker of hypothalamic-pituitary-adrenal axis activation in Friesian dairy cows clinically or physiologically compromised. *Livestock Science,* 152**,** 36–41.

COMIN, A., VERONESI, M. C., MONTILLO, M., FAUSTINI, M., VALENTINI, S., CAIROLI, F. & PRANDI, A. 2012. Hair cortisol level as a retrospective marker of hypothalamic–pituitary–adrenal axis activity in horse foals. *The Veterinary Journal,* 194**,** 131–132.

CONTRERAS, E. T., VANDERSTICHEL, R., HOVENGA, C. & LAPPIN, M. R. 2021. Evaluation of hair and nail cortisol concentrations and associations with behavioral, physical, and environmental indicators of chronic stress in cats. *Journal of Veterinary Internal Medicine*.

COOKE, S. 2011. Duties to companion animals. *Res Publica,* 17**,** 261–274.

COOPER, R. L., DROBATZ, K. J., LENNON, E. M. & HESS, R. S. 2015. Retrospective evaluation of risk factors and outcome predictors in cats with diabetic ketoacidosis (1997-2007): 93 cases. *J Vet Emerg Crit Care (San Antonio),* 25**,** 263–72.

CORADINI, M., RAND, J. S., FILIPPICH, L. J., MORTON, J. M. & O'LEARY, C. A. 2015. Associations between meal size, gastric emptying and post-prandial plasma glucose, insulin and lactate concentrations in meal-fed cats. *Journal of Animal Physiology and Animal Nutrition,* 99**,** 757–766.

CORNELL, K. K. & KOPCHA, M. 2007. Client-Veterinarian Communication: Skills for Client Centered Dialogue and Shared Decision Making. *Veterinary Clinics of North America: Small Animal Practice,* 37**,** 37–47.

CRENSHAW, K. L. & PETERSON, M. E. 1996. Pretreatment clinical and laboratory evaluation of cats with diabetes mellitus: 104 cases (1992–1994). *Journal of the American Veterinary Medical Association,* 209**,** 943–949.

CRENSHAW, K. L., PETERSON, M. E., HEEB, L. A., MOROFF, S. D. & NICHOLS, R. 1996. Serum Fructosamine Concentration as an Index of Glycemia in Cats With Diabetes Mellitus and Stress Hyperglycemia. *Journal of Veterinary Internal Medicine,* 10**,** 360–364.

DAVENPORT, M. D., TIEFENBACHER, S., LUTZ, C. K., NOVAK, M. A. & MEYER, J. S. 2006. Analysis of endogenous cortisol concentrations in the

hair of rhesus macaques. *General and Comparative Endocrinology,* 147**,** 255–261.

DAVISON, L. J. 2015. Diabetes mellitus and pancreatitis--cause or effect? *J Small Anim Pract,* 56**,** 50–9.

DE-OLIVEIRA, L. D., CARCIOFI, A. C., OLIVEIRA, M. C., VASCONCELLOS, R. S., BAZOLLI, R. S., PEREIRA, G. T. & PRADA, F. 2008. Effects of six carbohydrate sources on diet digestibility and postprandial glucose and insulin responses in cats. *J Anim Sci,* 86**,** 2237–46.

DE LANGE, M. S., GALAC, S., TRIP, M. R. J. & KOOISTRA, H. S. 2004. High Urinary Corticoid/Creatinine Ratios in Cats with Hyperthyroidism. *Journal of Veterinary Internal Medicine,* 18**,** 152–155.

DEBORAH L. DUFFY, R. T. D. D. M., JAMES A. SERPELL 2017. Development and evaluation of the Fe-BARQ: A new survey instrument for measuring behavior in domestic cats (Felis s. catus). *Behavioural Processes,* 141**,** 329–341.

DEELEN, E., MEIJBOOM, F. L. B., TOBIAS, T. J., KOSTER, F., HESSELINK, J. W. & RODENBURG, T. B. 2023a. Considering life and death: a qualitative vignette study among farm animal veterinarians in the Netherlands on considerations in end-of-life decision-making. *Frontiers in Animal Science,* 4.

DEELEN, E., MEIJBOOM, F. L. B., TOBIAS, T. J., KOSTER, F., HESSELINK, J. W. & RODENBURG, T. B. 2023b. Handling End-of-Life Situations in Small Animal Practice: What Strategies do Veterinarians Contemplate During their Decision-Making Process? *Journal of Applied Animal Welfare Science***,** 1–14.

DEL BALDO, F., FRACASSI, F., PIRES, J., TARDO, A. M., MALERBA, E., MANASSERO, E. & GILOR, C. 2021. Accuracy of a flash glucose monitoring system in cats and determination of the time lag between blood glucose and interstitial glucose concentrations. *Journal of Veterinary Internal Medicine,* 35**,** 1279–1287.

DICICCO-BLOOM, B. & CRABTREE, B. F. 2006. The qualitative research interview. *Medical Education,* 40**,** 314–321.

DRISCOLL, C. A., MENOTTI-RAYMOND, M., ROCA, A. L., HUPE, K., JOHNSON, W. E., GEFFEN, E., HARLEY, E. H., DELIBES, M., PONTIER, D., KITCHENER, A. C., YAMAGUCHI, N., O'BRIEN, S. J. & MACDONALD, D. W. 2007. The Near Eastern Origin of Cat Domestication. *Science,* 317**,** 519–523.

EGENVALL, A., BONNETT, B. N., OLSON, P. & HEDHAMMAR, Å. 1998. Validation of computerized Swedish dog and cat insurance data against veterinary practice records. *Preventive veterinary medicine,* 36**,** 51–65.

EGENVALL, A., NØDTVEDT, A., HÄGGSTRÖM, J., STRÖM HOLST, B., MÖLLER, L. & BONNETT, B. N. 2009. Mortality of Life-Insured Swedish Cats during 1999–2006: Age, Breed, Sex, and Diagnosis. *Journal of Veterinary Internal Medicine,* 23**,** 1175–1183.

ELZERMAN, A. L., DEPORTER, T. L., BECK, A. & COLLIN, J.-F. 2020. Conflict and affiliative behavior frequency between cats in multi-cat households: a survey-based study. *Journal of Feline Medicine and Surgery,* 22**,** 705–717.

ENDENBURG, N. & VORSTENBOSCH, J. M. G. 1992. Ethical issues in the ownership of companion animals: An empirical and normative analysis. *Veterinary Quarterly,* 14**,** 129–136.

FEDERATION OF VETERINARIANS OF EUROPE. 2023. *Survey of the veterinary profession in Europe 2023* [Online]. https://fve.org/cms/wp-content/uploads/FVE-Survey-2023-updated-13-Dec-23.pdf. [Accessed 04-08 2025].

FELDMAN, E. C., NELSON, R. W. & FELDMAN, M. S. 1997. Intensive 50-week evaluation of glipizide administration in 50 cats with previously untreated diabetes mellitus. *J Am Vet Med Assoc,* 210**,** 772–7.

FINKA, L. R. & FOREMAN-WORSLEY, R. 2022. Are multi-cat homes more stressful? A critical review of the evidence associated with cat group size and wellbeing. *Journal of Feline Medicine and Surgery,* 24**,** 65–76.

FINKLER, H. & TERKEL, J. 2010. Cortisol levels and aggression in neutered and intact free-roaming female cats living in urban social groups. *Physiology & Behavior,* 99**,** 343–347.

FINLAY, L. 2021. Thematic Analysis:: The 'Good', the 'Bad'and the 'Ugly'. *European Journal for Qualitative Research in Psychotherapy,* 11**,** 103–116.

FRANCHINI, M., PRANDI, A., FILACORDA, S., PEZZIN, E. N., FANIN, Y. & COMIN, A. 2019. Cortisol in hair: a comparison between wild and feral cats in the north-eastern Alps. *European Journal of Wildlife Research,* 65.

FREEMAN, L. M., RUSH, J. E., OYAMA, M. A., MACDONALD, K. A., CUNNINGHAM, S. M., BULMER, B., MACGREGOR, J. M., LASTE, N. J., MALAKOFF, R. L., HALL, D. J. & TRAFNY, D. J. 2012. Development and evaluation of a questionnaire for assessment of health-related quality of life in cats with cardiac disease. *Journal of the American Veterinary Medical Association,* 240**,** 1188–1193.

FUSI, J., PERIC, T., PROBO, M., COTTICELLI, A., FAUSTINI, M. & VERONESI, M. C. 2021. How Stressful Is Maternity? Study about Cortisol and Dehydroepiandrosterone-Sulfate Coat and Claws Concentrations in Female Dogs from Mating to 60 Days Post-Partum. *Animals,* 11**,** 1632.

GALUPPI, R., LEVEQUE, J. F. C., BEGHELLI, V., BONOLI, C., MATTIOLI, M., OSTANELLO, F., TAMPIERI, M. P. & ACCORSI, P. A. 2013. Cortisol levels in cats' hair in presence or absence of Microsporum canis infection. *Research in Veterinary Science,* 95**,** 1076–1080.

GERMAN, A. J. 2006. The growing problem of obesity in dogs and cats. *J Nutr,* 136**,** 1940S–1946S.

GLANVILLE, C., HEMSWORTH, P. & COLEMAN, G. 2020. Conceptualising dog owner motivations: The Pet Care Competency model and role of 'duty of care'. *Animal Welfare,* 29**,** 271–284.

GONZÁLEZ-DE-LA-VARA, M. D. R., ARTURO VALDEZ, R., LEMUS-RAMIREZ, V., VÁZQUEZ-CHAGOYÁN, J. C., VILLA-GODOY, A. & ROMANO, M. C. 2011. Effects of adrenocorticotropic hormone challenge and age on hair cortisol concentrations in dairy cattle. *The Canadian Journal of Veterinary Research,* 75**,** 216–221.

GOOSSENS, M. M. C., NELSON, R. W., FELDMAN, E. C. & GRIFFEY, S. M. 1998. Response to Insulin Treatment and Survival in 104 Cats with Diabetes Mellitus (1985-1995). *Journal of Veterinary Internal Medicine,* 12**,** 1–6.

GOSTELOW, R., FORCADA, Y., GRAVES, T., CHURCH, D. & NIESSEN, S. 2014. Systematic review of feline diabetic remission: separating fact from opinion. *Vet J,* 202**,** 208–21.

GOSTELOW, R. & HAZUCHOVA, K. 2023. Pathophysiology of Prediabetes, Diabetes, and Diabetic Remission in Cats. *Veterinary Clinics of North America: Small Animal Practice,* 53**,** 511–529.

GOTTLIEB, S. & RAND, J. 2018. Managing feline diabetes: current perspectives. *Veterinary Medicine: Research and Reports,* 9**,** 33–42.

GOTTLIEB, S., RAND, J., ANDERSON, S. T., MORTON, J. M., DIAS, D. A., BOUGHTON, B. A., ROESSNER, U. & RAMADAN, Z. 2020. Metabolic Profiling of Diabetic Cats in Remission. *Frontiers in Veterinary Science,* 7.

GOTTLIEB, S. & RAND, J. S. 2013. Remission in cats: including predictors and risk factors. *Vet Clin North Am Small Anim Pract,* 43**,** 245–9.

GOTTLIEB, S., RAND, J. S. & ANDERSON, S. T. 2024. Frequency of diabetic remission, predictors of remission and survival in cats using a low-cost, moderate-intensity, home-monitoring protocol and twice-daily glargine. *Journal of Feline Medicine and Surgery,* 26**,** 1098612X241232546.

GOTTLIEB, S., RAND, J. S., MARSHALL, R. & MORTON, J. 2015. Glycemic status and predictors of relapse for diabetic cats in remission. *J Vet Intern Med,* 29**,** 184–92.

GRECO, D. S. 2001. Diagnosis of Diabetes Mellitus in Cats and Dogs. *Veterinary Clinics of North America: Small Animal Practice,* 31**,** 845–853.

GREEN, T. & MELLOR, D. 2011. Extending ideas about animal welfare assessment to include 'quality of life' and related concepts. *New Zealand Veterinary Journal,* 59**,** 263–271.

GRIFFIN, B. 2001. Profilic Cats: The Estrous Cycle. *Compendium,* 23**,** 1049–1057.

GRIFFIN, B. 2011. Population wellness: Keeping cats physically and behaviorally healthy. *The Cat***,** 1312.

GRIGG, E. K. & KOGAN, L. R. 2019. Owners' Attitudes, Knowledge, and Care Practices: Exploring the Implications for Domestic Cat Behavior and Welfare in the Home. *Animals,* 9**,** 978.

GRIMM, H., BERGADANO, A., MUSK, G. C., OTTO, K., TAYLOR, P. M. & DUNCAN, J. C. 2018. Drawing the line in clinical treatment of companion animals: recommendations from an ethics working party. *Veterinary Record,* 182**,** 664.

GRUEN, M. E., JIAMACHELLO, K. N., THOMSON, A. & LASCELLES, B. D. X. 2014. Clinical trials involving cats. *Journal of Feline Medicine and Surgery,* 16**,** 727–735.

GUSE, B., LANGENSTEIN, J., BAUER, N. & HAZUCHOVA, K. 2024. Signalment and laboratory findings in cats with diabetes mellitus in Germany: a retrospective review of laboratory submissions of 129,505 cats. *Journal of Feline Medicine and Surgery,* 26**,** 1098612X241262669.

GUSE, B., LANGENSTEIN, J., BAUER, N. & HAZUCHOVA, K. 2025. Signalment, clinicopathological findings, management practices and comorbidities in cats with diabetes mellitus in Germany: cross-sectional study of 144 cases. *Journal of Feline Medicine and Surgery,* 27**,** 1098612X241303303.

HALL, T. D., MAHONY, O., ROZANSKI, E. A. & FREEMAN, L. M. 2009. Effects of diet on glucose control in cats with diabetes mellitus treated with twice daily insulin glargine. *J Feline Med Surg,* 11**,** 125–30.

HAZUCHOVA, K., GOSTELOW, R., SCUDDER, C., FORCADA, Y., CHURCH, D. B. & NIESSEN, S. J. 2018. Acceptance of home blood glucose monitoring by owners of recently diagnosed diabetic cats and impact on quality of life changes in cat and owner. *Journal of Feline Medicine and Surgery,* 20**,** 711–720.

HEATH, S. E. 2007. *The Welfare of Cats*. *In:* ROCHLITZ, I. (ed.). Dordrecht: Springer.

HEIMBÜRGE, S., KANITZ, E. & OTTEN, W. 2019. The use of hair cortisol for the assessment of stress in animals. *General and Comparative Endocrinology,* 270**,** 10–17.

HENDRIKS, W. H., TARTTELIN, M. F. & MOUGHAN, P. J. 1997. Seasonal Hair Growth in the Adult Domestic Cat (Felis catus). *Comparative Biochemistry and Physiology Part A: Physiology,* 116**,** 29–35.

HENRY, C. J., CLARK, T. P., YOUNG, D. W. & SPANO, J. S. 1996. Urine Cortisol:Creatinine Ratio in Healthy and Sick Cats. *Journal of Veterinary Internal Medicine,* 10**,** 123–126.

HEWSON-HUGHES, A. K., GILHAM, M. S., UPTON, S., COLYER, A., BUTTERWICK, R. & MILLER, A. T. 2011. Postprandial glucose and insulin profiles following a glucose-loaded meal in cats and dogs. *British journal of nutrition,* 106**,** S101–S104.

HEWSON, C. 2014. Grief for animal companions and an approach to supporting their bereaved owners. *Bereavement Care,* 33**,** 103–110.

HOELMKJAER, K. M., SPODSBERG, E. M. & BJORNVAD, C. R. 2015. Insulin detemir treatment in diabetic cats in a practice setting. *J Feline Med Surg,* 17**,** 144–51.

HOENIG, M., CLARK, M., SCHAEFFER, D. J. & REICHE, D. 2018. Effects of the sodium-glucose cotransporter 2 (SGLT 2) inhibitor velagliflozin, a new drug with therapeutic potential to treat diabetes in cats. *Journal of Veterinary Pharmacology and Therapeutics,* 41**,** 266–273.

HOENIG, M. & FERGUSON, D. C. 2002. Effects of neutering on hormonal concentrations and energy requirements in male and female cats. *American Journal of Veterinary Research,* 63**,** 634–639.

HOENIG, M., HALL, G., FERGUSON, D., JORDAN, K., HENSON, M., JOHNSON, K. & O'BRIEN, T. 2000. A Feline Model of Experimentally Induced Islet Amyloidosis. *The American Journal of Pathology,* 157**,** 2143–2150.

HOENIG, M., TRAAS, A. M. & SCHAEFFER, D. J. 2013. Evaluation of routine hematology profile results and fructosamine, thyroxine, insulin, and proinsulin concentrations in lean, overweight, obese, and diabetic cats. *Journal of the American Veterinary Medical Association,* 243**,** 1302–1309.

HOFFMANN, R., LAGERKVIST, C. J., HAGBERG GUSTAVSSON, M. & HOLST, B. S. 2018. An empirical examination of the conceptualization of companion animals. *BMC Psychol,* 6**,** 15.

INES, M., RICCI-BONOT, C. & MILLS, D. S. 2021. My cat and me—a study of cat owner perceptions of their bond and relationship. *Animals,* 11**,** 1601.

ITO, N., ITO, T., KROMMINGA, A., BETTERMANN, A., TAKIGAWA, M., KEES, F., STRAUB, R. H. & PAUS, R. 2005. Human hair follicles display a functional equivalent of the hypothalamic-pituitary-adrenal axis and synthesize cortisol. *The FASEB Journal,* 19**,** 1332–1334.

KESSLER, M. R. & TURNER, D. C. 1997. Stress and Adaptation of Cats (Felis Silvestris Catus) Housed Singly, in Pairs and in Groups in Boarding Catteries. *Animal Welfare,* 6**,** 243–254.

KIM, G.-H., LEE, K., CHOI, H.-S., HAN, J. S. & KIM, S.-A. 2025. Hair Cortisol and Fe-BARQ: Evaluating Chronic Stress and Behavior in Cats with Chronic Kidney Disease. *Animals,* 15**,** 889.

KIPPERMAN, B., MORRIS, P. & ROLLIN, B. 2018. Ethical dilemmas encountered by small animal veterinarians: characterisation, responses, consequences and beliefs regarding euthanasia. *Veterinary Record,* 182**,** 548.

KIPPERMAN, B. S., KASS, P. H. & RISHNIW, M. 2017. Factors that influence small animal veterinarians' opinions and actions regarding cost of care and effects of economic limitations on patient care and outcome and professional career satisfaction and burnout. *Journal of the American Veterinary Medical Association,* 250**,** 785–794.

KNESL, O., HART, B. L., FINE, A. H. & COOPER, L. 2016. Opportunities for incorporating the human-animal bond in companion animal practice. *Journal of the American Veterinary Medical Association,* 249**,** 42–44.

KOOLHAAS, J., KORTE, S., DE BOER, S., VAN DER VEGT, B., VAN REENEN, C., HOPSTER, H., DE JONG, I., RUIS, M. & BLOKHUIS, H. 1999. Coping styles in animals: current status in behavior and stress-physiology. *Neuroscience & Biobehavioral Reviews,* 23**,** 925–935.

KOOLHAAS, J. M., BARTOLOMUCCI, A., BUWALDA, B., DE BOER, S. F., FLÜGGE, G., KORTE, S. M., MEERLO, P., MURISON, R., OLIVIER,

B. & PALANZA, P. 2011. Stress revisited: a critical evaluation of the stress concept. *Neuroscience & Biobehavioral Reviews,* 35**,** 1291–1301.
KOREN, L., MOKADY, O., KARASKOV, T., KLEIN, J., KOREN, G. & GEFFEN, E. 2002. A novel method using hair for determining hormonal levels in wildlife. *Animal Behaviour,* 63**,** 403–406.
KRAUS, M. S., CALVERT, C. A., JACOBS, G. J. & BROWN, J. 1997. Feline diabetes mellitus: a retrospective mortality study of 55 cats (1982-1994). *Journal of the American Animal Hospital Association,* 33**,** 107–11.
KRISTENSEN, G. K. & RAVN, M. N. 2015. The voices heard and the voices silenced: Recruitment processes in qualitative interview studies. *Qualitative Research,* 15**,** 722–737.
KVALE, S. & BRINKMANN, S. 2009. *Interviews: Learning the craft of qualitative research interviewing*, Sage.
LAFLAMME, D. P. & HANNAH, S. S. 2005. Increased dietary protein promotes fat loss and reduces loss of lean body mass during weight loss in cats. *Int J Appl Res Vet Med,* 3**,** 62–68.
LEDERER, R., RAND, J., HUGHES, I. & FLEEMAN, L. Chronic or recurring medical problems, dental disease, repeated corticosteroid treatment, and lower physical activity are associated with diabetes in Burmese cats. 2003. ACVIM.
LEDERER, R., RAND, J., JONSSON, N., HUGHES, I. & MORTON, J. 2009. Frequency of feline diabetes mellitus and breed predisposition in domestic cats in Australia. *The Veterinary Journal,* 179**,** 254–258.
LINK, K. R., ALLIO, I., RAND, J. S. & EPPLER, E. 2013. The effect of experimentally induced chronic hyperglycaemia on serum and pancreatic insulin, pancreatic islet IGF-I and plasma and urinary ketones in the domestic cat (Felis felis). *Gen Comp Endocrinol,* 188**,** 269–81.
LINK, K. R. & RAND, J. S. 2008. Changes in blood glucose concentration are associated with relatively rapid changes in circulating fructosamine concentrations in cats. *J Feline Med Surg,* 10**,** 583–92.
LITTLEWOOD, K., BEAUSOLEIL, N., STAFFORD, K. & STEPHENS, C. 2021. "What Would You Do?": How Cat Owners Make End-of-Life Decisions and Implications for Veterinary-Client Interactions. *Animals,* 11**,** 1114.
LOWE, A. D., GRAVES, T. K., CAMPBELL, K. L. & SCHAEFFER, D. J. 2009. A pilot study comparing the diabetogenic effects of dexamethasone and prednisolone in cats. *J Am Anim Hosp Assoc,* 45**,** 215–24.
LUE, T. W., PANTENBURG, D. P. & CRAWFORD, P. M. 2008. Impact of the owner-pet and client-veterinarian bond on the care that pets receive. *Journal of the American Veterinary Medical Association,* 232**,** 531–540.
LUESCHER, A. U. 2003. Diagnosis and management of compulsive disorders in dogs and cats. *Veterinary Clinics: Small Animal Practice,* 33**,** 253–267.
LUND, E. M., ARMSTRONG, P., KIRK, C. & KLAUSNER, J. 2005. Prevalence and risk factors for obesity in adult cats from private US veterinary practices. *Intern J Appl Res Vet Med,* 3**,** 88–96.

MALTERUD K, S. V., GUASSORA AD. 2016. Sample Size in Qualitative Interview Studies: Guided by Information Power. *Qualitative Health Research,* 26**,** 1753–1760.

MARITI, C., BOWEN, J. E., CAMPA, S., GREBE, G., SIGHIERI, C. & GAZZANO, A. 2016. Guardians' Perceptions of Cats' Welfare and Behavior Regarding Visiting Veterinary Clinics. *Journal of Applied Animal Welfare Science,* 19**,** 375–384.

MARITI, C., GUERRINI, F., VALLINI, V., BOWEN, J. E., FATJÓ, J., DIVERIO, S., SIGHIERI, C. & GAZZANO, A. 2017. The perception of cat stress by Italian owners. *Journal of Veterinary Behavior,* 20**,** 74–81.

MARSHALL, R. D., RAND, J. S. & MORTON, J. M. 2009. Treatment of newly diagnosed diabetic cats with glargine insulin improves glycaemic control and results in higher probability of remission than protamine zinc and lente insulins. *J Feline Med Surg,* 11**,** 683–91.

MATTE, A. R., KHOSA, D. K., COE, J. B. & MEEHAN, M. P. 2019. Impacts of the process and decision-making around companion animal euthanasia on veterinary wellbeing. *Veterinary Record,* 185**,** 480.

MAZZAFERRO, E. M., GRECO, D. S., TURNER, A. S. & FETTMAN, M. J. 2003. Treatment of feline diabetes mellitus using an alpha-glucosidase inhibitor and a low-carbohydrate diet. *J Feline Med Surg,* 5**,** 183–9.

MCCANN, T. M., SIMPSON, K. E., SHAW, D. J., BUTT, J. A. & GUNN-MOORE, D. A. 2007. Feline diabetes mellitus in the UK: The prevalence within an insured cat population and a questionnaire-based putative risk factor analysis. *Journal of Feline Medicine and Surgery,* 9**,** 289–299.

MCCOBB, E. C., PATRONEK, G. J., MARDER, A., DINNAGE, J. D. & STONE, M. S. 2005. Assessment of stress levels among cats in four animal shelters. *Journal of the American Veterinary Medical Association,* 226**,** 548–555.

MCCONNELL, A. R., PAIGE LLOYD, E. & HUMPHREY, B. T. 2019. We Are Family: Viewing Pets as Family Members Improves Wellbeing. *Anthrozoös,* 32**,** 459–470.

MCCUNE, S. 1995. The impact of paternity and early socialisation on the development of cats' behaviour to people and novel objects. *Applied Animal Behaviour Science,* 45**,** 109–124.

MCMILLAN, C. V., HONEYFORD, R. J., DATTA, J., MADGE, N. J. & BRADLEY, C. 2004. The development of a new measure of quality of life for young people with diabetes mellitus: the ADDQoL-Teen. *Health and quality of life outcomes,* 2**,** 61.

MCMILLAN, F. D. 2000. Quality of life in animals. *Journal of the American Veterinary Medical Association,* 216**,** 1904–1910.

MCMILLAN, F. D. 2001. Rethinking euthanasia: death as an unintentional outcome. *Journal of the American Veterinary Medical Association,* 219**,** 1204–1206.

MEYER, J., NOVAK, M., HAMEL, A. & ROSENBERG, K. 2014. Extraction and Analysis of Cortisol from Human and Monkey Hair. *Journal of Visualized Experiments*.

MEYER, J. S. & NOVAK, M. A. 2012. Minireview: Hair Cortisol: A Novel Biomarker of Hypothalamic-Pituitary-Adrenocortical Activity. *Endocrinology,* 153**,** 4120–4127.

MILLER, G. E., CHEN, E. & ZHOU, E. S. 2007. If it goes up, must it come down? Chronic stress and the hypothalamic-pituitary-adrenocortical axis in humans. *Psychological bulletin,* 133**,** 25.

MOBERG, G. P. 1987. Problems in defining stress and distress in animals. *Journal of the American Veterinary Medical Association,* 191**,** 1207–1211.

MOBERG, G. P. 2000. *Biological responses to stress: implications for animal welfare.,* Wallingford, New York, CABI Publishing.

MOORE, A. S. 2011. Managing Cats with Cancer. *Journal of Feline Medicine and Surgery,* 13**,** 661–671.

MORGAN, C. A. 2009. *Stepping up to the plate: animal welfare, veterinarians, and ethical conflicts.* University of British Columbia.

MORGAN, C. A. & MCDONALD, M. 2007. Ethical dilemmas in veterinary medicine. *Veterinary Clinics of North America: Small Animal Practice,* 37**,** 165–79.

MORMÈDE, P., ANDANSON, S., AUPÉRIN, B., BEERDA, B., GUÉMENÉ, D., MALMKVIST, J., MANTECA, X., MANTEUFFEL, G., PRUNET, P., VAN REENEN, C. G., RICHARD, S. & VEISSIER, I. 2007. Exploration of the hypothalamic–pituitary–adrenal function as a tool to evaluate animal welfare. *Physiology & Behavior,* 92**,** 317–339.

MORRIS, P. H., DOE, C. & GODSELL, E. 2008. Secondary emotions in non-primate species? Behavioural reports and subjective claims by animal owners. *Cognition and Emotion,* 22**,** 3–20.

MOSES, L., MALOWNEY, M. J. & WESLEY BOYD, J. 2018. Ethical conflict and moral distress in veterinary practice: A survey of North American veterinarians. *Journal of Veterinary Internal Medicine,* 32**,** 2115–2122.

MULLAN, S. M. 2012. Ethical decision-making in veterinary practice: Using the head and the heart. *Vet. Rec,* 171**,** 443–444.

MÖSTL, E. & PALME, R. 2002. Hormones as indicators of stress. *Domestic Animal Endocrinology,* 23**,** 67–74.

NELSON, R., FELDMAN, E., FORD, S. & ROEMER, O. 1993. Effect of an orally administered sulfonylurea, glipizide, for treatment of diabetes mellitus in cats. *Journal of the American Veterinary Medical Association,* 203**,** 821–827.

NELSON, R., SPANN, D., ELLIOTT, D., BRONDOS, A. & VULLIET, R. 2004. Evaluation of the Oral Antihyperglycemic Drug Metformin in Normal and Diabetic Cats. *Journal of Veterinary Internal Medicine,* 18**,** 18–24.

NELSON, R. W., GRIFFEY, S. M., FELDMAN, E. C. & FORD, S. L. 1999. Transient clinical diabetes mellitus in cats: 10 cases (1989-1991). *J Vet Intern Med,* 13**,** 28–35.

NELSON, R. W., LYNN, R. C., WAGNER-MANN, C. C. & MICHELS, G. M. 2001. Efficacy of protamine zinc insulin for treatment of diabetes mellitus in cats. *Journal of the American Veterinary Medical Association,* 218**,** 38–42.

NERHAGEN, S., MOBERG, H. L., BOGE, G. S. & GLANEMANN, B. 2021. Prednisolone-induced diabetes mellitus in the cat: a historical cohort. *Journal of Feline Medicine and Surgery,* 23**,** 175–180.

NIELSON, S. A., KHOSA, D. K., VERBRUGGHE, A. & CLOW, K. M. 2024. Cat caregivers' perceptions, motivations, and behaviours for feeding treats: A cross sectional study. *PLOS ONE,* 19**,** e0296011.

NIESSEN, S., HAZUCHOVA, K., POWNEY, S., GUITIAN, J., NIESSEN, A., PION, P., SHAW, J. & CHURCH, D. 2017. The Big Pet Diabetes Survey: Perceived Frequency and Triggers for Euthanasia. *Veterinary Sciences,* 4**,** 27.

NIESSEN, S. J., BJORNVAD, C., CHURCH, D. B., DAVISON, L., ESTEBAN-SALTIVERI, D., FLEEMAN, L. M., FORCADA, Y., FRACASSI, F., GILOR, C. & HANSON, J. 2022. Agreeing Language in Veterinary Endocrinology (ALIVE): Diabetes mellitus-a modified Delphi-method-based system to create consensus disease definitions. *The Veterinary Journal,* 289**,** 105910.

NIESSEN, S. J., CHURCH, D. B. & FORCADA, Y. 2013. Hypersomatotropism, acromegaly, and hyperadrenocorticism and feline diabetes mellitus. *Vet Clin North Am Small Anim Pract,* 43**,** 319–50.

NIESSEN, S. J., FORCADA, Y., MANTIS, P., LAMB, C. R., HARRINGTON, N., FOWKES, R., KORBONITS, M., SMITH, K. & CHURCH, D. B. 2015. Studying Cat (Felis catus) Diabetes: Beware of the Acromegalic Imposter. *PLoS One,* 10**,** e0127794.

NIESSEN, S. J. M. 2011. Quality-of-life assessment: honouring our oath in practice and research. *Journal of Small Animal Practice,* 52**,** 453–454.

NIESSEN, S. J. M., BJORNVAD, C., CHURCH, D B., DAVISON, L., ESTEBAN-SALTIVERI, D., FLEEMAN, L M., FORCADA, Y., FRACASSI, F., GILOR, C., HANSON, J., HERRTAGE, M., LATHAN, P., LEAL, R O., LOSTE, A., REUSCH, C., SCHERMERHORN, T., STENGEL, C., THORESEN, S., THUROCZY, J. 2022. Agreeing Language in Veterinary Endocrinology (ALIVE): Diabetes mellitus - a modified Delphi-method-based system to create consensus disease definitions. *Vet J,* 29.

NIESSEN, S. J. M., POWNEY, S., GUITIAN, J., NIESSEN, A. P. M., PION, P. D., SHAW, J. A. M. & CHURCH, D. B. 2010. Evaluation of a Quality-of-Life Tool for Cats with Diabetes Mellitus. *Journal of Veterinary Internal Medicine,* 24**,** 1098–1105.

NOBLE, C. E., WISEMAN-ORR, L. M., SCOTT, M. E., NOLAN, A. M. & REID, J. 2019. Development, initial validation and reliability testing of a web-based, generic feline health-related quality-of-life instrument. *Journal of Feline Medicine and Surgery,* 21**,** 84–94.

NOLI, C. 2019. Assessing quality of life for pets with dermatologic disease and their owners. *Veterinary Clinics: Small Animal Practice,* 49**,** 83–93.

O'BRIEN, T., HAYDEN, D., JOHNSON, K. & FLETCHER, T. 1986. Immunohistochemical morphometry of pancreatic endocrine cells in diabetic, normoglycaemic glucose-intolerant and normal cats. *Journal of comparative pathology,* 96**,** 357–369.

O'NEILL, D. G., GOSTELOW, R., ORME, C., CHURCH, D. B., NIESSEN, S. J. M., VERHEYEN, K. & BRODBELT, D. C. 2016. Epidemiology of Diabetes Mellitus among 193,435 Cats Attending Primary-Care Veterinary Practices in England. *Journal of Veterinary Internal Medicine,* 30**,** 964–972.

O'NEILL, D. G., CHURCH, D. B., MCGREEVY, P. D., THOMSON, P. C. & BRODBELT, D. C. 2015. Longevity and mortality of cats attending primary care veterinary practices in England. *Journal of Feline Medicine and Surgery,* 17**,** 125–133.

OGDEN, U., KINNISON, T. & MAY, S. A. 2012. Attitudes to animal euthanasia do not correlate with acceptance of human euthanasia or suicide. *Veterinary Record,* 171**,** 174–174.

PACKER, R. M. A., DAVIES, A. M., VOLK, H. A., PUCKETT, H. L., HOBBS, S. L. & FOWKES, R. C. 2019. What can we learn from the hair of the dog? Complex effects of endogenous and exogenous stressors on canine hair cortisol. *PLOS ONE,* 14**,** e0216000.

PALM, C. A. & FELDMAN, E. C. 2013. Oral hypoglycemics in cats with diabetes mellitus. *Vet Clin North Am Small Anim Pract,* 43**,** 407–15.

PANCIERA, D. L., THOMAS, C. B., EICKER, S. W. & ATKINS, C. E. 1990. Epizootiologic patterns of diabetes mellitus in cats: 333 cases (1980-1986). *Journal of the American Veterinary Medical Association,* 197**,** 1504–1508.

PLANTINGA, E. A., BOSCH, G. & HENDRIKS, W. H. 2011. Estimation of the dietary nutrient profile of free-roaming feral cats: possible implications for nutrition of domestic cats. *British Journal of Nutrition,* 106**,** S35–S48.

PRAHL, A., GUPTILL, L., GLICKMAN, N. W., TETRICK, M. & GLICKMAN, L. T. 2007. Time trends and risk factors for diabetes mellitus in cats presented to veterinary teaching hospitals. *Journal of Feline Medicine and Surgery,* 9**,** 351–358.

PRUETT, S. B. 2003. Stress and the immune system. *Pathophysiology,* 9**,** 133–153.

QIN, D., RIZAK, J., CHU, X., LI, Z., YANG, S., LÜ, L., YANG, L., YANG, Q., YANG, B., PAN, L., YIN, Y., CHEN, L., FENG, X. & HU, X. 2015. A spontaneous depressive pattern in adult female rhesus macaques. *Scientific Reports,* 5:11267.

QUIMBY, J. M., SMITH, M. L. & LUNN, K. F. 2017. Evaluation of the effects of hospital visit stress on physiologic parameters in the cat. *Journal of Feline Medicine and Surgery,* 13**,** 733–737.
RAMOS, D. 2019. Common feline problem behaviors: Aggression in multi-cat households. *Journal of feline medicine and surgery,* 21**,** 221–233.
RAND, J. S., FLEEMAN, L. M., FARROW, H. A., APPLETON, D. J. & LEDERER, R. 2004. Canine and Feline Diabetes Mellitus: Nature or Nurture? *The Journal of Nutrition,* 134**,** 2072S–2080S.
RAND, J. S., KINNAIRD, E., BAGLIONI, A., BLACKSHAW, J. & PRIEST, J. 2002. Acute stress hyperglycemia in cats is associated with struggling and increased concentrations of lactate and norepinephrine. *J Vet Intern Med,* 16**,** 123–32.
RAY, M., CARNEY, H. C., BOYNTON, B., QUIMBY, J., ROBERTSON, S., ST DENIS, K., TUZIO, H. & WRIGHT, B. 2021. 2021 AAFP Feline Senior Care Guidelines. *Journal of Feline Medicine and Surgery,* 23**,** 613–638.
RE, M., DEL BALDO, F., TARDO, A. M. & FRACASSI, F. 2023. Monitoring of Diabetes Mellitus Using the Flash Glucose Monitoring System: The Owners' Point of View. *Veterinary Sciences,* 10**,** 203.
REUSCH, C. E., KLEY, S. & CASELLA, M. 2006. Home monitoring of the diabetic cat. *Journal of Feline Medicine and Surgery,* 8**,** 119–127.
REYNOLDS, C. A., OYAMA, M. A., RUSH, J. E., ROZANSKI, E. A., SINGLETARY, G. E., BROWN, D. C., CUNNINGHAM, S. M., FOX, P. R., BOND, B., ADIN, D. B., WILLIAMS, R. M., MACDONALD, K. A., MALAKOFF, R., SLEEPER, M. M., SCHOBER, K. E., PETRIE, J. P. & HOGAN, D. F. 2010. Perceptions of Quality of Life and Priorities of Owners of Cats with Heart Disease. *Journal of Veterinary Internal Medicine,* 24**,** 1421–1426.
RIEDERER, A., ZINI, E., SALESOV, E., FRACASSI, F., PADRUTT, I., MACHA, K., STOCKLE, T. M., LUTZ, T. A. & REUSCH, C. E. 2016. Effect of the Glucagon-like Peptide-1 Analogue Exenatide Extended Release in Cats with Newly Diagnosed Diabetes Mellitus. *J Vet Intern Med,* 30**,** 92–100.
ROCHLITZ, I. 2013. *Feline welfare issues,* Cambridge, Cambridge University Press.
ROCHLITZ, I., PODBERSCEK, A. L. & BROOM, D. M. 1998. Welfare of cats in a quarantine cattery. *Veterinary Record,* 143**,** 35–39.
ROLLIN, B. 2006. The ethics of referral. *The Canadian Veterinary Journal,* 47**,** 717.
ROLLIN, B. E. 2007. Ethical issues in geriatric feline medicine. *Journal of Feline Medicine and Surgery,* 9**,** 326–334.
ROLLIN, B. E. 2011. Euthanasia, Moral Stress, and Chronic Illness in Veterinary Medicine. *Veterinary Clinics of North America: Small Animal Practice,* 41**,** 651–659.
ROLLIN, B. E. 2013. *An introduction to veterinary medical ethics: theory and cases*, John Wiley & Sons.

ROOMP, K. & RAND, J. 2009. Intensive blood glucose control is safe and effective in diabetic cats using home monitoring and treatment with glargine. *J Feline Med Surg,* 11**,** 668–82.
ROOMP, K. & RAND, J. 2012. Evaluation of detemir in diabetic cats managed with a protocol for intensive blood glucose control. *J Feline Med Surg,* 14**,** 566–72.
ROSOFF, P. M., MOGA, J., KEENE, B., ADIN, C., FOGLE, C., RUDERMAN, R., HOPKINSO, H. & WEYHRAUCH, C. 2018. Resolving Ethical Dilemmas in a Tertiary Care Veterinary Specialty Hospital: Adaptation of the Human Clinical Consultation Committee Model. *The American Journal of Bioethics,* 18**,** 41–53.
ROTH, L. S. V., FARESJÖ, Å., THEODORSSON, E. & JENSEN, P. 2016. Hair cortisol varies with season and lifestyle and relates to human interactions in German shepherd dogs. *Scientific Reports,* 6**,** 19631.
SAKELLARIS, P. C. & VERNIKLOS-DANEILLIS, J. 1975. Increased Rate of Response of the Pituitary-Adrenal System in Rats Adapted to Chronic Stress. *Endocrinology,* 97**,** 597–602.
SALABERGER, T., MILLARD, M., MAKAREM, S. E., MÖSTL, E., GRÜNBERGER, V., KRAMETTER-FRÖTSCHER, R., WITTEK, T. & PALME, R. 2016. Influence of external factors on hair cortisol concentrations. *General and Comparative Endocrinology,* 233**,** 73–78.
SALLANDER, M., ELIASSON, J. & HEDHAMMAR, Å. 2012. Prevalence and risk factors for the development of diabetes mellitus in Swedish cats. *Acta Veterinaria Scandinavica,* 54**,** 61.
SANDERS, C. R. Killing with kindness: Veterinary euthanasia and the social construction of personhood. Sociological forum, 1995. Springer, 195–214.
SANDS, L. P., FERREIRA, P., STEWART, A. L., BROD, M. & YAFFE, K. 2004. What explains differences between dementia patients' and their caregivers' ratings of patients' quality of life? *The American journal of geriatric psychiatry,* 12**,** 272–280.
SAPOLSKY, R. M., ROMERO, L. M. & MUNCK, A. U. 2000. How Do Glucocorticoids Influence Stress Responses? Integrating Permissive, Suppressive, Stimulatory, and Preparative Actions*. *Endocrine Reviews,* 21**,** 55–89.
SAUNDERS, H. M., VANWINKLE, T. J., DROBATZ, K., KIMMEL, S. E. & WASHABAU, R. J. 2002. Ultrasonographic findings in cats with clinical, gross pathologic, and histologic evidence of acute pancreatic necrosis: 20 cases (1994–2001). *Journal of the American Veterinary Medical Association,* 221**,** 1724–1730.
SCARLETT, J. M. & DONOGHUE, S. 1998. Associations between body condition and disease in cats. *Journal of the American Veterinary Medical Association,* 212**,** 1725–1731.
SCHAER, M. 1977. A clinical survey of thirty cats with diabetes mellitus.

SCHATZ, S. & PALME, R. 2001. Measurement of faecal cortisol metabolites in cats and dogs: a non-invasive method for evaluating adrenocortical function. *Veterinary research communications,* 25**,** 271–287.

SCHRECK, C. 2000. Accumulation and long-term effects of stress in fish. *The biology of animal stress: basic principles and implications for animal welfare.*: Cabi Publishing Wallingford UK.

SCOTT-MONCRIEFF, J. C. 2010. Insulin resistance in cats. *Veterinary Clinics: Small Animal Practice,* 40**,** 241–257.

SERGIEL, A., CATTET, M., KAPRONCZAI, L., JANZ, D. M., SELVA, N., BARTOŃ, K. A., SWENSON, J. E. & ZEDROSSER, A. 2020. Do follicles matter? Testing the effect of follicles on hair cortisol levels. *Conservation Physiology,* 8.

SERPELL, J. 2002. Anthropomorphism and Anthropomorphic Selection—Beyond the "Cute Response". *Society & Animals,* 10**,** 437–454.

SHAW, J. R., BONNETT, B. N., ADAMS, C. L. & ROTER, D. L. 2006. Veterinarian-client-patient communication patterns used during clinical appointments in companion animal practice. *Journal of the American Veterinary Medical Association,* 228**,** 714–721.

SINGH, R., RAND, J. S., CORADINI, M. & MORTON, J. M. 2015. Effect of acarbose on postprandial blood glucose concentrations in healthy cats fed low and high carbohydrate diets. *J Feline Med Surg,* 17**,** 848–57.

SJAASTAD, O. V., SAND, O. & HOVE, K. 2010. *Physiology of domestic animals*, Scan. Vet. Press.

SKK, A. 2024. *Katten - Populäraste sällskapsdjuret i Sverige* [Online]. [Accessed 04-22 2025].

SLATER, M., GARRISON, L., MILLER, K., WEISS, E., MAKOLINSKI, K., DRAIN, N. & MIRONTSHUK, A. 2013. Practical Physical and Behavioral Measures to Assess the Socialization Spectrum of Cats in a Shelter-Like Setting during a Three Day Period. *Animals,* 3**,** 1162–1193.

SLATER, M. R., BARTON, C. L., ROGERS, K. S., PETERSON, J. L., HARRIS, C. K. & WALLACE, K. 1996. Factors affecting treatment decisions and satisfaction of owners of cats with cancer. *Journal of the American Veterinary Medical Association,* 208**,** 1248–1252.

SLINGERLAND, L. I., FAZILOVA, V. V., PLANTINGA, E. A., KOOISTRA, H. S. & BEYNEN, A. C. 2009. Indoor confinement and physical inactivity rather than the proportion of dry food are risk factors in the development of feline type 2 diabetes mellitus. *The Veterinary Journal,* 179**,** 247–253.

SPARKES, A. H., CANNON, M., CHURCH, D., FLEEMAN, L., HARVEY, A., HOENIG, M., PETERSON, M. E., REUSCH, C. E., TAYLOR, S. & ROSENBERG, D. 2015. ISFM consensus guidelines on the practical management of diabetes mellitus in cats. *Journal of Feline Medicine and Surgery,* 17**,** 235–50.

SPITZNAGEL, M. B. & CARLSON, M. D. 2019. Caregiver Burden and Veterinary Client Well-Being. *Veterinary Clinics of North America: Small Animal Practice,* 49**,** 431–444.

SPITZNAGEL, M. B., JACOBSON, D. M., COX, M. D. & CARLSON, M. D. 2017. Caregiver burden in owners of a sick companion animal: a cross-sectional observational study. *Vet Rec,* 181**,** 321.

SPITZNAGEL, M. B., MARCHITELLI, B., GARDNER, M. & CARLSON, M. D. 2020. Euthanasia from the Veterinary Client's Perspective: Psychosocial Contributors to Euthanasia Decision Making. *The Veterinary clinics of North America. Small animal practice,* 50**,** 591–605.

SPRINGER, S., SANDØE, P., BØKER LUND, T. & GRIMM, H. 2019. "Patients' interests first, but …" Austrian Veterinarians' Attitudes to Moral Challenges in Modern Small Animal Practice. *Animals,* 9**,** 241.

STALDER, T. & KIRSCHBAUM, C. 2012. Analysis of cortisol in hair – State of the art and future directions. *Brain, Behavior, and Immunity,* 26**,** 1019–1029.

STALDER, T., STEUDTE, S., MILLER, R., SKOLUDA, N., DETTENBORN, L. & KIRSCHBAUM, C. 2012. Intraindividual stability of hair cortisol concentrations. 37**,** 602–610.

STAMMBACH, K. B. & TURNER, D. C. 1999. Understanding the Human—Cat Relationship: Human Social Support or Attachment. *Anthrozoös,* 12**,** 162–168.

STELLA, J. & CRONEY, C. 2019. Coping styles in the domestic cat (Felis silvestris catus) and implications for cat welfare. *Animals,* 9**,** 370.

STELLA, J., CRONEY, C. & BUFFINGTON, T. 2013. Effects of stressors on the behavior and physiology of domestic cats. *Applied Animal Behaviour Science,* 143**,** 157–163.

STUBSJØEN, S. M., BOHLIN, J., DAHL, E., KNAPPE-POINDECKER, M., FJELDAAS, T., LEPSCHY, M., PALME, R., LANGBEIN, J. & ROPSTAD, E. 2015. Assessment of chronic stress in sheep (part I): The use of cortisol and cortisone in hair as non-invasive biological markers. *Small Ruminant Research,* 132**,** 25–31.

SUNDMAN, A.-S., VAN POUCKE, E., SVENSSON HOLM, A.-C., FARESJÖ, Å., THEODORSSON, E., JENSEN, P. & ROTH, L. S. V. 2019. Long-term stress levels are synchronized in dogs and their owners. *Scientific Reports,* 9.

TANNENBAUM, J. 1985. Ethics and human-companion animal interaction. A plea for a veterinary ethics of the human-companion animal bond. *The Veterinary Clinics of North America. Small Animal Practice,* 15**,** 431–447.

TERWISSEN, C. V., MASTROMONACO, G.F. , MURRAY D.L. 2013. Influence of adrenocorticotrophin hormone challenge and external factors (age, sex, and body region) on hair cortisol concentration in Canada lynx (Lynx canadensis). *General and Comparative Endocrinology,* 194**,** 162–167.

THORNTON, L. A., CAVE, N., BRIDGES, J. P. & STELL, A. J. 2018. Owner perceptions of their cat's quality of life when treated with a modified University of Wisconsin-Madison protocol for lymphoma. *J Feline Med Surg,* 20**,** 356–361.

TZANNES, S., HAMMOND, M. F., MURPHY, S., SPARKES, A. & BLACKWOOD, L. 2008. Owners 'perception of their cats' quality of life during COP chemotherapy for lymphoma. *Journal of Feline Medicine and Surgery,* 10**,** 73–81.

VERBRUGGHE, A. & HESTA, M. 2017. Cats and Carbohydrates: The Carnivore Fantasy? *Vet Sci,* 4.

VILLAVERDE, C. & HERVERA, M. 2025. Feline comorbidities: a nutritional approach to management. *Journal of Feline Medicine and Surgery,* 27**,** 1098612X251320877.

VOGELNEST, L. J. 2017. Skin as a marker of general feline health: Cutaneous manifestations of systemic disease. *Journal of Feline Medicine and Surgery,* 19**,** 948–960.

WAITE, O., GOSTELOW, R., WRIGHT, E., JEPSON, R. E., BRODBELT, D. C. & O'NEILL, D. G. 2025. Frequency, Risk Factors, and Mortality for Diabetes Mellitus in 1 225 130 Cats Under Primary Veterinary Care in the United Kingdom in 2019. *Journal of Veterinary Internal Medicine,* 39.

WEAVER, K. E., ROZANSKI, E. A., MAHONY, O. M., CHAN, D. L. & FREEMAN, L. M. 2006. Use of glargine and lente insulins in cats with diabetes mellitus. *J Vet Intern Med,* 20**,** 234–8.

WEI, A., FASCETTI, A. J., VILLAVERDE, C., WONG, R. K. & RAMSEY, J. J. 2011. Effect of water content in a canned food on voluntary food intake and body weight in cats. *Am J Vet Res,* 72**,** 918–23.

WEICH, K. & GRIMM, H. 2018. Meeting the Patient's Interest in Veterinary Clinics. Ethical Dimensions of the 21st Century Animal Patient. *Food Ethics,* 1**,** 259–272.

WOJTAŚ, J. 2023. Hair cortisol levels in cats with and without behavioural problems. *Journal of Feline Medicine and Surgery,* 25**,** 1098612X221150624.

YAMANASHI, Y. M., NARUKI; MORI, YUSUKE; HAYASHI, & MISATO; SUZUKI, J. 2013. Cortisol analysis of hair of captive chimpanzees (Pantroglodytes). *General and comparative endocrinology,* 194**,** 55–63.

YEATES, J. & MAIN, D. 2009. Assessment of companion animal quality of life in veterinary practice and research. *Journal of Small Animal Practice,* 50**,** 274–281.

YEATES, J. W. 2010. Death is a Welfare Issue. *Journal of Agricultural and Environmental Ethics,* 23**,** 229–241.

YEATES, J. W. & MAIN, D. C. J. 2010. The ethics of influencing clients. *Journal of the American Veterinary Medical Association,* 237**,** 263–267.

YEATES, J. W., MULLAN, S., STONE, M. & MAIN, D. C. J. 2011. Promoting discussions and decisions about dogs' quality-of-life. *Journal of Small Animal Practice,* 52**,** 459–463.

ZAMPROGNO, H., HANSEN, B. D., BONDELL, H. D., SUMRELL, A. T., SIMPSON, W., ROBERTSON, I. D., BROWN, J., PEASE, A. P., ROE, S. C., HARDIE, E. M., WHEELER, S. J. & LASCELLES, B. D. X. 2010. Item generation and design testing of a questionnaire to assess degenerative joint disease–associated pain in cats. *American Journal of Veterinary Research,* 71**,** 1417–1424.

ZASLOFF, R. L. 1996. Measuring attachment to companion animals: a dog is not a cat is not a bird. *Applied Animal Behaviour Science,* 47**,** 43–48.

ZINI, E., HAFNER, M., KOOK, P., LUTZ, T. A., OHLERTH, S. & REUSCH, C. E. 2015. Longitudinal Evaluation of Serum Pancreatic Enzymes and Ultrasonographic Findings in Diabetic Cats Without Clinically Relevant Pancreatitis at Diagnosis. *Journal of Veterinary Internal Medicine,* 29**,** 589–596.

ZINI, E., HAFNER, M., OSTO, M., FRANCHINI, M., ACKERMANN, M., LUTZ, T. A. & REUSCH, C. E. 2010. Predictors of clinical remission in cats with diabetes mellitus. *J Vet Intern Med,* 24**,** 1314–21.

ZINI, E., OSTO, M., FRANCHINI, M., GUSCETTI, F., DONATH, M. Y., PERREN, A., HELLER, R. S., LINSCHEID, P., BOUWMAN, M., ACKERMANN, M., LUTZ, T. A. & REUSCH, C. E. 2009. Hyperglycaemia but not hyperlipidaemia causes beta cell dysfunction and beta cell loss in the domestic cat. *Diabetologia,* 52**,** 336–346.

ZINI, E., SALESOV, E., DUPONT, P., MORETTO, L., CONTIERO, B., LUTZ, T. A. & REUSCH, C. E. 2018. Glucose concentrations after insulin-induced hypoglycemia and glycemic variability in healthy and diabetic cats. *Journal of Veterinary Internal Medicine,* 32**,** 978–985.

ÖHLUND, M., EGENVALL, A., FALL, T., HANSSON-HAMLIN, H., RÖCKLINSBERG, H. & HOLST, B. S. 2017. Environmental Risk Factors for Diabetes Mellitus in Cats. *Journal of Veterinary Internal Medicine,* 31**,** 29–35.

ÖHLUND, M., FALL, T., STRÖM HOLST, B., HANSSON-HAMLIN, H., BONNETT, B. & EGENVALL, A. 2015. Incidence of Diabetes Mellitus in Insured Swedish Cats in Relation to Age, Breed and Sex. *Journal of Veterinary Internal Medicine,* 29**,** 1342–7.

ÖHLUND, M., PALMGREN, M. & HOLST, B. S. 2018. Overweight in adult cats: a cross-sectional study. *Acta Vet Scand,* 60**,** 5.

ÖSTENSSON, K. 2010. Från manligt till kvinnligt. *Veterinär-yrke i förvandling. Red. LE. Appelgren, I. Jämte & K. Östensson. Sveriges veterinär förbund,* 150.

Popular science summary

Diabetes mellitus (DM) is one of the most common hormonal disorders in cats. It occurs when the body produces too little insulin or does not respond to it properly, leading to high blood sugar. Since sugar regulation is vital for many body functions, DM is life-threatening without treatment. Medical care can lead to good outcomes and even reversal of the disease, or diabetic remission, meaning that the cat no longer needs medication to maintain normal blood sugar levels. However, handling the disease requires daily care and lifestyle adjustments, creating challenges for both cats and their owners. Managing DM involves insulin injections, blood sugar monitoring, and dietary changes. It also touches on broader issues of quality of life, decision-making, moral values, and the relationship between veterinarians, owners, and cats. In this thesis, four studies were carried out to explore different aspects of DM in cats.

In the first study, owners answered a questionnaire related to experiences and clinical outcomes in cats with DM. Within four weeks of diagnosis, 15% of cats were euthanised, a decision influenced by the cat's age and complex owner-related circumstances. One third of cats achieved diabetic remission, some shortly after diagnosis and others after more than a year of treatment. Feeding a commercially available wet diet increased both the chance of remission and of maintaining remission. Remission was linked to higher quality of life for the cat, but in cats that continued to need for treatment, quality of life was still often rated as high, underlining quality of life as an important outcome on its own. However, many owners reported practical and emotional challenges related to DM management.

In the second and third studies, interviews were conducted with owners and veterinarians to further explore the experiences and considerations of DM management in cats. Both owners and veterinarians were guided by a

strong sense of responsibility in their decision-making, agreeing that the cat's quality of life should always come first. For owners, this responsibility was perceived as a moral duty inherited when acquiring the cat, and shaped by the human–cat bond, the cat's role in the household, and family dynamics. For veterinarians, responsibility focused on the cat's wellbeing while also including the owner, to varying degrees. Recognising that the owner's ability and willingness to provide care were inseparable from the veterinary responsibility of safeguarding the cat's welfare made decision-making a complex and sometimes emotionally charged process. Caring for a cat with DM could be both a joy and burden for owners, with feelings of guilt, especially when euthanasia was considered. Veterinarians also found these situations difficult, particularly when an owner's choice conflicted with what they believed was best for the cat.

Both the disease itself and its management may contribute to stress in the cat. Stress can affect the welfare of the cat but is often difficult to assess. Upon activation of the stress axis, the hormone cortisol is released into the bloodstream. Cortisol is gradually incorporated into the body's hair shafts, and therefore, cortisol can be measured in hair to assess long-term cortisol levels and evaluate stress. In the fourth study, this approach was used to assess long-term stress axis activity in healthy cats and cats with chronic disease, including DM. A novel hair sampling method, in which cats were combed, was also evaluated. Cats with chronic diseases had higher hair cortisol levels, suggesting that illness and different aspects of disease management may influence stress physiology. Combing appears to be a promising method for collecting hair samples. However, interpreting hair cortisol requires consideration of individual characteristics and living conditions, and further research is needed.

Taken together, these studies provide new insights into the clinical, emotional, and ethical aspects of diabetes management and monitoring in cats. They emphasise that successful treatment involves not only controlling blood sugar, but also safeguarding the cat's quality of life, supporting owners, and helping veterinarians navigate complex decisions.

Populärvetenskaplig sammanfattning

Diabetes mellitus (DM) är en av de vanligaste hormonella sjukdomarna hos katter. Den uppstår när kroppen producerar för lite insulin eller inte svarar korrekt på det, vilket leder till för högt blodsocker. Eftersom sockerreglering är avgörande för många kroppsfunktioner är DM livshotande utan behandling. Med rätt vård kan dock goda resultat uppnås, och sjukdomen kan till och med gå i remission, vilket innebär att katten inte längre behöver medicin för att upprätthålla normala blodsockernivåer. Att hantera sjukdomen kräver daglig omvårdnad och olika livsstilsanpassningar vilket kan skapa utmaningar för både katten och dess ägare. Sjukdomshantering innebär en behandling med dagliga insulininjektioner, blodsockermätningar och kostanpassningar, men inbegriper också bredare frågor om livskvalitet, beslutsfattande, moraliska värderingar och relationen mellan veterinär, ägare och katt. I denna avhandling genomfördes fyra studier för att undersöka olika aspekter av DM hos katt.

I den första studien besvarade kattägare en enkät om erfarenheter av DM och sjukdomsutfall. Inom fyra veckor efter diagnos hade 15% av katterna avlivats, ett beslut som påverkades av kattens ålder och olika ägarrelaterade omständigheter. Knappt en tredjedel av de katter som behandlades uppnådde remission, vissa kort efter diagnos och andra efter mer än ett års behandling. Utfodring med kommersiellt tillgänglig blötmat ökade chansen till remission. Remission var kopplad till högre livskvalitet hos katten, men även bland katter som fortsatt behövde behandling skattades livskvaliteten som hög för många. Detta understryker livskvalitet som ett viktigt utfall i sig. Samtidigt rapporterade många ägare både olika praktiska och känslomässiga utmaningar kopplade till sjukdomshanteringen, exempelvis svårigheter att resa på semester eller oro för kattens behandling.

I den andra och tredje studien genomfördes kvalitativa intervjuer med ägare och veterinärer för att fördjupa förståelsen för erfarenheter av att hantera DM hos katt och hur beslut om vård fattas. Både ägare och veterinärer styrdes av en stark känsla av ansvar och var överens om att kattens livskvalitet alltid ska komma i första hand. För ägarna sågs detta ansvar som en moralisk plikt kopplas till ägarskapet. Beslut om behandling formades av relationen till katten, kattens roll som familjemedlem, och dynamiken i hushållet. För veterinärerna låg fokus på kattens välfärd, men för att kunna säkerställa kattens livskvalitet måste de förhålla sig till ägarens förmåga och vilja att ge vård. Detta gjorde beslutsfattandet komplext och ibland känslomässigt krävande. Att vårda en katt med DM kunde både skänka glädje och orsaka belastning för ägaren, med upplevelser av skuld när avlivning övervägdes. Även veterinärer upplevde dessa situationer som svåra, särskilt när ägarens beslut stred mot vad de ansåg vara bäst för katten.

Sjukdomen i sig, liksom dess behandling, kan bidra till stress hos katten. Stress kan påverka kattens välfärd men är ofta svår att bedöma. Vid aktivering av stressaxeln frisätts hormonet kortisol i blodet, vilket successivt lagras in i kroppens hårstrån. Därför kan kortisol mätas i hår för att undersöka långvariga kortisolnivåer och uppskatta stress. I den fjärde studien användes denna metod för att bedöma långvarig aktivitet över stressaxeln och stress hos friska katter och hos katter med kronisk sjukdom, inklusive DM. En ny metod för hårprovstagning, där katterna kammades, utvärderades också. Katter med kronisk sjukdom hade högre hårkortisol, vilket tyder på att sjukdom i sig och olika moment kopplade till hantering och behandling kan påverka stressfysiologin. Kamning verkar vara en lovande metod för att samla in hårprover. Dock kräver tolkning av hårkortisol hänsyn till kattens levnadsförhållanden och olika individuella egenskaper, och mer forskning behövs.

Sammanfattningsvis ger dessa studier nya insikter i de kliniska, känslomässiga och etiska dimensionerna av DM hos katt. De visar att framgångsrik behandling inte bara handlar om att kontrollera blodsockret, utan också om att säkerställa kattens livskvalitet, stödja ägare och vägleda veterinärer i komplexa beslut.

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STANDARD ARTICLE

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Survival, remission, and quality of life in diabetic cats

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Abstract

Background: Remission is documented in a substantial proportion of cats with diabetes. The effects of diabetes mellitus (DM) on the lives of cats and their owners should be considered when evaluating treatment success.

Objectives: To study outcome in cats with DM and the impact DM has on the life situation of cat and owner.

Animals: Domestic and pedigree cats with a diagnosis of DM (n = 477) insured by a Swedish insurance company during 2009 to 2013.

Methods: Retrospective cross-sectional study. A questionnaire was sent to 1369 owners of cats diagnosed with DM. The questions concerned the cat, treatment, owner perceptions of the disease and treatment and disease outcome. Data were analyzed using multiple linear and logistic regression, with outcomes set as survival for more than 4 weeks after diagnosis, survival time, achieving remission, remission without relapse and quality of life (QoL) for the cat.

Results: The response rate was 35%, leaving 477 questionnaires for analysis. The remission rate among treated cats was 29% (118/405). Feeding a commercially available wet diet was associated with both remission (OR 3.16, 95% confidence interval 1.27-8.12) and remission without relapse (OR 14.8, 95% confidence interval 2.25-153.8). Remission was associated with a better QoL for the cat.

Conclusions and Clinical Importance: The association between feeding a commercially available wet diet and remission is important and strengthens the role of diet in treatment of DM in cats. Linking remission and a better QoL for the cat emphasizes remission as a goal in disease management.

KEYWORDS
feline, outcome, owner, perceptions, treatment, wet diet

1 | INTRODUCTION

The quality of life of chronically sick animals and their owners is attracting increased attention, and its importance for owners and clinicians is substantial.[1-7] Diabetes mellitus (DM) is a common chronic endocrine disease in cats.[8-11] Caring for a diabetic cat entails

Abbreviations: CA, commercially available; CI, confidence interval; DM, diabetes mellitus; HBGM, home blood glucose monitoring; LC, low carbohydrate; OR, odds ratio; QoL, quality of life.

potentially adversely effects on owners' and cats' lifestyle and quality of life (QoL). Long time management of DM includes minimization of clinical signs, and diabetic remission is documented in a substantial proportion of cats.

Associations between treatment regimen and remission have been investigated,[12-20] but because of shortage of well-designed studies no clear evidence of a superior treatment protocol exists.[21] Adjustments toward an ultralow carbohydrate diet are widely considered optimal for disease control,[22-24] although only a few veterinary trials have compared low carbohydrate diets to others.[18-20]

Despite DM having a fairly good prognosis, it has been estimated that 1 out of 10 owners choose euthanasia upon DM diagnosis[1] and 10% to 17% of cats are euthanized within a few weeks of diagnosis.[25-27] Alongside glycemic control, the psychological and social effects of DM and its treatment on both owner and cat should be considered when evaluating treatment success.[2] Owners' perceptions of disease management and concern for the wellbeing of their diabetic cat might influence their choice of treatment or euthanasia. These perceptions are thus crucial for the owners' commitment to and care for the diabetic cat, and hence common sources of owner distress need to be recognized by the treating veterinarian for successful management of DM. Studies reveal that feeling tied up and worrying about costs related to treatment are commonly reported issues among owners of diabetic cats,[1-3,28] whereas initial concerns and negative impact associated with treatment seem to decrease significantly with time.[3,29]

Answers from a questionnaire sent to owners of cats diagnosed with DM were analyzed to investigate associations between treatment regime and owners' perceptions of outcome, including QoL, for the cat. The aim of this study was to study disease outcome in cats diagnosed with DM and the impact DM has on the life situation of the cat and its owner.

2 | MATERIALS AND METHODS

2.1 | Study sample and questionnaire

A questionnaire was sent to all owners of cats insured by Agria Pet Insurance with a DM diagnosis during 2009 to 2013 (n = 1369). The cats were identified based on 4 diagnostic codes (DM, DM without complication, DM with complication and DM with ketoacidosis). The cat owners were recruited to the study by e-mail with a web link to the questionnaire.

The questionnaire was available during a 4-month period through an online provider (Netigate) and consisted of 46 questions. Some of the results—those relating to environmental risk factors for DM in cats—have been published.[30] The answers to 37 questions were analyzed in the present study. To confirm case status, all respondents had to give a positive answer to the question "Has your cat ever been diagnosed with diabetes? The diagnosis must have been made by a veterinarian. Diabetes means that the cat´s blood sugar is elevated for a longer period of time." To confirm cases of diabetic remission, the respondents had to give a positive answer to the question "Has your cat recovered from its diabetes? Recovery meaning a normalized blood sugar and the cat no longer needing medication (insulin or oral tablets)." For a summary of the questions, see Table 1. For detailed information about the questions, see Appendix S1.

2.2 | Data analysis

In the case of missing answers for any of the variables of interest, the cat was excluded. In the case of conflicting answers, the respondent was contacted if possible and the answers were then corrected or excluded accordingly. See Table 1 for an overview of the questionnaire and, where relevant, how the answers were grouped for data analysis.

As no specific dates were requested, the cat's age at diagnosis and age at death were set to 1 January of each year. Initial survival was defined as surviving for more than 4 weeks after diagnosis. Survival time was estimated as from 31 December of the year of diagnosis to 1 January of the year of the cat's death. For a cat that was diagnosed in 2010 and died in 2012, the survival time was thus set to a minimum of 1 year.

In the data analysis for all cats, outcomes were initial survival (meaning surviving for more than 4 weeks after diagnosis) and a QoL not negatively affected by DM. For cats still alive at 4 weeks after diagnosis, disease outcome (survival time and achieving remission, with or without diabetic relapse) was analyzed.

Data analysis was performed using R.[31] For summary statistics, frequency distribution (histogram) was used to check for normality. Mean and SD (±) were used when normality was assumed, and median and inter-quartile range (IQR) when this was not the case. The main outcome variables were survival time, remission, and quality of life. Five different regression models were used, with outcomes set as initial survival (more than 4 weeks after diagnosis), survival time, remission, remission without relapse and quality of life for the cat not being negatively affected by DM. Univariate logistic or linear regression were used for selection of variables, including variables with $P < .2$ in further analysis. To estimate and investigate the direction and strength of the associations, multiple logistic regression analysis and linear regression were used. The final regression model was decided with a backwards elimination process combined with a lowered Akaike information criterion (AIC), and variables with $P > .05$ were excluded. In the logistic regression, analysis odds ratio (OR) was calculated with a 95% confidence interval (CI). In linear regression analysis, a 95% CI with a significance level of 5% was used. Quantile-quantile plots (QQ-plots) were used to assess the regression residuals for normality. Biologically plausible interactions were included and possible confounders were controlled in each regression model. Significant interactions were interpreted separately and investigated using interaction plots.

3 | RESULTS

In total, 484/1369 (35%) complete questionnaires were received and 7 were excluded, leaving 477 questionnaires for analysis.

TABLE 1 Overview of the questions asked to owners of diabetic cats and the answer options, including answer grouping for data analysis (n = 477)

Questions	Answer options and grouping of answers for data analysis (all questions included an "Other/Decline to answer" alternative and a free text section)
Cat characteristics and survival time	
Breed	Domestic, Burmese, Norwegian Forest Cat, Exotic/Persian, Other pedigree[a]
Year of birth	For example, 2002
Sex	Male, Neutered male, Female, Neutered female
Confinement	Indoor, Outdoor[b]
Multicat household	Yes, No[c]
Cat alive at time of survey?	Yes, No
If not alive, what year did your cat die?	For example, 2006
Main reason for death/euthanasia	Trauma/accident, Age, Disease
If disease, what kind of disease?[d]	Airways, Circulatory system, Diabetes or other endocrine, Gastrointestinal, Oral cavity, Orthopedic or neurological, Tumor, Urinary system
Cat health through life (before diabetes diagnosis)	Never/rarely sick or hurt, Occasionally sick or hurt, Often sick/recurrent problems/chronic disease
If often sick/recurrent problems/chronic disease, what systems were affected?[d]	Airways, Circulatory system, Endocrine, Gastrointestinal, Infectious, Oral cavity, Orthopedic or neurological, Reproductive, Skin, Tumor, Urinary system
Vaccination status	Yearly doses, Every other year, Occasionally, As a kitten, Not vaccinated
Treatment with progestins or corticosteroids the year before diabetes diagnosis	Yes, corticosteroids, Yes, progestins, No[e]
Body condition score of your cat the year before diabetes diagnosis[f]	1-5
Owner and household	
Year of birth	Decade of birth, for example, 1960-69
Sex	Male, Female
Number of adults in household	1, 2, 3 or more
Children <18 years old in household	Yes, No
Place of residence	City (>200 000 inhabitants), Town (200-200 000 inhabitants), Countryside
Diabetes diagnosis, initial survival and treatment	
What year did your cat contract diabetes? (When clinical signs were first seen or, if no clinical signs, when your cat received its diagnosis)	For example, 2013
What happened to your cat after diagnosis?	Euthanized/died within 4 weeks, Survived for more than 4 weeks
Reasons for euthanasia[d]	The cat did not survive despite initiated treatment, Presence of other diseases, The treatment did not work, Treatment was too difficult for me/my family, Wanted to limit the suffering for the cat, The treatment was too expensive, The cat did not receive any treatment, Experienced poor support from veterinarian
What treatment did your cat receive?[d]	Insulin[g], Dietary adjustments, Hypoglycemic tablets (eg, glipizide), Admitted to hospital for care, No particular treatment
Change of diet upon diabetes diagnosis	Yes, Yes, partly, No
What diet has your cat predominantly eaten since diagnosis? ("predominantly" meaning ≥75% of one diet; if approximately 50% of two diets, two alternatives could be chosen)[d]	Veterinary diabetes prescription dry diet (eg, Hill's m/d, Purina DM, Royal Canin Diabetic), Veterinary diabetes prescription wet diet (eg, Hill's m/d, Purina DM, Royal Canin Diabetic), Veterinary weight loss/obesity prescription diet (eg, Hills r/d or w/d), Commercially available wet food[h]
Did you practice blood glucose monitoring at home?[d]	Yes, with blood samples, Yes, with urine sticks, No
Remission	
Has your cat "recovered" from diabetes? (meaning a normal blood glucose without insulin treatment)	Yes, Yes, with relapse[i], No
If Yes or Yes with relapse: Time from diagnosis until "recovery"	0-3 months, 4-6 months, 7-12 months, 1 year or longer

(Continues)

TABLE 1 (Continued)

Questions	Answer options and grouping of answers for data analysis (all questions included an "Other/Decline to answer" alternative and a free text section)
Owner perceptions	
How were you affected by having a cat with diabetes?[d]	Worried about the cat's medication, Worried about complications (eg, hypoglycemia), Difficult to administer insulin, Difficult to perform blood sampling, Worried about hurting the cat during medication or blood sampling, Perceiving limitations in life due to cat's diabetes (eg, difficulties traveling), Worried about limitations to the cat's life due to diabetes, Worried about costs, Experienced expectations from others to start treatment, Experienced expectations from others to euthanize, I have not been affected by my cat's diabetes diagnosis
Describe your attitude to your cat	My cat is everything to me, My cat means a lot to me, My cat is quite important to me, My cat is not that important to me
Did you experience any conflicts in your family regarding the care of your cat?	Yes, often, Yes, sometimes, No, we agree, No, I make the decisions myself
How was the relationship with your cat affected by diabetes?[d]	I have developed a stronger bond with my cat, My cat has developed a stronger bond with me, Relationship as before, I have developed a weaker bond with my cat, My cat has developed a weaker bond with me
Quality of life (QoL)	
How has the QoL of your cat been affected by diabetes, in general, compared to before the cat got sick?	Better, no change/as before, worse[i]
Assessment of QoL of your cat at time of survey/last time alive	Excellent, good, less good, bad

[a]<8 individuals per breed: Abyssinian, Bengal, Birman, British Shorthair, Cornish Rex, Devon Rex, European Shorthair, Maine Coon, Ocicat, Oriental Shorthair, Ragdoll, Russian Blue, Siamese, Siberian incl. Neva Masquerade, Somali, Sphynx, Other pedigree; mixed breed cats were grouped as domestic cats.
[b]Indoor = Indoor only, Indoor with access to balcony/play pen/leash walks. Outdoor = Indoor with access to outdoors for part of the year, Outdoor and indoor, Outdoor only.
[c]Yes = Two to three cats, Four to eight cats, Nine or more cats.
[d]Multiple answers possible.
[e]Yes, corticosteroids = per oral tablets or injection. Yes, progestins = per oral tablets or injection.
[f]Assessment template of BCS provided.
[g]Insulin = insulin injection once and/or twice day.
[h]Other = diets or combinations of diets representing the choice of fewer than 15 (5%) owners, including commercially available dry food and Low carbohydrate dry.
[i]Dichotomized before logistic regression analysis: Better compared to before the disease or No change/as before = Positively affected/unaffected QoL, Worse compared to before the disease = Negatively affected QoL.

3.1 | Cats and owners

Mean cat age at diagnosis was 10.7 years (±3.1). Almost 100% of the cats were neutered (99.9%), of which 71% were males and 29% were females, and most cats were not pedigrees (77%). For general information on the cats, see Table 2. The majority of the cats (333/477, 70%) were not alive at the time when their owners answered the questionnaire.

The majority (85%) of the cat owners responding were females, and the owners' median age at cat diagnosis was 46 to 55 years (range 16-90 years).

3.2 | Treatment

Of the 477 cats, 405 were alive 4 weeks after diagnosis. For general information on treatment and disease outcome, see Table 2. Dietary adjustments were made for 93% of the cats and 89% were treated with insulin. Among the owners of cats receiving insulin, 181 (50%) practiced home blood glucose monitoring, 44 (12%) measured urine glucose and 23 (6%) practiced both, while 112 (31%) did not monitor blood or urine glucose. Of the 27 cats (7%) that received oral hypoglycemics, 26 also had dietary adjustments. Nine of the cats treated with oral hypoglycemic agents also received insulin at some point.

The most commonly fed diet was dry veterinary prescription diet for treatment of DM (253/405, 62%), either as a predominant diet or combined with other diets (see Table 2). Of the 405 cats, 11% were predominantly fed a CA wet diet, generally meaning a low carbohydrate diet (as obtained from free text answers).

3.3 | Owners' perceptions and cat-human relationship

Worries and difficulties associated with treatment of the diabetic cat are described in Table 3. The most frequently reported concern was limits to daily life, for example, difficulties traveling and finding a cat

TABLE 2 General information on cat characteristics, disease outcome, and treatment for cats diagnosed with diabetes mellitus (n = 477)

General information	All cases (n = 477)	Survival ≤4 weeks (n = 72)	Survival >4 weeks (n = 405)	Remission			No remission (n = 287)
				All (n = 118)	Relapse (n = 45)	No relapse (n = 73)	
Breed							
Domestic	365 (76%)	46 (64%)	319 (79%)	83 (70%)	29 (64%)	54 (74%)	236 (82%)
Burmese	18 (4%)	4 (6%)	14 (3%)	5 (4%)	2 (4%)	3 (4%)	9 (3%)
Norwegian Forest Cat	38 (8%)	6 (8%)	32 (8%)	15 (13%)	6 (13%)	9 (12%)	17 (6%)
Exotic/Persian	8 (2%)	2 (3%)	6 (1%)	2 (2%)	1 (2%)	1 (1%)	4 (1%)
Other purebred	48 (10%)	14 (19%)	34 (8%)	13 (11%)	7 (16%)	6 (8%)	21 (7%)
Sex							
Neutered male	337 (71%)	52 (72%)	285 (70%)	88 (75%)	37 (82%)	51 (70%)	197 (69%)
Neutered female	137 (29%)	20 (28%)	117 (29%)	29 (25%)	8 (18%)	21 (29%)	88 (31%)
Intact female	3 (0%)	0	3 (1%)	1 (0%)	0	1 (1%)	2 (1%)
Mean age at diagnosis, years (SD)	10.7 (±3.1)	11.6 (±3.6)	10.6 (±3)	10.6 (±3)	10.6 (±3.6)	10.6 (±2.6)	10.5 (±2.9)
Presence of other chronic disease	35 (7%)	8 (11%)	27 (7%)	10 (8%)	5 (11%)	5 (7%)	17 (6%)
Indoor confinement	258 (54%)	41 (57%)	217 (54%)	76 (64%)	28 (62%)	48 (66%)	141 (49%)
Outdoor confinement	217 (45%)	31 (43%)	186 (46%)	42 (36%)	17 (38%)	25 (34%)	144 (50%)
Presence of other animals in household	321 (67%)	52 (72%)	269 (66%)	87 (74%)	34 (76%)	53 (73%)	182 (63%)
Treatment							
Insulin			360 (89%)	104 (88%)	41 (91%)	63 (86%)	256 (89%)
Dietary adjustments			378 (93%)	116 (98%)	44 (98%)	72 (99%)	262 (91%)
Oral hypoglycemics			27 (7%)	5 (4%)	2 (4%)	3 (4%)	22 (8%)
Home blood glucose monitoring							
Blood glucose			208 (51%)	70 (59%)	33 (73%)	37 (51%)	138 (48%)
Urine glucose			74 (18%)	22 (19%)	12 (27%)	10 (14%)	52 (18%)
None			147 (36%)	34 (29%)	7 (16%)	27 (37%)	113 (39%)
Diet							
DM prescription diet, dry			124 (31%)	33 (28%)	15 (33%)	18 (25%)	91 (32%)
DM prescription diet, dry and wet			60 (15%)	14 (12%)	8 (18%)	6 (8%)	46 (16%)
CA wet food and DM prescription, dry			48 (12%)	14 (12%)	7 (16%)	7 (10%)	34 (12%)
CA wet food			44 (11%)	22 (19%)	2 (4%)	20 (27%)	22 (8%)
Weight management prescription diet			27 (7%)	10 (8%)	1 (2%)	9 (12%)	17 (6%)
Other[a]			102 (25%)	25 (21%)	12 (27%)	13 (18%)	77 (27%)

Abbreviations: CA, commercially available; DM, diabetes mellitus.

[a]Other = diets or combinations of diets representing the choice of fewer than 15 (5%) owners, including commercially available dry food and low carbohydrate dry food.

TABLE 3 Owner-perceived difficulties and worries about treatment and monitoring their cat's diabetes mellitus (n = 405, multiple answers possible)

		Remission			
	All treated cats (n = 405)	All (n = 118)	Relapse (n = 45)	No relapse (n = 73)	No remission (n = 287)
Owner feeling limited	208 (51%)	55 (47%)	24 (53%)	31 (42%)	153 (53%)
Worry about complications	182 (45%)	41 (35%)	17 (38%)	24 (33%)	141 (49%)
Worry about cat's medication	117 (29%)	27 (23%)	10 (22%)	17 (23%)	90 (31%)
Difficulty measuring blood glucose	84 (21%)	25 (21%)	7 (16%)	18 (25%)	59 (21%)
Worry about costs	61 (15%)	17 (14%)	7 (16%)	10 (14%)	44 (15%)
Worry about limits to cat's life	54 (13%)	4 (3%)	3 (7%)	1 (1%)	50 (17%)
Worry about hurting the cat	40 (10%)	12 (10%)	6 (13%)	6 (8%)	28 (10%)
Difficulty injecting insulin	25 (6%)	8 (7%)	2 (4%)	6 (8%)	17 (6%)
No perceived worries or difficulties	79 (20%)	32 (27%)	8 (18%)	24 (33%)	47 (16%)

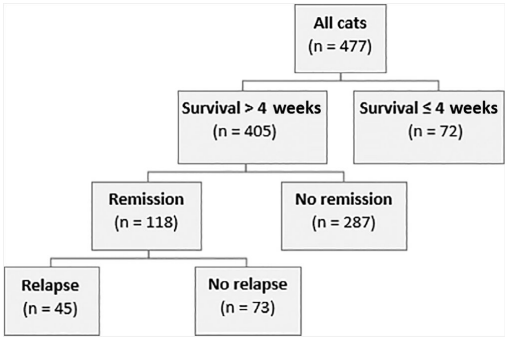

FIGURE 1 Overview of different outcomes for the studied population of cats with diabetes mellitus (n = 477)

sitter. Worrying about complications involving treatment or DM itself (eg, hypoglycemia) was most common among owners of cats that had not achieved remission, as were concerns about DM entailing limits to the cat's daily life. Only 1% of owners of cats in remission without relapse expressed concern about DM limiting their cat's life. Owners of cats in remission without relapse were less worried than owners of cats with relapse or cats that had not achieved remission.

Of the 84 owners experiencing difficulties measuring blood glucose, 29 did not perform HBGM.

Of all owners, 54% (258/477) answered that their cat meant a lot to them, 41% (197/477) said that their cat was everything to them, and 3% (15/477) deemed the cat to be "quite important." There were no associations between owners' attitudes toward their cats and the 5 different outcomes analyzed using univariable logistic regression analysis.

More than half of the owners (58%, 277/477) said that their relationship with their cat had been strengthened after the DM diagnosis, while about a third (38%, 180/477) deemed the relationship to be unchanged. Only 1% (5/477) of owners said the relationship had been worsened.

3.4 | Outcomes for cats with diabetes mellitus diagnosis

3.4.1 | Survival for more than 4 weeks

Of the 477 cats, 405 (85%) were still alive 4 weeks or more after diagnosis, whereas 72/477 (15%) had been euthanized—see Figure 1. The most common reason for euthanasia was that the owners did not want their cats to suffer (53%) or that the prognosis was poor (32%). Other reasons for euthanasia were concurrent disease (21%), treatment being too difficult (13%) or poor support from the veterinarian (4%).

In the multiple logistic regression model, factors remaining significant for surviving for more than 4 weeks were cat age at diagnosis, owner experiencing limitations in their lifestyle, expectations from others to euthanize the cat, owner worrying about costs and the effect of DM on the cat's QoL, alongside 2 interactions: cat age at diagnosis and worrying about costs, and cat age at diagnosis and expectation to euthanize—see Table 4.

For every additional year of the cat's age at diagnosis, the odds of surviving for more than 4 weeks decreased by 0.13. If the owner experienced expectations from others to euthanize the cat, the odds of surviving for more than 4 weeks decreased by a third (OR 0.33) with every year. This negative effect of expectations of euthanasia on initial survival was most pronounced in cats over approximately 15 years of age. In cats whose owners were worried about costs related to the cat's DM, the odds of surviving were lower in younger cats and were most pronounced in cats younger than approximately 10 years, and the odds of initial survival increased with every additional year of the cat's age (OR 1.52).

Surviving for more than 4 weeks was positively associated with owners experiencing lifestyle limitations, owner worries about

TABLE 4 Multiple logistic regression analysis of factors associated with different outcomes in cats with diabetes mellitus (n = 477)

Outcome and variables	OR	CI 95% (OR)		P
Survival for more than 4 weeks				
Worries about limitations in owner's life vs no limitations in owner's life	13.6	4.85	45.7	<.001
Worries about complications vs no worries about complications	3.00	1.33	7.11	.01
QoL better or same as before vs QoL worse	23.8	8.16	89.5	<.001
Cat age				
When worrying about costs	1.52	0.98	2.3	.05
When experiencing expectation to euthanize	0.33	0.11	0.64	.01
When no worries about costs or not experiencing expectations to euthanize	−0.14	0.76	0.99	.04
Remission				
CA wet diet vs veterinary prescription DM diet wet and/or dry	3.16	1.27	8.12	.01
Breed: Norwegian Forest Cat vs domestic cat	2.92	1.27	6.76	.01
QoL better or same as before vs QoL worse	5.25	2.86	10.3	<.001
Remission without relapse				
CA wet diet vs veterinary prescription DM diet wet and/or dry	14.8	2.25	153.8	.01
QoL better or same as before vs QoL worse	31.4	5.1	646	.002
QoL better or same				
Insulin treatment vs no insulin treatment	5.6	2.4	14	<.001
Remission without relapse vs no remission	53.9	10.6	994.6	<.001
Worries about medication vs no worries about medication	0.31	0.17	0.54	<.001
Worries about limitations in cat's life vs no worries about limitations	0.07	0.03	0.16	<.001

Abbreviations: CA, commercially available; CI, confidence interval; OR, odds ratio; QoL, quality of life.

complications (eg, hypoglycemia) and the cat's QoL not being negatively affected by DM.

3.4.2 | Survival time

Almost two thirds of the cats (299/477, 63%) survived for more than 1 year after diagnosis, 118 (25%) survived for more than 3 years, 47 (10%) survived for more than 5 years and 7 (1.4%) survived for more than 8 years. The median survival time for cats that survived the initial 4 weeks after diagnosis but were dead at time of the questionnaire (n = 261) was 1 year (IQR 3, 0-14 years), and for cats that were alive at the time of the questionnaire (n = 144) the median survival time was 2 years (IQR 2).

Factors remaining significant for survival time in the final linear regression model were insulin treatment, the cat's QoL and the owner's worries about medication—see Table 5. One interaction remained, between cat age at diagnosis and insulin.

In cats that were treated with insulin (n = 360), survival time was longest in young cats, and declined by 0.25 years for every additional year of the cat's age at diagnosis. In cats that did not receive insulin (n = 45), the effect of age on survival time was not significant ($P = .77$).

Survival time increased by 0.6 years in cats with a QoL assessed as better or the same as before DM and in cats belonging to owners that did not experience worries about medication.

3.4.3 | Remission

Of the 405 cats that survived for more than 4 weeks, 29% (n = 118) achieved remission. Of these, 62% (n = 73) achieved remission without relapse (until the death of the cat, n = 20, or until the time of the survey, n = 53)—see Figure 1. The time from diagnosis to remission was 0 to 3 months for 22% (26/118), 4 to 6 months for 29% (34/118), 7 to 12 months for 19% (n = 22/118), and >12 months for 25% (n = 30/118).

Factors remaining significant for achieving remission in the final multiple logistic regression model were breed, type of diet and the effect of DM on the cat's QoL—see Table 4. Cats that were fed predominantly CA wet food after diagnosis had an increased chance of remission, compared to cats that were fed DM prescription diet (wet and/or dry). Norwegian Forest Cats had a higher chance of achieving remission than domestic cats. Remission was associated with a better QoL for the cat or a QoL unaffected by DM.

TABLE 5 Multiple linear regression analysis of factors associated with survival time in cats with diabetes mellitus that survived more than 4 weeks after diagnosis (n = 405)

Outcome and factors	B	CI 95% (B)		P
Survival time				
Worries about medication vs no worries about medication	−0.64	−1.05	−0.23	.002
QoL better or same as before diagnosis vs a worsened QoL	0.60	0.16	1.05	.01
Cat age				
When treatment with insulin	−0.25	−0.33	−0.19	<.001
When no treatment with insulin	−0.03	−0.245	0.18	.77

Abbreviations: B, regression coefficient; CL, confidence interval; QoL, quality of life.

TABLE 6 How diabetes mellitus affected the general quality of life for the cat according to owners, compared to before diabetes (n = 477)

				Remission			
	All cats (n = 477)	Survival ≤4 weeks (n = 72)	Survival >4 weeks (n = 405)	All (n = 118)	Relapse (n = 45)	No relapse (n = 73)	No remission (n = 287)
QoL as affected by DM							
Better[a]	36 (8%)	2 (3%)	34 (8%)	17 (14%)	3 (7%)	14 (19%)	17 (6%)
Same as before DM[a]	217 (45%)	3 (4%)	214 (53%)	79 (67%)	26 (58%)	53 (72%)	135 (47%)
Worse[b]	163 (34%)	32 (44%)	131 (32%)	14 (12%)	13 (29%)	1 (1%)	117 (41%)
Cannot assess	61 (13%)	35 (49%)	26 (6%)	0	0	0	18 (6%)

Abbreviations: DM, diabetes mellitus; QoL, quality of life.

3.4.4 | Remission without relapse

The significant variables that were positively associated with remission without relapse were type of diet and the cat's QoL—see Table 4. Predominantly feeding a CA wet diet, compared to DM prescription diet (wet and/or dry), was associated with remission without relapse. Cats without relapse from remission were more likely to have a better QoL.

3.4.5 | Quality of life

Most owners of cats that were alive at the time of the survey (67%, 96/144) assessed their cat's overall QoL to be the same as before diagnosis. QoL was assessed to be better than before in 16% (n = 23) and worse than before diagnosis in 10% (n = 15). Almost all owners of cats that had survived for more than 4 weeks after diagnosis and were alive at the time of the survey assessed their cat's QoL at the time of the survey as excellent or good (97%, 140/144).

Most owners of cats that were dead at the time of the questionnaire assessed their cat's QoL, as affected by DM, to be worse than before diagnosis (44%, 148/333). About a third (36%, n = 121) assessed QoL as the same as before diagnosis, and 4% as better than before DM (n = 13).

The overall effect of DM on the cat's QoL is presented in Table 6.

The final multiple logistic regression model on the association between DM and the cat's general QoL included answers from owners of cats that survived for more than 4 weeks after diagnosis (n = 405). An unaffected or better QoL compared to before diagnosis was associated with both achieving remission without relapse and treatment with insulin. Expressing concern about DM limiting the life of the cat and worrying about the cat's medication were associated with an estimated QoL that was worse (Table 4).

4 | DISCUSSION

This survey combined information on treatment, monitoring, owner perceptions and disease outcome of cats with DM. Of the cats diagnosed with DM, 85% survived for more than 4 weeks, and 63% for more than 1 year. In younger cats, a negative association was found between owner concerns about costs and survival for more than 4 weeks. Further, survival time was positively associated with a better QoL for the cat and negatively associated with owner worries about the cat's medication. The remission rate among treated cats was 29%. The chance of both achieving and staying in remission was higher for cats that were fed a CA wet diet. Remission was positively associated with a better QoL.

4.1 | Initial survival and survival time

The initial survival rate was 85%, which is comparable to previous studies.[1,25-27] The odds of surviving for more than 4 weeks decreased

slightly with increasing cat age. If the owners were worried about costs, the odds of surviving for more than 4 weeks after diagnosis were lower in younger cats, and increased with increasing cat age. This might mirror 2 things. First, the younger the cat is at diagnosis, the longer the prospective treatment will be, possibly making owners less prone to agree to treatment. Second, worries could reflect a more severe or complicated disease course among the younger cats in this study. On the contrary, the effect of age on initial survival among cats belonging to owners who experienced expectations of euthanasia was pronounced in older cats, with decreased odds of survival in cats over 15 years of age. This might be explained by less acceptance of disease negatively affecting the life of an older cat, compared to younger cats.

Survival time was positively associated with a better QoL for the cat, and was negatively associated with an owner worrying about medication. Survival time was associated with cat age in cats treated with insulin, with shorter survival time in older cats as expected.

Insulin is a general recommendation when treating DM in cats, and almost 90% of the cats surviving for more than 4 weeks after diagnosis received insulin injections. Previous research has shown that survival time is affected by the presence of concurrent diseases,[26,27] remission,[26] and glycemic control.[27] Here, no associations between survival time and comorbidities or achieving remission were seen. This could be partly attributable to the study design, and owners might have misinterpreted medical information about the cat. Information on glycemic control was not obtained, and the course of disease might have differed among individuals and between studied groups. Also, in the present study, cats were included with no regard to where the cat was treated, compared to studies performed at referring clinics.[26,27]

In the present study, survival time was calculated as the shortest possible survival time after diagnosis, and many cats can therefore be expected to have survived for longer. There was no association between owner concerns about costs and survival time, potentially reflecting actual costs related to DM being described as having been experienced as lower than expected after a time of treatment, although still being a concern for many owners.[3,29] These results highlight the importance of informative owner communication upon DM diagnosis, discussing treatment options and the financial impact that treatment might have over a period of time.

4.2 | Remission

The remission rate was 29%, with a 3-fold higher chance of achieving remission for cats fed a CA wet diet (low carbohydrate, LC) compared to cats fed a veterinary prescription diet (wet and/or dry). Remission is thought to occur as a result of reversal of glucotoxicity.[21,32] By lowering and stabilizing postprandial blood glucose,[33] facilitating the reversal of glucotoxicity, LC diets are now recommended for disease control.[23,24] Previously, reported remission rates have varied greatly. In the present study, detailed data on how remission was confirmed was not included. A presence of falsely confirmed remission cases can therefore not be excluded, and the remission rate might be exaggerated.

More than a third of the cats that achieved remission (38%) experienced relapse. There was a strong association between CA wet diet and remission without relapse, supporting the current recommendations of continuing a LC diet after remission.[22,23] An LC diet during the non-insulin-dependent period has previously been associated with a relapse rate of 26%,[14] compared to relapse rates of around 30% when type of diet was not known.[34,35]

The most common form of DM in cats is type 2 DM,[36] although hypersomatotropism is attracting increased attention as a cause of insulin resistance and DM.[37] Hypersomatotropism in cats is most likely an underdiagnosed disease,[37] and in affected cats, successful treatment of excess growth hormone[38]—alongside traditional hypoglycemic treatment—is necessary for a chance of achieving diabetic remission. The importance of a CA wet diet to achieve remission thus indicates that many cats were type 2 diabetics, supported by the importance of diet management for treatment of T2DM in humans.[39,40]

The macronutrient content of the different diets in this study was not known. The LC properties of the CA wet diet was obtained from free text answers, where a few well-known brands of canned diet were repeatedly mentioned. The effect of a CA wet diet on remission might be caused by a high protein content,[20,41] by differing carbohydrate sources[42] or by weight loss as a consequence of the high water content in canned foods.[43]

In the present study, Norwegian Forest Cats—a breed with an increased risk of DM[9,11,30]—also had increased odds of remission compared to domestic cats. To our knowledge, no previous study has reported an association between breed and disease outcome. The association between Norwegian Forest Cats and remission is interesting and requires further investigation.

There was no association between insulin treatment and remission in the present study. Previously, the associations between remission and a variety of treatment protocols, including different types of insulin, HBGM routines and diets, have been studied,[12-20] with merely weak evidence of any solid associations.[21] In the present study, 90% of the cats received insulin treatment, and about half of them (57%) practiced HBGM. The type of insulin administered, how rigorous monitoring was among owners practicing HBGM and when in relation to diagnosis insulin treatment was instituted was not known. Although most cats received insulin twice per day, no differentiation was made between cats given insulin once or twice daily upon data analysis. A suboptimal treatment protocol in a proportion of cats might have contributed to the lack of association. Also, cats with a more advanced disease course might have been treated with insulin to a higher degree, compared to cats with less progressive disease. More severely affected beta cells could have affected the chance of achieving remission in the former group. It is also possible that for some cats with a less advanced disease course, the introduction of LC diet alone is sufficient for reversal of glucotoxicity and promoting remission.

In the present study, the time until remission varied from the interval 0 to 3 months to >12 months, and no association between time until remission and maintained remission was seen. As prompt glycemic control preserves more vital beta cells,[12,14] an association

between a shorter time until remission and remission without relapse would be expected. However, the time between disease onset and initiation of treatment was unknown, and no such analysis could be carried out. Also, it is somewhat surprising that a similarly large proportion of cats achieved remission more than a year after diagnosis compared to a few months after diagnosis. This might suggest that hypoglycemic treatment, although not always sufficiently instituted for early reversal of glucotoxicity, might be enough to relieve the beta cells, preserving function for a later remission. This might also reflect the role of insulin resistance in the treatment of DM in cats, where obesity and concurrent diseases have to be addressed to achieve satisfactory glycemic control. In the present study, information on how the veterinarians confirmed the DM diagnosis was not available. Inclusion of isolated cases of hyperglycemia (eg, stress hyperglycemia) can therefore not be excluded, and would influence the remission rates. However, this would have led to a high proportion of early remissions, something that was not seen.

Of the 73 cats without relapse from remission, more than two thirds (73%) were still alive at the time of the study and could still potentially relapse. Of the cats that had not achieved remission (n = 287), almost a third (27%) were alive at the time of the study, but almost all of these (97%) had received their DM diagnosis more than 2 years before the study, making remission less probable.[14]

Both achieving remission and remission without relapse were associated with a better QoL for the cat. Assessment of QoL in companion animals is complicated.[44] In the present study, QoL was interpreted by owners, and was thus affected by their personal views. The glycemic status of the treated cats was not known. Nevertheless, the association between remission and a better QoL indicates that for an insulin-dependent cat, the disease and its monitoring and treatment negatively affect QoL. This further emphasizes remission as a desired goal in disease management, and shows the importance of including assessment of QoL in the treatment of the diabetic cat.

4.3 | Owners' perceptions and concerns

In the present study, around half of the owners perceived limitations in their daily life because of the cat's DM, and more than a third were concerned about complications. However, neither this perception of limitation nor worrying about complications were associated with decreased odds of the cat surviving the initial 4 weeks, that is, whether or not euthanasia was chosen in conjunction with diagnosis. A possible explanation for this is that these limitations or concerns were not experienced until after a period of treatment.

Previously recognized owner concerns include costs, limitations in owner lifestyle, worries about complications and worries about the cat's wellbeing.[2,3,28,29] Studies have shown that these concerns decreased with treatment time.[3,29] Positive matters include more attention being given to the cat after diagnosis[2] and a stronger bond between the owner and the cat.[2,28,29] In the present study, more than half of the owners reported a strengthened relationship with their cat.

5 | LIMITATIONS OF THE STUDY

The main limitation of the study is that all information was obtained from owners and that a majority of the cats were not alive when their owners answered the questionnaire. This might have resulted in recall bias, as well as misinterpretations concerning the cat's medical history. In addition, detailed information about several aspects was missing. Owners who participated could represent a more motivated fraction. The definitions of diabetes mellitus and diabetic remission used in the study were formulated to fit owners, and did not conform to internationally agreed definitions,[45] which might limit comparison with other studies. To reduce the risk of overestimating survival time, since time frames were set as the year of diagnosis and death, and not a specific date, survival time was recorded from 31 December in the year of diagnosis to 1 January in the year of death. Survival time was therefore recorded as the shortest possible time, and will be longer in reality. The present study included insured cats, and some results might differ for non-insured cats.

6 | CONCLUSIONS

Diabetes mellitus is a complex disease, and treatment affects the lives of both the owner and the cat. Feeding the cat a CA wet diet was associated with achieving and maintaining diabetic remission. Achieving remission is associated with a better quality of life for the cat. Therefore there is a need for further studies investigating factors associated with diabetic remission. More than 1 in 10 cats were euthanized in the first weeks following DM diagnosis. Despite this, almost two thirds of the cats (63%) survived for more than 1 year, and a quarter (25%) for more than 3 years. If the owner was worried about limitations to the cat's life and about medication, survival time was shortened. The results accentuate the association between diet and disease outcome. Also, it is crucial to recognize and manage owner distress as a part of disease management, in order to improve welfare for both owner and cat, and to improve the chances of a favorable outcome for the diabetic cat.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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REFERENCES

1. Niessen S, Hazuchova K, Powney S, et al. The big pet diabetes survey: perceived frequency and triggers for euthanasia. *Vet Sci*. 2017;4(2):27. doi:10.3390/vetsci4020027
2. Niessen SJ, Powney S, Guitian J, et al. Evaluation of a quality-of-life tool for cats with diabetes mellitus. *J Vet Intern Med*. 2010;24(5):1098-1105.
3. Albuqurque CS, Bauman BL, Rzeznitzeck J, et al. Priorities on treatment and monitoring of diabetic cats from the owners' points of view. *J Feline Med Surg*. 2019;22(6):506-513.
4. Bijsmans ES, Jepson RE, Syme HM, Elliott J, Niessen SJM. Psychometric validation of a general health quality of life tool for cats used to compare healthy cats and cats with chronic kidney disease. *J Vet Intern Med*. 2016;30(1):183-191.
5. Noble CE, Wiseman-Orr LM, Scott ME, Nolan AM, Reid J. Development, initial validation and reliability testing of a web-based, generic feline health-related quality-of-life instrument. *J Feline Med Surg*. 2019;21(2):84-94.
6. Freeman LM, Rush JE, Oyama MA, et al. Development and evaluation of a questionnaire for assessment of health-related quality of life in cats with cardiac disease. *J Am Vet Med Assoc*. 2012;240(10):1188-1193.
7. Noli C, Borio S, Varina A, Schievano C. Development and validation of a questionnaire to evaluate the quality of life of cats with skin disease and their owners, and its use in 185 cats with skin disease. *Vet Dermatol*. 2016;27(4):247-258.
8. McCann TM, Simpson KE, Shaw DJ, et al. Feline diabetes mellitus in the UK: the prevalence within an insured cat population and a questionnaire-based putative risk factor analysis. *J Feline Med Surg*. 2007;9(4):289-299.
9. Öhlund M, Fall T, Ström Holst B, Hansson-Hamlin H, Bonnett B, Egenvall A. Incidence of diabetes mellitus in insured Swedish cats in relation to age, breed and sex. *J Vet Intern Med*. 2015;29(5):1342-1347.
10. Prahl A, Guptill L, Glickman NW, Tetrick M, Glickman LT. Time trends and risk factors for diabetes mellitus in cats presented to veterinary teaching hospitals. *J Feline Med Surg*. 2007;9(5):351-358.
11. O'Neill DG, Gostelow R, Orme C, et al. Epidemiology of diabetes mellitus among 193,435 cats attending primary-care veterinary practices in England. *J Vet Intern Med*. 2016;30(4):964-972.
12. Marshall RD, Rand JS, Morton JM. Treatment of newly diagnosed diabetic cats with glargine insulin improves glycemic control and results in higher probability of remission than protamine zinc and lente insulins. *J Feline Med Surg*. 2009;11(8):683-691.
13. Roomp K, Rand J. Evaluation of detemir in diabetic cats managed with a protocol for intensive blood glucose control. *J Feline Med Surg*. 2012;14(8):566-572.
14. Roomp K, Rand J. Intensive blood glucose control is safe and effective in diabetic cats using home monitoring and treatment with glargine. *J Feline Med Surg*. 2009;11(8):668-682.
15. Mazzaferro EM, Greco DS, Turner AS, Fettman MJ. Treatment of feline diabetes mellitus using an alpha-glucosidase inhibitor and a low-carbohydrate diet. *J Feline Med Surg*. 2003;5(3):183-189.
16. Weaver KE, Rozanski EA, Mahony OM, Chan DL, Freeman LM. Use of glargine and lente insulins in cats with diabetes mellitus. *J Vet Intern Med*. 2006;20(2):234-238.
17. Nelson RW, Lynn RC, Wagner-Mann CC, Michels GM. Efficacy of protamine zink insulin for treatment of diabetes mellitus in cats. *J Am Vet Med Assoc*. 2001;218(1):38-42.
18. Bennet N, Greco DS, Peterson ME, et al. Comparison of a low carbohydrate-low fiber diet and a moderate carbohydrate-high fiber diet in the management of feline diabetes mellitus. *J Feline Med Surg*. 2006;8(2):73-84.
19. Hall TD, Mahony O, Rozanski EA, Freeman LM. Effects of diet on glucose control in cats with diabetes mellitus treated with twice daily insulin glargine. *J Feline Med Surg*. 2009;11(2):125-130.
20. Frank G, Anderson W, Pazak H, Hodgkins E, Ballam J, Laflamme D. Use of a high-protein diet in the management of feline diabetes mellitus. *Vet Ther*. 2001;2(3):238-246.
21. Gostelow R, Forcada Y, Graves T, Church D, Niessen S. Systematic review of feline diabetic remission: separating fact from opinion. *Vet J*. 2014;202(2):208-221.
22. Sparkes AH, Cannon M, Church D, et al. ISFM consensus guidelines on the practical management of diabetes mellitus in cats. *J Feline Med Surg*. 2015;17(3):235-250.
23. Behrend E, Holford A, Lathan P, Rucinsky R, Schulman R. 2018 AAHA diabetes management guidelines for dogs and cats. *J Am Anim Hosp Assoc*. 2018;54(1):1-21.
24. Gottlieb S, Rand J. Managing feline diabetes: current perspectives. *Vet Med (Auckl)*. 2018;9:33-42.
25. Kraus MS, Calvert CA, Jacobs GJ, Brown J. Feline diabetes mellitus: a retrospective mortality study of 55 cats (1982-1994). *J Am Anim Hosp Assoc*. 1997;33(2):107-111.
26. Callegari C, Mercuriali E, Hafner M, et al. Survival time and prognostic factors in cats with newly diagnosed diabetes mellitus: 114 cases (2000-2009). *J Am Anim Hosp Assoc*. 2013;243(1):91-95.
27. Gossens MM, Nelson RW, Feldman EC, et al. Response to insulin treatment and survival in 104 cats with diabetes mellitus (1985-1995). *J Vet Intern Med*. 1998;12(1):1-6.
28. Aptekmann KP, Armstrong J, Coradini M, Rand J. Owner experiences in treating dogs and cats diagnosed with diabetes mellitus in the United States. *J Am Anim Hosp Assoc*. 2014;50(4):247-253.
29. Hazuchova K, Gostelow R, Scudder C, Forcada Y, Church DB, Niessen SJM. Acceptance of home blood glucose monitoring by owners of recently diagnosed diabetic cats and impact on quality of life changes in cat and owner. *J Feline Med Surg*. 2018;20(8):711-720.
30. Öhlund M, Egenvall A, Fall T, Hansson-Hamlin H, Röcklinsberg H, Holst BS. Environmental risk factors for diabetes mellitus in cats. *J Vet Intern Med*. 2017;31(1):29-35.
31. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2021.
32. Link KR, Allio I, Rand JS, et al. The effect of experimentally induced chronic hyperglycaemia on serum and pancreatic insulin, pancreatic islet IGF-I and plasma and urinary ketones in the domestic cat (*Felis felis*). *Gen Comp Endocrinol*. 2013;188:269-281.
33. Singh R, Rand JS, Coradini M, Morton JM. Effect of acarbose on postprandial blood glucose concentrations in healthy cats fed low and high carbohydrate diets. *J Feline Med Surg*. 2015;17(10):848-857.
34. Zini E, Hafner M, Osto M, et al. Predictors of clinical remission in cats with diabetes mellitus. *J Vet Intern Med*. 2010;24(6):1314-1321.
35. Gottlieb S, Rand JS, Marshall R, Morton J. Glycemic status and predictors of relapse for diabetic cats in remission. *J Vet Intern Med*. 2015;29(1):184-192.
36. Nelson RW, Reusch CE. Classification and etiology of diabetes in dogs and cats. *J Endocrinol*. 2014;222(3):T1-T9.
37. Niessen SJ, Forcada Y, Mantis P, et al. Studying cat (*Felis catus*) diabetes: beware of the acromegaly imposter. *PLoS One*. 2015;10(5):e0127794.

38. Fleeman L, Gostelow R. Updates in feline diabetes mellitus and hypersomatotropism. *Vet Clin Small Anim*. 2020;50(5):1085-1105.
39. Dyson PA, Kelly T, Deakin T, et al. Diabetes UK evidence-based nutrition guidelines for the prevention and management of diabetes. *Diabet Med*. 2011;28(11):1282-1288.
40. American Diabetes Association. Standards of medical care in diabetes—2011. *Diabetes Care*. 2011;34(Suppl 1):S11-S61.
41. Nguyen P, Leray V, Dumon H, et al. High protein intake affects lean body mass but not energy expenditure in nonobese neutered cats. *J Nutr*. 2004;134(8 Suppl):2084s-2086s.
42. de Oliveira LD, Carciofi AC, Oliviera MC, et al. Effects of six carbohydrate sources on diet digestibility and postprandial glucose and insulin responses in cats. *J Anim Sci*. 2008;86(9):2237-2246.
43. Wei A, Fascetti AJ, Liu KJ, et al. Effect of water content in a canned food on voluntary food intake and body weight in cats. *Am J Vet Res*. 2011;72(7):918-923.
44. Freeman LM, Rodenberg C, Narayanan A, Olding J, Gooding MA, Koochaki PE. Development and initial validation of the cat health and wellbeing (CHEW) questionnaire: a generic health-related quality of life instrument for cats. *J Feline Med Surg*. 2016;18(9):689-701.
45. Niessen SJM, Bjornvad C, Church DB, et al. Agreeing language in veterinary endocrinology (ALIVE): diabetes mellitus—a modified Delphi-method-based system to create consensus disease definitions. *Vet J*. 2022;289. doi:10.1016/j.tvjl.2022.105910

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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IV

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Hair cortisol concentrations in clipped and combed hair and associations with characteristics, health status and stress in domestic cats

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Hair cortisol concentrations (HCC) are measured to assess long-term HPA-axis activity and may represent a valuable non-invasive tool to evaluate chronic stress in cats. This study investigated combing as a novel, low-stress method for HCC assessment, as well as possible associations between HCC and cat characteristics in 167 owned cats. Hair was sampled at veterinary clinics through clipping and/or combing the cat, or at home by the owner combing the cat. A questionnaire was sent to cat owners, including inquiries about the cat's sex, health status, and exposure to stress. HCC was quantified using a commercial cortisol assay kit. Despite variations within and between sampling methods, Spearman's correlation and Bland–Altman plots revealed a moderate correlation between clipped and combed samples ($r_s = 0.61$, LOA -5.51 ± 22.54). In multiple linear regression, variations in HCC were observed based on sex, health status and cat group size. No associations were found between HCC and stress as assessed by owners. Despite study limitations and remaining uncertainty regarding factors influencing HCC, combing presents a convenient approach for evaluating long-term HPA-axis activity in clinical settings. The association between health and HCC suggests alterations in cortisol levels that are related to disease processes and stress-inducing events associated with the disease.

Keywords Cats, Noninvasive measures, Cortisol, Chronic disease, Estrus, Pregnancy

Chronic stress is a critical concern for animal welfare[1–3], drawing increased attention in association with different physiological and behavioral alterations in cats[4–10]. Despite its significance to both cat and owner, signs of stress are frequently overlooked or underestimated by owners[11]. Stress is best estimated by combining behavioral and physiological data[12,13], and as the hypothalamic–pituitary–adrenal (HPA) axis is central in stressor responses, measurement of HPA-axis activity is a common approach.

Over the past two decades, the use of hair cortisol concentration (HCC) to evaluate long-term HPA-axis activity has gained prominence[14–18]. HCC, reflecting cortisol incorporation into actively growing hair, is regarded as a reliable marker for long-term cortisol secretion in various species[19]. The benefits of using HCC include an easy and non-invasive sampling, convenient storage of hair[20], and an excellent stability of cortisol in hair over time in investigated species[18,20–22]. Striving for a low-stress and convenient sampling method is beneficial for both cats and their owners. Traditionally, hair for analysis of cortisol concentration is sampled through shaving, often using the shave-reshave method, where hair is shaved at the beginning of the time frame of interest, and then shaved again after a period of regrowth[23]. Shed hair has been collected from sleeping nests[24] and from fencing[25].

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However, our understanding of HCC has limitations, and recognizing them is essential, particularly when intending to evaluate animal welfare and stress. The mechanisms of cortisol incorporation into the hair are not fully understood[23], and both hair and species-specific factors have to be considered when evaluating HCC[18,22–24,26–32]. In domestic cats this includes the varying distribution of primary and secondary hairs and seasonal hair follicular activity[33,34]. Higher HCC have been associated with litterbox issues[35,36], aggressive behavior[36,37], and neutering status in cats[37], and both physiological and behavioral alterations have been suggested to affect cortisol concentrations in reproductively active females[37,38]. Lower HCC was measured in cats with well-kept hair coats compared to cats with poor hair coat conditions [35]. An unkempt hair coat is reported in association with stress[39] and with chronic diseases like hyperthyroidism and diabetes mellitus in cats[40–42]. However, when considering other factors, owner-reported chronic diseases in cats did not reveal significant associations with cortisol concentrations in either hair or nails[35]. Higher HCC were measured in shelter cats with dermatophyte infections[43], but the only other factors available for data analysis were age and sex. This study aims to investigate a new low-stress hair sampling method in cats, building on previously used hair clipping techniques[35–37,43,44], by combing the thoracic and abdominal regions. The objective was to develop a method that minimizes the need for sampling equipment, simplifies recruitment by lowering barriers for cat owners, and ensures low-stress handling of the cats. Another aim was to evaluate HCC in relation to owner-reported cat characteristics, health status, stressors, and signs of stress. We hypothesize that HCC from different sampling locations, sampled using different methods, will be positively correlated, and that HCC will be influenced by chronic disease and stress.

Materials and methods

Ethical approval

According to Swedish (SJVFS 2019:9, case no. L 150) and EU (EU Directive 2010/63) legislation, hair sampling by combing or clipping from privately owned cats does not require ethical permission. As required by L150, the owners received both written and oral information about the study and signed informed consent prior to inclusion. They were informed that they could withdraw their consent at any time. The experimental protocol was approved by The Board for Animals in Research and Teaching at The Swedish University of Agricultural Sciences. Data were handled in accordance with the General Data Protection Regulation. Hair samples were the only samples collected from the cats in this study, and all sampling took place in conjunction with veterinary appointments or by the owners at home. This study is reported in accordance with the ARRIVE guidelines[45].

Study sample and questionnaire

Cats were recruited, and hair was sampled during veterinary visits to four participating veterinary clinics. Cats were also recruited through personal contacts, and in these cases, hair was sampled by the owners at home. Recruitment was limited to cats aged ≥ 6 months living in Sweden, whose owners consented to their participation. Participation was entirely voluntary, and no remuneration was provided. Information about the cats was obtained from a questionnaire. The exclusion criteria encompassed an incomplete questionnaire, contradictory information on health status of the cat, and the presence of acute injury, acute disease, or treatment with glucocorticoids 2–16 weeks before hair sampling.

Questions for the questionnaire were formulated taking into account previous studies and knowledge on stress in cats and the role of the owner in assessment[3,7,11,46–48]. The questions were assessed for comprehensibility and accurate interpretation by four cat owners, who were not part of the study. Based on the feedback from this pilot testing, the questionnaire was revised before digital distribution to participating cat owners via an online provider (Netigate), by e-mail, or, in case of missing e-mail, by mail.

Most questions were related to the time frame 2–16 weeks before hair sampling, roughly representative of HPA activity and cortisol incorporation in sampled hair strands. In addition, some questions concerned basic information about sex (male or female), the cat's age at hair sampling, hair color and pattern. Further, two inquiries were about the owners' perception about the cat's quality of life and welfare. All owners had to answer the question "Is your cat healthy?" with answer options "Yes, my cat is healthy", "Yes, my cat is healthy but has suffered from acute disease or injury", "No, my cat has a chronic disease" and "No, my cat has a chronic disease and has suffered from acute disease or injury". This formed the basis for grouping the cats according to their owner-reported health status. To assess the presence of stress, information was gathered on owner-reported exposure to potential stressors (e.g., new animal in household, house renovation, or cat relocation) and owner-observed signs of stress (e.g., house soiling, increased conflicts with other animals, changes in appetite or in activity levels). For cats with chronic disease, information on the presence of clinical signs related to the disease was gathered as a measure of disease impact on affected cats. For a summary of the questions and answer options, refer to Table 1. The answers from twenty-five questions were analyzed in this study.

Hair sampling

All hair sampling occurred between June 2020 and November 2022. Hair was sampled on one occasion from every cat. At least one hair sample was obtained from each cat: by clipping the dorsal area of the front leg or the caudoventral area of the abdomen, or by combing the dorsal back and lateral sides of the cat. Hair sampling was conducted either at veterinary visits (both clipping and combing) or by owners at home (combing only). For owners visiting veterinary clinics, paired samples were taken from more than one of the three different locations and methods. Clipping areas were selected for ease of retrieval, representing common venipuncture sites (dorsal area of the front leg) or areas prepared for abdominal ultrasound or surgery (the abdomen). This also ensured that no cat had to be clipped when not medically indicated, creating an opportunistic sampling process.

Detailed written instructions were provided to both veterinary staff and owners before sampling. Front leg and abdominal samples were obtained using well-cleaned mechanical clippers designed for small animals. The

Questions	Answer options and grouping of answers for data analysis (all questions included an "Other/Decline to answer" alternative and a free text section)
Cat characteristics	
Year of birth	e.g., 2014
Sex and neutering status	Spayed female, Neutered male, Intact female, Intact male, Female with experience of estrus/pregnancy
Color pattern*	Tabby/striped, Tortoise/patchy, Full colored, Masked, Other
Main color*	Black, White, Grey, Brown, Red, Other
Hair length	Short, Semi-long, Long
Living conditions	
Living location	Centrally in a city, Outside city center (e.g., residential area), In a smaller town, In the countryside
Cat age when arrived at owners home	Introduced as a kitten, 6–12 months of age, Older than 12 months
Presence of children < 18 years of age in household	No, Yes
Outdoor or indoor confinement	Indoor (strictly indoor and indoor with access to patio/balcony/leash walks), Outdoor (both out- and indoor and strictly outdoor)
Number of cats in household	Single cat household, Multi-cat household
Presence of other animals in household (e.g., dog)	No, Yes
Harmony in animal group	Occasional conflicts or occurrence of cat withdrawal, Many conflicts or occurrences of cat withdrawal, No the animal group is harmonious, No other animals in household
Health status	
Presence of chronic disease	Yes (Hyperthyroidism, Diabetes mellitus, Chronic kidney disease, Other), No
Presence of clinical signs related to chronic disease?*	No, Yes (Polyuria/polydipsia, Changes in appetite, Weight loss, Weight gain, Other)
Welfare and stress	
Exposure to potential stressors*	No, Experience of potential stressors (Moved to a new home, Big changes in family/household (e.g., new family member), House renovation, Travels/relocation of the cat, New animal in household, Move or death of former animal friend, Diet change, Other)
Display of signs of stress*	No, Displaying signs of stress (House soiling, Altered grooming activity, Behavioral changes, Increased occurrence of conflicts/aggressive behavior, Scratching furniture, Signs of withdrawal, Changes in appetite, Reluctant to play, Spending more time outdoor/indoor, Seeking more contact, More vigilant, Strong reaction when scared, Other)
Other	
Treatment with glucocorticoids	No, Yes (Oral tablets, Salve, Ear drops, Injection, Other)
Treatment with other medications or supplements	No, Yes (Free text answer on what medication)
*Multiple answers available	

Table 1. Summary of merged questions and answer options, as they were grouped for data analysis, as completed by owners of cats encompassed in the study (n = 167).

hair was cut at the level of the skin surface. For the front leg, a square of hair approximately 1.5 × 1.5 cm was cut from the dorsal area of the radius. Abdominal samples involved clipping hair from the caudoventral abdominal area in the anterior direction towards the costal arch, covering an area of approximately 5 × 10 cm, depending on the cat's size. Instructions for combing included using a fine-toothed, cleaned comb on the dorsum and lateral area of the cat's thorax and abdomen, and combing until an amount of hair equivalent to approximately 1 cm in diameter, when compressed, was achieved.

The hair samples were assigned a code for blinding, were placed in aluminum foil, and were stored at room temperature in a dark, dry place for a maximum time of 7 months before cortisol quantification.

Cortisol extraction

All laboratory work was performed by the research team, at the laboratory at the department of Clinical Sciences, Swedish University of Agricultural Sciences, Uppsala, Sweden. Based on previously measured hair growth rates in domestic cats[34,49], the sampled hair was cut to a length of 40 mm, estimated to roughly represent the hair growth during 16 weeks. Extraction of cortisol from hair was performed and partly modified after Meyer et al.[15], as follows: roughly 50 mg of hair was clipped into smaller parts with scissors and washed twice in 1.5 ml of isopropanol using a vortex mixer. When dried, excess hair was removed for a final hair weight of 50 mg. For samples containing hair < 50 mg, the lower weight was noted. In preparation for grinding the hair, three steel balls (Ø3.2 mm) were added to each sample and samples were deposited in liquid nitrogen for 4 min, increasing hair brittleness. Hair grinding was performed using a BeadBeater (5000 RPM, 6 × 30 s with a 30 s pause between sets). Freezing and grinding were repeated once. For cortisol extraction, 1.2 ml of methanol was added to the ground samples in a 22 h incubation phase on a laboratory rocker. After centrifugation, 0.6 ml of supernatant were extracted from each sample and then dried and reconstituted in a phosphate buffer (0.01 M PBS, pH 7.4). Reconstituted samples were stored frozen (-80°C) until cortisol quantification.

Assay performance and determination of cortisol concentration

For quantification of cortisol in hair, a commercial competitive high sensitivity ELISA kit (Salimetrics® Salivary Cortisol Enzyme Immunoassay Kit, LCC 2021) developed for quantitative measurement of human salivary cortisol and previously validated for analysis of cortisol in cat hair was used[35]. The minimum concentration of cortisol that could be distinguished from 0 was 0.007 µg/dL, and for samples with cortisol concentrations greater than 3.0 µg/dL, dilution was recommended. Results were converted from µg/dL to pg/mg hair[15].

Hair from 13 cats and three 96-well plates were used to evaluate assay performance. Mean within-assay variation (CV) was determined on ten samples with low (2–3.6 pg/mg, three samples), medium (5.4–6.5 pg/mg, three samples) and high (8.7–85 pg/mg, four samples) cortisol concentrations, run in duplicates on one plate. Mean between-assay variation (CV) was determined by using three samples run in quadruplicates on three plates. For linearity and recovery upon dilution, one feline sample with high HCC was serially diluted with the assay diluent provided by the manufacturer 1:1, 1:1.33, 1:2, 1:4, 1:8, 1:16, and 1:32, and analyzed in triplicates on one plate. Recovery ([observed concentration/expected concentration]*100) was calculated. For recovery upon addition, three feline samples were spiked 1:1 in three different combinations (low and high sample, low and medium sample, low sample and high calibrator, as provided by the manufacturer) and analyzed in triplicates on one plate. To determine cortisol concentration, non-spiked samples from the three cats were also analyzed. Expected concentration ([concentration of non-spiked sample + concentration of the added sample or calibrator]*0.5) was calculated.

To evaluate stability of cortisol in cat hair over time, hair from two cats were prepared and the cortisol concentration was analyzed after 1, 8, and 24 months of storage in aluminum foil. For stability of extracted cortisol under deep frozen conditions, frozen reconstituted samples from the same two cats were re-run 8 and 24 months after initial cortisol analysis.

All individual samples were run in duplicates on a total of ten 96-well plates. In case of high CV ($\geq$10%) between duplicates that could not be explained by low concentrations, samples were re-run. Samples with the lowest CV proceeded to data analysis. Samples exceeding the highest assay limit (3 µg/dL = 240 pg/mg) were set to 240 pg/mg.

Data analysis

In the case of missing or conflicting answers for any of the variables of interest, the respondent was contacted, and the answers were then adjusted, or the cat excluded accordingly. Cat age at the time of hair sampling was set to January 1st of each year. Cat sex was defined as spayed/neutered female or male, intact female or male, and females that, regardless of neutering status, had experienced pregnancy or estrus 2–16 weeks preceding hair sampling. For cats that were sampled in connection with neutering or spaying procedures, without experience of pregnancy or estrus, sex was set as intact. For owner-assessed stress, cats were assigned three different stress groups; no stress (no experience of potential stressors and no display of signs of stress), experience of potential stressors (but not displaying signs of stress), and displaying signs of stress. Cats that had experienced pregnancy or estrus were included in the group of cats displaying signs of stress, regardless of the owners' assessment of stress signs. Cats in an owner-reported state of diabetic remission were included in the healthy group. For a summary of the questions and grouping of answers, see Table 1.

Data analysis was performed using R [50] and Minitab [51]. Data was checked for normality using frequency distribution (histogram) and the Shapiro–Wilk normality test. Means and standard deviations were used when normality could be assumed, and median and inter-quartile ranges (IQR) were utilized when this was not the case. For evaluation of the relationship and differences of HCC between the three different hair sampling locations and methods, Spearman´s rank correlation and Bland–Altman plots were used, with 95% confidence intervals. Bland–Altman plots were interpreted graphically and by calculating the mean difference between paired values (bias). In cases where markedly differing datapoints, introducing a larger bias to the plot, were identified, they were removed prior to plotting. Limits of agreement (LOA, bias $\pm$ 1.96 SD) were constructed based on the standard variation (SD) of the differences between paired measurements. Multiple linear regression was used for evaluation of associations between HCC and owner reported cat characteristics, stress or health status. Two regression models were built; one with HCC quantified from clipped front leg samples as dependent variable, and one with HCC derived from combed samples as dependent variable. To improve model fit, the outcome variable HCC was log transformed for both regression models. Univariable linear regression was used for selection of variables, including variables with $p < 0.2$ in further model building. Based on previous studies[35,43], the variables health status, presence of other animal species in the household, occurrence of potential stressors and signs of stress were included in building of the multivariable regression model, regardless of univariable regression outcome. The final regression model was decided with a backwards elimination process, where a lowered Akaike information criterion (AIC) was combined with exclusion of variables with $p \geq 0.05$. Confidence intervals were set to 95% with a significance level of 5%. Quantile–quantile plots (QQ plots) and normality tests were used to assess regression residuals for normality. Biologically plausible interactions were included, and possible confounders were controlled in each regression model.

Results

Cats and general characteristics

In total 200 cats were recruited. Of these, 33 were excluded due to regular treatment with glucocorticoids, incomplete or obviously misinterpreted questionnaire answers, acute injury or disease, or contradictory information on health status. Complete questionnaires and hair from 167 cats remained for analysis (Fig. 1). One-hundred and three cats were reported as healthy, and 64 cats as chronically ill.

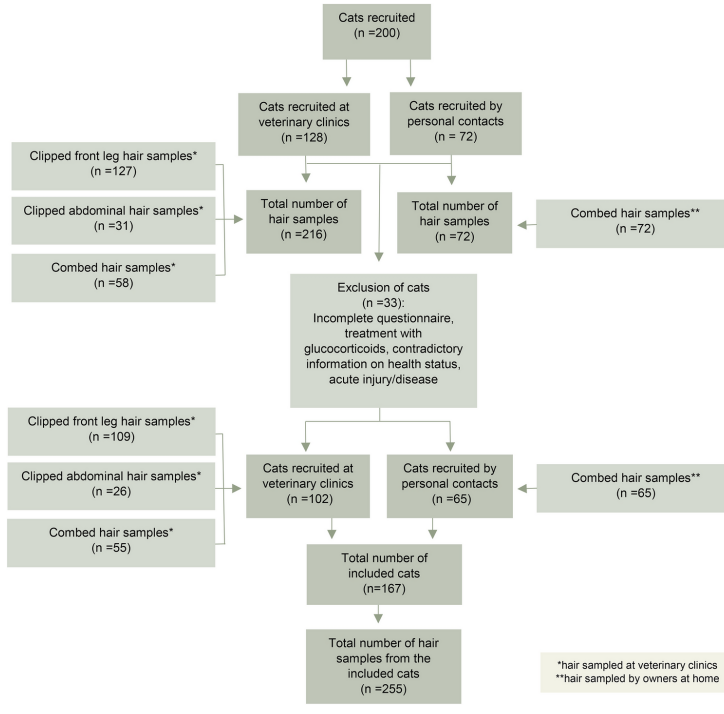

Fig. 1. Overview of cats recruited and included in the study, including the different methods and body locations from where hair was sampled from the cats. Not all cats were sampled from all three locations.

In healthy cats (n = 103), median age at sampling was 3 years (IQR 2–8). The majority of cats were spayed/neutered (63%), 15.5% were intact females, 5% were intact males, and 16.5% were females that, irrespective of neutering status at the time of sampling, had experienced pregnancy or a period of estrus.

In cats with chronic disease (n = 64), median age at hair sampling was 14 years (IQR 11–16). All cats were spayed or neutered, and no cat had experienced pregnancy or estrus. Type of chronic illness included one or more of the following conditions; diabetes mellitus (n = 28), hyperthyroidism (n = 19), chronic kidney disease (n = 14), hypertension (n = 5), arthritis (n = 3), chronic pancreatitis (n = 1), inflammatory bowel disease (n = 1), asthma (n = 1), chronic rhinitis (n = 1), allergy (n = 1), and tooth resorption (n = 1).

Assay performance

Mean within assay CV was 26.7% for low, 11.5% for medium and 10.1% for high concentrations, respectively. Mean within-assay CV for all analyzed 10 samples was 15.5%. Mean between-assay CV was 7.6% for concentrations 5.9–30.1 pg/mg. To determine recovery after dilution, a pooled sample with known concentration of cortisol (25.9 pg/mg) was diluted 1:1/3, 1:2, 1:4, 1:8, 1:16 and 1:32. Recovery after dilution was adequately linear, and was 109%–460%, where the most diluted sample represented the highest recovery percentage. Recovery upon addition was 80%-85% for concentrations 8.5–134 pg/mg.

A higher consistency was seen between original and re-run frozen reconstituted samples, compared to original samples and samples prepared from hair that had been stored in aluminum foil, see Table 2.

Hair samples and hair sampling location and sampling method

A total of 255 hair samples were collected (see Fig. 1). Median HCC in clipped samples from the front leg was 5.6 pg/mg (IQR 4–7.2, n = 109), in clipped samples from the abdomen 4.8 pg/mg (IQR 3.4–8, n = 26) and in samples obtained through combing 7.2 pg/mg (IQR 4.8–11.5, n = 120). The HCC range was widest in samples obtained from combing (2.4–240 pg/mg) compared to front leg (1.4–134 pg/mg) and abdomen (1.6–13.6 pg/mg).

Twenty-three cats had hair sampled from both the front leg and from the abdomen, with a Spearman´s Rho of 0.72 (CI 0.39–0.89, n = 23). In Bland–Altman analysis, the mean difference between paired HCC was 0.38 pg/mg and the limits of agreement was -6.74 and 7.50 (LOA, 0.38 ± 1.96 SD). One observation was beyond

	Storage method	0–1 months of storage	8 months of storage	24 months of storage	Mean	SD
Cat AHCC (pg/mg)	Hair in RT*	11.2	8.0	12.8	10.7	2.4
	Extraction in PBS** at – 80°	11.2	9.6	12.8	11.2	1.6
Cat B HCC (pg/mg)	Hair in RT*	18.0	12.0	12.3	14.1	3.4
	Extraction in PBS** at – 80°	18.0	17.3	18.8	18.0	0.75

Table 2. Stability of cortisol concentrations in two cats (A and B), in samples where cortisol was extracted from hair stored at room temperature (RT), and in samples where cortisol was reconstituted in a phosphate buffer (PBS) and then stored at –80°, for 0–1, 8 and 24 months respectively before cortisol quantification. *Hair stored in aluminum foil at room temperature (RT) until extraction of cortisol and cortisol quantification, **Extracted cortisol in a phosphate buffer (PBS), all samples prepared and frozen at the same time, and stored at –80° until cortisol quantification

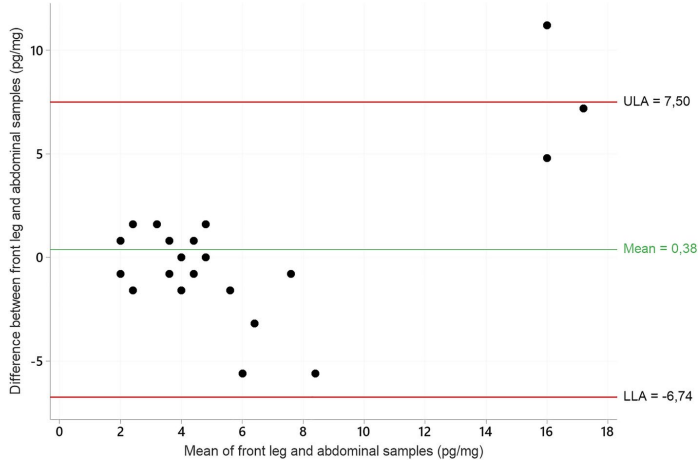

Fig. 2. Bland–Altman plot of agreement between hair cortisol concentrations (pg/mg) in hair samples from the dorsal area of the front leg and the ventral area of the abdomen in cats (n = 23). ULA = upper limit of agreement, LLA = lower limit of agreement.

LOA. Agreement between measurements was higher for lower HCC concentrations (mean ≤ 5.6 pg/mg) than for higher concentrations, see Fig. 2.

Sixty-two cats had hair sampled from both the front leg and by combing, with a Spearman´s Rho of 0.61 (CI 0.41–0.76, n = 62). For the Bland Altman plot, three observational outliers were removed – see Fig. 3. The mean difference in paired values was -5.51 pg/mg and the limits of agreement was -28.05 and 17.02 (LOA, -5.51 ± 1.96 SD, n = 59). Three observations were beyond LOA. As for the comparison between clipped front leg and abdominal samples, agreement between measurements was highest in lower HCC concentrations (mean ≤ 10 pg/mg) and decreased with increasing HCC.

HCC and associations with cat characteristics, health status and stress

Regression analysis with HCC quantified from clipped front leg samples comprised every included cat with front leg samples (n = 109). From univariable linear regression models, sex (p = 0.18) and multi-cat household (p = 0.04), were included in building the multiple linear regression model. Further, the variables health (p = 0.228), presence of other animal species in the household (p = 0.750), occurrence of potential stressors (p = 0.503), and presence of signs of stress (p = 0.270), were included [35,43]. In the final linear multivariable regression model, the only factor remaining significant for prediction of HCC were sex and multi-cat household. Females that had experienced pregnancy or heat had higher HCC than spayed females (p = 0.008), and cats that lived in a household with at least one more cat had higher HCC than cats in single cat household (p = 0.042). See Table 3. and 4 for details.

Regression analysis with HCC quantified from combed hair samples comprised every included cat with combed samples (n = 120). From univariable linear regression models, sex (p = 0.102) and health (p = 0.190), were included in building the multiple linear regression model. As previously mentioned, the variables presence of other animal species in the household (p = 0.737), occurrence of potential stressors (p = 0.311), and presence

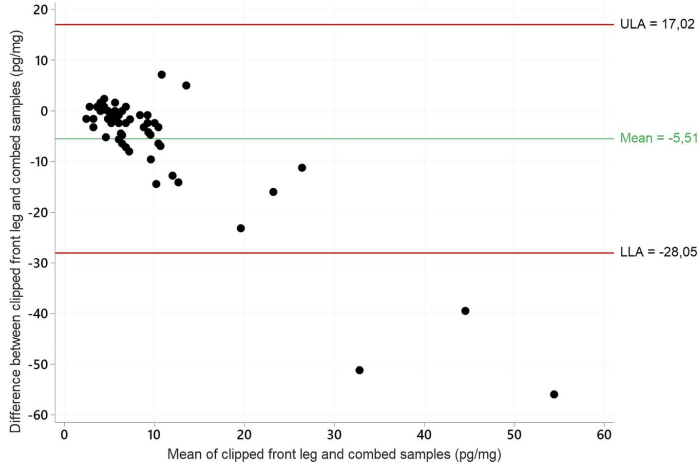

Fig. 3. Bland–Altman plot of agreement between hair cortisol concentrations (pg/mg) in hair samples from the dorsal area of the front leg and combed samples in cats (n = 59). ULA = upper limit of agreement, LLA = lower limit of agreement.

Variable		Clipped front leg hair samples (n=109)	Combed hair samples (n=120)
Sex and neutering status*	Neutered male	34	58
	Spayed female	41	34
	Intact male	5	2
	Intact female	13	11
	Female with experience of estrus/pregnancy	16	15
Number of cats in household*	Single-cat household	47	61
	Multi-cat household	62	59
Presence of other animals in household (e.g., dog)**	No	95	101
	Yes	14	19
Presence of chronic disease* **	No	67	83
	Yes	42	37
Exposure to potential stressors**	No	49	58
	Yes	60	62
Display of signs of stress**	No	85	94
	Yes	24	26

Table 3.. Overview of variables included in multivariable linear regression analysis of hair cortisol concentrations (pg/mg) from hair samples collected by clipping the front leg (n=109) or by combing the dorsum and lateral sides (n=120) of the cat (n=167). Note that 62 cats were sampled in both ways and are thus represented in both groups. Hair cortisol concentrations were log-transformed for regression analysis. *Variables were selected for multiple regression analysis if $p < 0.200$ in univariable analysis **Variables were selected for multiple regression analysis regardless of univariable outcome, based on results from previous studies

of signs of stress ($p = 0.989$), were included[35,43]. In the final linear multivariable regression model, factors remaining significant for prediction of HCC were sex and health. Intact males had higher HCC than spayed females ($p = 0.013$) and cats with chronic disease had higher HCC than healthy cats ($p = 0.025$). See Table 3. and 4 for details.

Discussion

This study measured cortisol concentrations in hair from domestic cats, sampled by two different methods and from three different body locations. HCC varied with and within different body locations and sampling

	HCC measured in hair clipped from the dorsal area of the front leg			HCC measured in hair combed from the dorsal and lateral areas of the body		
	Change in HCC (%)	CI (%)	p	Change in HCC (%)	CI (%)	p
Outcome and variables						
Sex						
Intact female vs spayed female	56	-7 – 158	0.085	89	-4 – 274	0.066
Intact male vs spayed female	125	-6 – 439	0.068	499	46 – 2356	0.013 *
Female with experience of pregnancy or heat vs spayed female	76	16 – 167	0.008**	84	-0.2 – 239	0.051
Chronic disease vs healthy	49	-0.9 – 124	0.055	61	6 – 144	0.025*
Multicat household	38	1 – 89	0.042*	-	-	-
CI; confidence interval						

Table 4. Back-transformed predictions of hair cortisol concentrations (HCC) in two final linear regression models, where hair was sampled by clipping the dorsal area of the front leg (n = 109), and by combing the dorsum and lateral area of the thorax and abdomen (n = 120) in the cat.

methods. Despite this, agreement between methods was found, and both sex and health were associated with HCC. Being a female with experience of pregnancy or estrus or living in a multi-cat household was associated with elevated HCC in hair sampled from the front leg. Presence of chronic disease was associated with increased HCC in combed hair samples, as was being an intact male. Exposure to potential stressors or displaying signs of stress were not associated with changes in HCC. Based on the results of the present study, storing samples as reconstituted samples is preferable for HCC quantification compared to storing hair.

The common practice in hair cortisol analysis involves initially shaving a specific area and then repeating the process after a designated period of hair regrowth, known as the shave-reshave method. This ensures the inclusion of actively growing hairs in the sample, aligning with the time frame of interest, as cortisol is incorporated into actively growing hair strands[23,52]. Differences in cortisol concentrations among hair from different body regions have been seen in various species[22,24,35,53]. Therefore, it is recommended to sample hair from one single body region when measuring HCC. In the present study, sampling areas were chosen based on convenience in a clinical setting and to minimize sampling-associated stress for the cat. The aim was to retrospectively study a time frame of 2–16 weeks, with a questionnaire designed to cover the cat's history during this period in relation to hair sampling.

The specific properties of cat hair have to be considered when using HCC. Hair growth varies with different seasons and photoperiods[34,49], factors that were not investigated in the present study. A slower growth rate could result in prolonged cortisol incorporation in the hair, leading to higher concentrations of cortisol, and representing a longer retrospective time for cortisol incorporation. The cat pelage includes primary (guard) and secondary (wool) hairs, and their distribution over the body, their growth rate and follicular activity varies[34]. These factors, as well as shedding patterns[34], and varying hair lengths across different body parts, could have contributed to the variations in HCC seen between different body locations in the present study.

Given the differences in both body location and retrieval method, different HCC between the clipped and combed hair samples was expected. This expectation was confirmed, with the highest variation observed among the combed samples. The influence of a few individuals with very high HCC, predominantly measured from combed samples, could explain some of this variation. Additionally, the broader area of the body from which hair strands are sampled during combing, as opposed to the front leg, may have introduced further variability. Combing involves sampling a large proportion of loose hairs, which could make this method more susceptible to seasonal and individual shedding, and to grooming behaviors. No information on grooming behavior was collected in the present study. Combing may include more skin material in the hair sample, but thorough washing prior to cortisol quantification minimizes external contribution to HCC variability[23], and skin material is thus not likely contributing to the wide HCC range with this method. For clipped front leg samples and combed samples, there was consistency in paired measurements, especially for lower HCC. The same pattern of consistency was also evident in paired measurements from hair clipped from the front leg and the abdomen. Similar associations between HCC and cat characteristics and health were found between clipped front leg samples and combed samples, though not all statistically significant at $p < 0.050$. It is important to note that not all cats were sampled using both methods and from all three locations, and a larger sample size would have been beneficial for comparison. This highlights the challenges faced when collecting samples for research in a clinical setting. Combing is a less standardized method of hair sampling. However, avoiding repeated sampling is beneficial for increasing compliance among cat owners, and hair sampled by combing has potential as an owner- and cat-friendly method of hair sampling for HCC analysis.

Presence of chronic disease was associated with higher HCC, compared to healthy cats. Previously, chronically elevated cortisol levels, as measured in HCC, have been associated with dermatophyte infection in shelter cats[43]. A higher urine cortisol-creatinine ratio has been described in cats with hyperthyroidism[54] and in hospitalized cats with various diseases[55], as well as in shelter cats with signs of systemic disease [12]. Higher cortisol concentrations could be associated with both the disease process[54], and with events that are related to, but not directly associated with disease. This may include veterinary visits and transportation of the cat

to the clinic[56], cat synchronization with owner stress[57], and daily administration of medications. Although hyperthyroidism, chronic kidney disease, and diabetes mellitus were the most commonly represented diseases in the studied population, a diverse range of diseases was observed, and the cats exhibited various stages of illness. Further examination of specific diseases could provide deeper insights into the influence of individual diseases and disease states on HCC. Interestingly, the presence of clinical signs reported by owners did not show an association with HCC. This discrepancy could be attributed to factors such as questionnaire design, inaccurate owner reporting, or the owners' ability to recognize clinical signs of disease. Furthermore, HPA-axis dysregulation, manifesting as hypocortisolism following a period of chronic HPA-axis hyperactivity, might contribute to this observed discrepancy[58]. The possibility of a disparity between the observable condition of a chronically ill cat and its actual impact, as measured by HCC, warrants additional investigation.

Our results reveal a sex-associated difference in HCC. In clipped front leg hair, females with reported experiences of pregnancy or estrus, had higher HCC than spayed females. In combed hair, intact males had higher HCC than spayed females. Suggested causes for effect of sex on HCC in different species include the influence of social rank[59], territorial behavior[60], differences in body condition[25], and effect of gonadal steroids on HPA-axis activity [61]. During pregnancy, cortisol is crucial for fetal development, leading to increased circulating cortisol concentrations until parturition[31,62]. A lower HCC has been reported in spayed free-roaming domestic female cats compared to intact females, possibly influenced by agonistic behavior or reproductive status[37]. The associations in our study may result from hormonal changes during pregnancy, parturition, increased energetic expenditures, and general maternal efforts post-partum[38,63]. The majority of intact females (15/16) without owner-reported estrus or pregnancy were at least one year old at the time of hair sampling, suggesting potential estrus experiences not reported by the owner [64]. In a study of wildcats and feral cats, higher HCC was observed in male cats compared to females, although this difference was not statistically significant, possibly due to a small sample size[65]. In our study, we found an association between male sex and HCC. However, similar to the previous study, the limited number of cats in our sample influenced the results, with uncertainty highlighted by a wide confidence interval. A larger sample size is necessary for a more comprehensive exploration of HCC and sex in domestic cats.

In the present study, no association between HCC and exposure to potential stressors or display of stress-related behaviors were seen. Previously, HCC in cats has been positively associated to defecating or urinating outside the litterbox[35,36] and to displaying aggressive behavior towards family members [36], and negatively associated to a groomed and soft hair coat[35]. In one of these studies, owner-reported stress levels were not significantly associated with HCC when other factors related to the cat and its home environment were considered [35]. An explanation for the lack of association between stress and HCC may be failure of owners to recognize signs of stress in their cats [11], or variability in HPA-axis activity related to individual stressor response [58,66,67]. In the present study, no consideration of different cat temperaments and personalities were made, which could affect both stress coping mechanisms and stress responses [3,68].

Cats living in multi-cat households had higher HCC than cats in single cat households. A multi-cat household was defined as the cat sharing living space with at least one other cat, and in the data analysis no differentiation on the total number of cohabitating cats were made. In a multi-cat household, cats need to share resources, with potential emergence of inter-cat aggression and other stress-linked behaviors [69]. However, a multitude of potential factors influence cat behavior in both single and multi-cat households [7,46].

This study has several limitations. First, this is an observational study, and as such, there is limited control over the included subjects. The cat population at large is probably well represented, but confounding factors may go undetected. The sample size is small, and the hair sampling performed at home by owners lacked standardization, introducing variability into the collection process. Also, reliance on owner obtained information about the cats may introduce subjectivity and potential inaccuracies, including recall bias and misinterpretations. No clinical confirmation of the cats' health status or other related information was available. The lack of a validated stress scale or evaluation tool could have limited the accuracy of stress assessment.

Chronic stress has profound implications for feline welfare. Given that stress often goes unnoticed by owners, there is a need for methods to facilitate stress evaluation in cats. The quantification of HCC holds promise for a non-invasive aid in assessment of long-term HPA-axis activity in felines. This study explored a novel, low-stress hair sampling method for cortisol quantification. Although much remains unknown about the factors influencing HCC, samples obtained by combing demonstrate potential for simplified sample collection and assessment of HCC in relation to various cat characteristics. Despite variations between the studied sampling methods, a concordance between them was observed, and associations between HCC and sex and health was seen. Combing showed potential as a cat-friendly sampling method, addressing the challenges encountered in sample collection within a clinical setting. The limitations of this study warrants caution in interpreting results. However, the findings contribute to the potential use of a low-stress combing method for HCC assessment, emphasizing the need for research to further explore this approach.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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References

1. Moberg, G. P. *Biological responses to stress: implications for animal welfare.*, 1–21 (CABI Publishing, 2000).

2. Levine, E. D. Feline Fear and Anxiety. *Veterinary Clinics of North America: Small Animal Practice* **38**, 1065–1079. https://doi.org/10.1016/j.cvsm.2008.04.010 (2008).
3. Amat, M., Camps, T. & Manteca, X. Stress in owned cats: behavioural changes and welfare implications. *Journal of Feline Medicine and Surgery* **18**, 577–586. https://doi.org/10.1177/1098612x15590867 (2016).
4. Tanaka, A., Wagner, D. C., Kass, P. H. & Hurley, K. F. Associations among weight loss, stress, and upper respiratory tract infection in shelter cats. *Journal of the American Veterinary Medical Association* **240**, 570–576. https://doi.org/10.2460/javma.240.5.570 (2012).
5. Stella, J. L., Lord, L. K. & Buffington, C. A. T. Sickness behaviors in response to unusual external events in healthy cats and cats with feline interstitial cystitis. *Journal of the American Veterinary Medical Association* **238**, 67–73. https://doi.org/10.2460/javma.238.1.67 (2011).
6. Stella, J., Croney, C. & Buffington, T. Effects of stressors on the behavior and physiology of domestic cats. *Applied Animal Behaviour Science* **143**, 157–163. https://doi.org/10.1016/j.applanim.2012.10.014 (2013).
7. Carlstead, K., Brown, J. L. & Strawn, W. Behavioral and physiological correlates of stress in laboratory cats. *Applied Animal Behaviour Science* **38**, 143–158. https://doi.org/10.1016/0168-1591(93)90062-t (1993).
8. Luescher, A. U. Diagnosis and management of compulsive disorders in dogs and cats. *Clinical Techniques in Small Animal Practice* **19**, 233–239. https://doi.org/10.1053/j.ctsap.2004.10.005 (2004).
9. Cameron, M. E., Casey, R. A., Bradshaw, J. W. S., Waran, N. K. & Gunn-Moore, D. A. A study of environmental and behavioural factors that may be associated with feline idiopathic cystitis. *Journal of Small Animal Practice* **45**, 144–147. https://doi.org/10.1111/j.1748-5827.2004.tb00216.x (2004).
10. Heath, S. E. in *The Welfare of Cats* (ed I. Rochlitz) Ch. Behaviour problems and welfare, 91–118 (Springer Netherlands, 2007).
11. Mariti, C. *et al.* The perception of cat stress by Italian owners. *Journal of Veterinary Behavior* **20**, 74–81. https://doi.org/10.1016/j.jveb.2017.04.002 (2017).
12. McCobb, E. C., Patronek, G. J., Marder, A., Dinnage, J. D. & Stone, M. S. Assessment of stress levels among cats in four animal shelters. *Journal of the American Veterinary Medical Association* **226**, 548–555. https://doi.org/10.2460/javma.2005.226.548 (2005).
13. Broom, D. M. The scientific assessment of animal welfare. *Applied Animal Behaviour Science* **20**, 5–19. https://doi.org/10.1016/0168-1591(88)90122-0 (1988).
14. Davenport, M. D., Tiefenbacher, S., Lutz, C. K., Novak, M. A. & Meyer, J. S. Analysis of endogenous cortisol concentrations in the hair of rhesus macaques. *General and Comparative Endocrinology* **147**, 255–261. https://doi.org/10.1016/j.ygcen.2006.01.005 (2006).
15. Meyer, J., Novak, M., Hamel, A. & Rosenberg, K. Extraction and Analysis of Cortisol from Human and Monkey Hair. *Journal of Visualized Experiments* https://doi.org/10.3791/50882 (2014).
16. Koren, L. *et al.* A novel method using hair for determining hormonal levels in wildlife. *Animal Behaviour* **63**, 403–406. https://doi.org/10.1006/anbe.2001.1907 (2002).
17. Cirimele, V., Kintz, P., Dumestre, V., Goullé, J. P. & Ludes, B. Identification of ten corticosteroids in human hair by liquid chromatography–ionspray mass spectrometry. *Forensic Science International* **107**, 381–388. https://doi.org/10.1016/S0379-0738(99)00180-2 (2000).
18. González-de-la-Vara, M. D. R. *et al.* Effects of adrenocorticotropic hormone challenge and age on hair cortisol concentrations in dairy cattle. *The Canadian Journal of Veterinary Research* **75**, 216–221 (2011).
19. Heimbürge, S., Kanitz, E. & Otten, W. The use of hair cortisol for the assessment of stress in animals. *General and Comparative Endocrinology* **270**, 10–17. https://doi.org/10.1016/j.ygcen.2018.09.016 (2019).
20. Russell, E., Koren, G., Rieder, M. & Van Uum, S. Hair cortisol as a biological marker of chronic stress: Current status, future directions and unanswered questions. *Psychoneuroendocrinology* **37**, 589–601. https://doi.org/10.1016/j.psyneuen.2011.09.009 (2012).
21. Yumi Yamanashi, M. T. Naruki Morimura, Satoshi Hirata, Juri Suzuki, Misato Hayashi, Kodzue Kinoshita, Miho Murayama, Gen'ichi Idani Analysis of hair cortisol levels in captive chimpanzees: Effect of various methods on cortisol stability and variability. *MethodsX* **3**, 110–117. https://doi.org/10.1016/j.mex.2016.01.004 (2016).
22. Macbeth, B. J., Cattet, M. R. L., Stenhouse, M. L., Gibeau, K. L. & Janz, D. M. Hair cortisol concentration as a noninvasivemeasure of long-term stress in free-ranginggrizzly bears (Ursusarctos): considerations withimplications for other wildlife. *Can. J. Zool.* **88**, 935–949 (2010).
23. Meyer, J. S. & Novak, M. A. Minireview: Hair Cortisol: A Novel Biomarker of Hypothalamic-Pituitary-Adrenocortical Activity. *Endocrinology* **153**, 4120–4127. https://doi.org/10.1210/en.2012-1226 (2012).
24. Carlitz, E. H. D. *et al.* Measuring Hair Cortisol Concentrations to Assess the Effect of Anthropogenic Impacts on Wild Chimpanzees (Pan troglodytes). *PLOS ONE* **11**, e0151870. https://doi.org/10.1371/journal.pone.0151870 (2016).
25. Cattet, M., Macbeth, B. J., Janz, D. M., Zedrosser, A., Swenson, J. E., Dumond, M., Stenhouse, G. B. . Quantifying long-term stress in brown bears with the hair cortisol concentration: a biomarker that may be confounded by rapid changes in response to capture and handling. *Conservation Physiology* **2**, https://doi.org/10.1093/conphys/cou026 (2014).
26. Ito, N. *et al.* Human hair follicles display a functional equivalent of the hypothalamic-pituitary-adrenal axis and synthesize cortisol. *The FASEB Journal* **19**, 1332–1334. https://doi.org/10.1096/fj.04-1968fje (2005).
27. Salaberger, T. *et al.* Influence of external factors on hair cortisol concentrations. *General and Comparative Endocrinology* **233**, 73–78. https://doi.org/10.1016/j.ygcen.2016.05.005 (2016).
28. Bennett, A. & Hayssen, V. Measuring cortisol in hair and saliva from dogs: coat color and pigment differences. *Domestic Animal Endocrinology* **39**, 171–180. https://doi.org/10.1016/j.domaniend.2010.04.003 (2010).
29. Burnett, T. A. *et al.* Short communication: Factors affecting hair cortisol concentrations in lactating dairy cows. *Journal of Dairy Science* **97**, 7685–7690. https://doi.org/10.3168/jds.2014-8444 (2014).
30. Roth, L. S. V., Faresjö, Å., Theodorsson, E. & Jensen, P. Hair cortisol varies with season and lifestyle and relates to human interactions in German shepherd dogs. *Scientific Reports* **6**, 19631. https://doi.org/10.1038/srep19631 (2016).
31. Bacci, M. L. *et al.* Hair cortisol determination in sows in two consecutive reproductive cycles. *Reproductive Biology* **14**, 218–223. https://doi.org/10.1016/j.repbio.2014.06.001 (2014).
32. Sharpley, C. F., Kauter, K. G. & McFarlane, J. R. An Investigation of Hair Cortisol Concentration Across Body Sites and within Hair Shaft. *Clinical Medicine Insights* **3**, 17–23 (2010).
33. Ryder, M. L. Seasonal changes in the coat of the cat. *Research in Veterinary Science* **21**, 280–283 (1976).
34. Baker, K. P. Hair growth and replacement in the cat. *British Veterinary Journal* **130**, 327–335. https://doi.org/10.1016/S0007-1935(17)35835-9 (1974).
35. Contreras, E. T., Vanderstichel, R., Hovenga, C. & Lappin, M. R. Evaluation of hair and nail cortisol concentrations and associations with behavioral, physical, and environmental indicators of chronic stress in cats. *Journal of Veterinary Internal Medicine* https://doi.org/10.1111/jvim.16283 (2021).
36. Wojtaś, J. Hair cortisol levels in cats with and without behavioural problems. *Journal of Feline Medicine and Surgery* **25**, 1098612X221150624, https://doi.org/10.1177/1098612X221150624 (2023).
37. Finkler, H. & Terkel, J. Cortisol levels and aggression in neutered and intact free-roaming female cats living in urban social groups. *Physiology & Behavior* **99**, 343–347. https://doi.org/10.1016/j.physbeh.2009.11.014 (2010).
38. Alekseeva, G. S., Loshchagina, J. A., Erofeeva, M. N. & Naidenko, S. V. Stressed by Maternity: Changes of Cortisol Level in Lactating Domestic Cats. *Animals* **10**, 903. https://doi.org/10.3390/ani10050903 (2020).

39. Arhant, C., Wogritsch, R. & Troxler, J. Assessment of behavior and physical condition of shelter cats as animal-based indicators of welfare. *Journal of Veterinary Behavior* **10**, 399–406. https://doi.org/10.1016/j.jveb.2015.03.006 (2015).
40. Carney, H. C. *et al.* 2016 AAFP Guidelines for the Management of Feline Hyperthyroidism. *Journal of Feline Medicine and Surgery* **18**, 400–416. https://doi.org/10.1177/1098612x16643252 (2016).
41. Greco, D. S. Diagnosis of Diabetes Mellitus in Cats and Dogs. *Veterinary Clinics of North America: Small Animal Practice* **31**, 845–853. https://doi.org/10.1016/S0195-5616(01)50002-9 (2001).
42. Vogelnest, L. J. Skin as a marker of general feline health: Cutaneous manifestations of systemic disease. *Journal of Feline Medicine and Surgery* **19**, 948–960. https://doi.org/10.1177/1098612X17723246 (2017).
43. Galuppi, R. *et al.* Cortisol levels in cats' hair in presence or absence of Microsporum canis infection. *Research in Veterinary Science* **95**, 1076–1080. https://doi.org/10.1016/j.rvsc.2013.07.023 (2013).
44. Accorsi, P. A. *et al.* Cortisol determination in hair and faeces from domestic cats and dogs. *General and Comparative Endocrinology* **155**, 398–402. https://doi.org/10.1016/j.ygcen.2007.07.002 (2008).
45. Percie Du Sert, N. *et al.* The ARRIVE guidelines 2.0: Updated guidelines for reporting animal research. *PLOS Biology* **18**, e3000410, https://doi.org/10.1371/journal.pbio.3000410 (2020).
46. I, R. *Feline welfare issues*. 3rd edn, 131–154 (Cambridge University Press, 2013).
47. Deborah L. Duffy, R. T. D. d. M., James A. Serpell. Development and evaluation of the Fe-BARQ: A new survey instrument for measuring behavior in domestic cats (Felis s. catus). *Behavioural Processes* **141**, 329–341, https://doi.org/10.1016/j.beproc.2017.02.010 (2017).
48. Heath, S. E. *91–118* (Springer, 2007).
49. Hendriks, W. H., Tarttelin, M. F. & Moughan, P. J. Seasonal Hair Growth in the Adult Domestic Cat (Felis catus). *Comparative Biochemistry and Physiology Part A: Physiology* **116**, 29–35. https://doi.org/10.1016/s0300-9629(96)00113-2 (1997).
50. RStudio: Integrated Development Environment for R (2022).
51. Minitab v. 19.2020.1 (2020).
52. Gow, R., Thomson, S., Rieder, M., Van Uum, S. & Koren, G. An assessment of cortisol analysis in hair and its clinical applications. *Forensic Science International* **196**, 32–37. https://doi.org/10.1016/j.forsciint.2009.12.040 (2010).
53. Terwissen, C. V., Mastromonaco, G. F. & Murray, D. L. Influence of adrenocorticotrophin hormone challenge and external factors (age, sex, and body region) on hair cortisol concentration in Canada lynx (Lynx canadensis). *General and Comparative Endocrinology* **194**, 162–167. https://doi.org/10.1016/j.ygcen.2013.09.010 (2013).
54. De Lange, M. S., Galac, S., Trip, M. R. J. & Kooistra, H. S. High Urinary Corticoid/Creatinine Ratios in Cats with Hyperthyroidism. *Journal of Veterinary Internal Medicine* **18**, 152–155. https://doi.org/10.1111/j.1939-1676.2004.tb00154.x (2004).
55. Henry, C. J., Clark, T. P., Young, D. W. & Spano, J. S. Urine Cortisol: Creatinine Ratio in Healthy and Sick Cats. *Journal of Veterinary Internal Medicine* **10**, 123–126. https://doi.org/10.1111/j.1939-1676.1996.tb02043.x (1996).
56. Quimby, J. M., Smith, M. L. & Lunn, K. F. Evaluation of the Effects of Hospital Visit Stress on Physiologic Parameters in the Cat. *Journal of Feline Medicine and Surgery* **13**, 733–737. https://doi.org/10.1016/j.jfms.2011.07.003 (2017).
57. Sundman, A.-S. *et al.* Long-term stress levels are synchronized in dogs and their owners. *Scientific Reports* **9**, https://doi.org/10.1038/s41598-019-43851-x (2019).
58. Packer, R. M. A. *et al.* What can we learn from the hair of the dog? Complex effects of endogenous and exogenous stressors on canine hair cortisol. *PLOS ONE* **14**, e0216000. https://doi.org/10.1371/journal.pone.0216000 (2019).
59. Lafferty, D. J. R., Laudenslager, M. L., Mowat, G., Heard, D. & Belant, J. L. Sex, Diet, and the Social Environment: Factors Influencing Hair Cortisol Concentration in Free-Ranging Black Bears (Ursus americanus). *PLOS ONE* **10**, e0141489. https://doi.org/10.1371/journal.pone.0141489 (2015).
60. Azevedo, A. *et al.* Age, sex and storage time influence hair cortisol levels in a wild mammal population. *PLOS ONE* **14**, e0221124. https://doi.org/10.1371/journal.pone.0221124 (2019).
61. Laudenslager, M. L., Jorgensen, M. J. & Fairbanks, L. A. Developmental patterns of hair cortisol in male and female nonhuman primates: Lower hair cortisol levels in vervet males emerge at puberty. *Psychoneuroendocrinology* **37**, 1736–1739. https://doi.org/10.1016/j.psyneuen.2012.03.015 (2012).
62. Braun, U. C., G ; Baumgartner, M R ; Riond, Barbara ; Binz, T M. Hair cortisol concentration and adrenal gland weight in healthy and ill cows. *Schweizer Archiv für Tierheilkunde* **159**, 493–495, https://doi.org/10.17236/sat00128 (2017).
63. Fusi, J. *et al.* How Stressful Is Maternity? Study about Cortisol and Dehydroepiandrosterone-Sulfate Coat and Claws Concentrations in Female Dogs from Mating to 60 Days Post-Partum. *Animals* **11**, 1632. https://doi.org/10.3390/ani11061632 (2021).
64. Griffin, B. Profilic Cats: The Estrous Cycle. *Compendium* **23**, 1049–1057 (2001).
65. Franchini, M. *et al.* Cortisol in hair: a comparison between wild and feral cats in the north-eastern Alps. *European Journal of Wildlife Research* **65**, https://doi.org/10.1007/s10344-019-1330-2 (2019).
66. Miller, G. E., Chen, E. & Zhou, E. S. If it goes up, must it come down? Chronic stress and the hypothalamic-pituitary-adrenocortical axis in humans. *Psychological bulletin* **133**, 25 (2007).
67. Stella, J. & Croney, C. Coping styles in the domestic cat (Felis silvestris catus) and implications for cat welfare. *Animals* **9**, 370 (2019).
68. McCune, S. The impact of paternity and early socialisation on the development of cats' behaviour to people and novel objects. *Applied Animal Behaviour Science* **45**, 109–124. https://doi.org/10.1016/0168-1591(95)00603-P (1995).
69. Elzerman, A. L., Deporter, T. L., Beck, A. & Collin, J.-F. Conflict and affiliative behavior frequency between cats in multi-cat households: a survey-based study. *Journal of Feline Medicine and Surgery* **22**, 705–717. https://doi.org/10.1177/1098612x19877988 (2020).

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Author contributions

The sampling was performed by NRZ, EJ, FJB, and SS. Data collection and laboratory analyses were performed by NRZ, EJ, and FJB. NRZ analyzed the data and wrote the main manuscript, in collaboration with HR, MÖ, CM, and BSH. All authors reviewed the manuscript.

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Competing interests
The authors declare no competing interests.

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Diabetes mellitus is a common endocrine disease in cats. Treatment may offer a favourable prognosis, but disease management often encompass challenges and a proportion of cats is euthanised at diagnosis. This thesis investigated disease outcomes, owner and veterinarian experiences of disease management and the use of hair cortisol measurement in assessment of the chronically ill cat, providing new insights into the clinical, emotional and ethical dimensions of DM management in cats.

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