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Prevalence of feline hyperthyroidism in Hungary and factors associated with the incidence of the disease

Thesis by

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1. Introduction

It has become evident in small animal veterinary practices that there is an increasing incidence of feline hyperthyroidism (FHT). In fact, a large proportion of small animal veterinarians may say that hyperthyroid cats are a fairly common occurrence in their practices. It was stated in an article by Carney *et al*. (2016), that "initially, FHT was a disease that only referral clinicians treated. Now it is a disease that primary clinicians routinely manage." There has been a significant increase in the prevalence of the disease since the 1970s. It is unclear, however, whether this is specifically due to an increase in the number of cases or because there is a greater awareness of the disease amongst veterinarians. Alternatively, it could be related to an increased lifespan of our pets or the ever-improving diagnostics that modern day medicine can provide (Scarlett *et al.,* 1988). It is now thought to be the most common endocrine disease of older felines (Edinboro *et al.,* 2010; Léga *et al.,* 2013; McLean *et al*. 2014; Taylor, 2017, Poutasse *et al.,* 2019) which may be why we are seeing it more often due to the increasing life spans of our cats.

Hyperthyroidism is due to an increased production of thyroid hormones, T_3 (Triiodothyronine) and T_4 (Thyroxine), from one or both lobes of the thyroid gland which may be enlarged due to hyperplasia, a benign tumour, or rarely, a malignant tumour (Kornreich, 2017). It is stated on the UC Davis School of Veterinary Medicine website (2018) that greater than 80% of hyperthyroid cats have hyperplasia, 15% have a benign tumour (adenoma) and roughly 2-3% have a malignant carcinoma. An elevation in the levels of circulating T_3 and T_4 results in further clinical manifestations such as kidney and heart disease because of an increase in basal metabolic rate (Léga *et al.,* 2013).

There have been many studies over the past 40 years focusing on the potential causes of the rising incidence of FHT across the world. Some reason it to be related to chemicals in the home such as sprays, flame retardants or anti-flea treatments; others believe the major cause to be iodine levels in manufactured cat food or the flavour/type of food fed to cats. Perhaps genetics and sex play an important role or even neuter status. There appear to be a huge variety of risk factors that are thought to be potential causative agents of the disease but none of them are officially confirmed and perhaps that could be because it is due to a combination of many factors.

2. Review of Literature

As mentioned in the introduction, FHT has only really come to our attention since the 1970s, with the first officially diagnosed cases in the literature in 1979 (Peterson *et al.,* 1979). Carney *et al*., (2016) detailed that it was believed to be a 'new' disease as opposed to a previously undiagnosed one, due to the lack of pathological cases of thyroid adenomas in studies over the previous decade. Whether it was a new disease at that time or not, the number of studies relating to FHT dramatically rose since its exposure in the 1970s.

2.1. Aetiology of hyperthyroidism

The aetiology of FHT is not known but there are several factors that the literature suggests could be possible causes of the disease. It is believed that a combination of these factors, rather than just one alone, is likely to be associated with the incidence of FHT (Edinboro *et al*., 2004 & McLean *et al.,* 2014). However, these suggested risk factors could just be coincidental findings and not have a causal relationship or, alternatively, they could be related to the changes that have occurred with cat husbandry since the 1970s. Potential causal risk factors stated in the literature are as follows.

2.1.1. Breed

It is believed that genetics and breed predisposition have a significant relationship with the incidence of FHT. Edinboro *et al.* (2010) compared the results from four case control studies from the US and three others from Hong Kong, New Zealand and the UK, between the years 1982 and 2007. The seven studies looked at a number of risk factors such as breed, age, food consumed, lifestyle and environment. Edinboro *et al.* (2010) summarised their findings. The results of the breed-related risk factors for these studies can be seen in *Table 1*.

Study Location	Year	Reported breed-related risk factor
New York State College of Veterinary Medicine, USA	1982-85	Non-Siamese breed
University of California, Davis and Animal Medical Centre, New York, USA	1986	Non-Siamese or Non-Himalayan breeds
Seattle, WA, USA	1996-97	No significant data
New Zealand	1996-98	Domestic Shorthair
Purdue University, IN, USA	1998-2000	No significant data
Hong Kong	2006-07	Non-Domestic Shorthair breed
United Kingdom	2006-07	Non-purebred

Table 1. Relationship between breed and risk of FHT from seven case-controlled studies (Edinboro *et al*, 2010).

The study done by Scarlett *et al.* in 1988 stated that "non-Siamese cats were ~10 times more likely to develop FHT than Siamese". This statement was supported by Edinboro *et al.* (2004) who found in their study that mixed breed cats were three times more likely to have FHT than pure-bred cats, such as Siamese. Conversely, Martin *et al.* (2000) noticed this finding by Scarlett *et al.* (1988) and in their own study found that there was not a significant association between breed and the incidence of FHT. They did, however, note that the risks for purebred cats, such as Siamese, was reduced. A more recent study conducted by Stephens *et al.* (2014) produced similar data to those by Scarlett *et al.* (1988) and Edinboro *et al.* (2004). They stated that "Burmese, Persian, Siamese and purebred cats overall has lower odds of FHT than non-purebred cats".

Conversely to other studies, Domestic Shorthair (DSH) breeds were the least likely to have FHT in a study by De Wet *et al.* (2009). However, there were only 12 cats diagnosed with FHT in this study, 4 of 181 (2%) DSH cats compared to 3 hyperthyroid Persian cats of 49 in total (6%). De Wet *et al*. (2009) also stated that many of their DSH cats in Hong Kong were of "oriental descent and this could explain the possible contribution of a genetic protective factor".

It does appear to be evident from the literature that breed/genetics could play a significant role in the incidence of FHT. It could be that there is a significantly reduced risk

to purebred cats, alternatively it could be that fewer purebred cats were owned by those partaking in the questionnaires used in some of the studies and so the ratio of purebreds to other breeds was not equal and skewed the results slightly. The decreased number of purebred cats included in most of these studies and often the small sample size, does not allow for reliable statistical analysis, therefore the results of breed predisposition of these studies could be unreliable.

2.1.2. Age

Age may also play an important role in the incidence of FHT. Perhaps the incidence of FHT is related to the increased life span of our felines (Gerber *et al.,* 1994) due to better and more modern veterinary care. In the study by Edinboro *et al.* (2010), five of the seven case control studies confirmed that increasing age was a reported risk factor of FHT. The study also mentioned that often cats above 6 years of age are diagnosed with the disease. In a study by Olczak *et al.* (2005), it was reported that 81% of the hyperthyroid cats in their study were older than 12 years and only 3% were younger than 9. Edinboro *et al.* (2004) discovered in their study that with every year added to a cat's life, the relative risk of FHT increased by 21%. Interestingly, a study conducted in Ireland found that increasing age was the only significant risk factor for FHT despite also investigating lifestyle, environment, feed etc. (Bree *et al.*, 2018).

None of the previous studies have found that young age and FHT are associated, therefore it could be that increasing age is a determinant of FHT in cat populations. Perhaps above a certain age, all cats should be given the opportunity to have a geriatric blood test to exclude FHT before the symptoms become too severe.

2.1.3. Sex

Many studies have looked into the relationship between sex and the incidence of hyperthyroidism in cats. It appears so far that all studies investigating the relationship between sex and FHT have found that the incidence of FHT is greater in females than males or that sex has no significant relationship with hyperthyroidism. Edinboro *et al.* (2004) found in their study that "the relative risk of hyperthyroidism for female cats was twice that for male cats". Similarly, Olczak *et al.* (2005) stated that "females were 3.3 times more likely to be diagnosed than were males" and they also discovered that cats with hyperthyroidism were more likely to be female when compared to the cats from the control group who do not have the disease.

2.1.4. Neuter status

The neuter status of cats has also been investigated in previous studies. Kass *et al.* (1999), Gójska-Zygner *et al.* (2014) and Stephens *et al.* (2014) did not find a significant relationship between FHT and neuter status. Stephens *et al.* (2014) noted that neuter status was not often investigated due to a lack of non-neutered cats available in previous studies to do a proper investigation. In some studies, there have been sample sizes too small to gather reliable results and often only neutered cats in these studies had FHT, making it impossible to reliably investigate the relationship between FHT and neuter status.

In a study by Skinner (1998) looking at the relationship between sex and healthy thyroid hormone levels, it was noted that neuter state could be an influencing factor in their study, however, they did not include entire females and castrated males, so they were unable to confirm this.

2.1.5. Food

The relationship between the incidence of FHT and the consumption of canned cat food or, more specifically, cat food with inappropriate iodine levels is another topic of interest. The concentration of iodine in commercial cat foods vary widely. Between the 1960s and 2010 the recommended iodine concentration of commercial cat food was constantly being altered by the National Research Council (NRC). In the 1970's, for example, the iodine content of food was revised resulting in lower iodine levels in food (Edinboro *et al.*, 2010). Several previous studies looked at the effects of varying levels of iodine in the diets of cats on the circulating levels of thyroxine in the blood. At the end of these studies, a hypothesis was created suggesting that long term variation of iodine levels in the diets of cats could contribute to the development of FHT due to the cat's inability to adapt efficiently to these changing levels of iodine (Tarttelin *et al.*, 1992; Kyle *et al*. 1994; Tarttelin and Ford, 1994). The thyroid gland adapts to reduced iodine levels by trapping iodide and metabolizing iodine which aids the synthesis and secretion of T_3. Overworking the gland to produce thyroid hormones can ultimately result in the formation of a goitre, also known as hypertrophy and nodular hyperplasia of the thyroid gland, a symptom of FHT (Delange, 1994 & Edinboro *et al.* 2010).

There is a huge quantity of commercial cat food available on the market that vary based on their target animal, raw or cooked, wet or dry, canned or bagged. A number of studies have looked into the relationship between the type of cat food consumed and the

incidence of FHT. Scarlett *et al.* (1988) reported that with more canned food in the cat's diet there was a greater the risk of FHT. This was supported by a study done in 2005 by Olczak *et al.* where cats with hyperthyroidism were compared with those unaffected (control) and they concluded that "hyperthyroid cats were twice as likely to have eaten at least half of their daily food requirements as canned commercial cat food compared with unaffected cats". They also noted that consumption of a variety of flavours of canned food meant that cats were more likely to be diagnosed with hyperthyroidism. Similarly, Martin *et al.* (2000) discovered in their study that certain flavours of canned food, specifically fish, liver and giblets, resulted in cats having a greater risk of developing hyperthyroidism.

The relationship between consumption of canned food and FHT is believed to likely be due to bisphenol A (BPA). BPA is an ingredient in the lining of cans used to maintain the quality of the contents. It is an endocrine disruptor and goitrogen that is proven to affect thyroid gland function. It is believed to cause damage due to it having a similar structure to T_3 and T_4 therefore working as a receptor antagonist (Peterson, 2012).

Conversely, a study done in Hong Kong, which looked at the prevalence of FHT and the risk factors involved, found no notable relationship between the type of food consumed and the incidence of FHT (De Wet *et al.*, 2009).

2.1.6. Environment

Finally, several studies have looked into the effects of the cat's environment, including chemicals used in the home and directly on the cat, to see if it has a relationship with the incidence of FHT. Indoor cats or predominantly indoor cats are exposed to a number of household chemicals such as phenols or halogenated hydrocarbons. These chemicals can be found in cat litter for example (Carney *et al.* 2016), therefore, indoor cats who use a litter tray multiple times per day are believed to be at greater risk of developing FHT than cats that are allowed outdoors and therefore do not require a litter tray. Scarlett *et al.* (1988) support this as they found that indoor cats, who therefore use a litter tray, were at a greater risk of developing FHT when compared to cats that spend greater than three quarters of their time outside. This can also be maintained through the research conducted by Kass *et al.* (1999). Their results suggested that cats using litter had an increased risk of developing FHT compared to those who do not.

An example of a chemical used directly on the cats is ectoparasite treatment. The use of anti-flea and fly sprays have also been evaluated and found to considerably increase the

risk of FHT (Olczak *et al*., 2005). Conversely to Olczak *et al.*, there was no correlation between indoor living or the use of ectoparasite treatment and FHT in a study conducted in South Africa (McLean *et al.*, 2016).

Polybrominated diphenyl ethers (PBDEs) are another artificial substance used in the home that might be goitrogens or perhaps direct mitogens (Carney *et al.*, 2016). They were used as fire retardants and were commonly found in/on household objects prior to the restrictions put into place in 2003 by several new EU directives such as Directive 2003/11/EC (European Food Safety Authority, 2019). PBDEs are thyroid disruptors/goitrogens, perhaps also due to their similar structure to thyroid hormones and are proven to accumulate in the environment and food chain (Peterson, 2012). It was because of this that the restrictions were put into place in order to reduce the negative effects of these substances on both humans and animals. Olczak *et al*. (2005) found that "hyperthyroid cats were 6.6 times more likely to be reported to sleep predominantly on the floor than control cats", perhaps the increased incidence of FHT was related to the levels of PBDEs or other flame retardants on the carpet/flooring. Although there is no specific data to prove that PBDEs are directly related to the incidence of hyperthyroidism, the data suggesting that indoor cats are at greater risk of FHT could be related to the presence of PBDEs and/or other chemicals in the environment.

A more recent study that looked at the relationship between flame retardants and FHT supports the idea that there is an association between the two. Silicone pet tags were attached to the cat's collars to assess their exposure to a number of different household flame retardants. Tris (1,3-dichloro-2-isopropyl) phosphate (TDCIPP) was found to be on the tags of hyperthyroid cats in greater concentration than unaffected cats. This was believed to be associated with the use of air freshener, buildings built since 2005 when compared to those built before 1989 and cats with a preference to sleep on upholstered furniture. (Poutasse *et al.*, 2019).

2.2. Diagnosis of hyperthyroidism

Hyperthyroidism can be diagnosed using a combination of several different methods. A general clinical exam can raise suspicion of the disease and then blood sampling or use of scintigraphy to visualise an overactive thyroid gland can be used to diagnose the disease.

A hyperthyroid cat entering the consulting room could present with one or some of the following clinical signs: weight loss and reduced muscle mass, increased activity, unkempt hair coat, vomiting and diarrhoea, polyphagia, polydipsia, polyuria, palpable mass in the thyroid region of the neck (goitre), retinopathies, heart murmurs or arrhythmias and hypertension (Jones, 2004; Carney *et al.*, 2016; UC Davis School of Veterinary Medicine, 2018). Although some of these clinical signs are often indicators of hyperthyroidism, none of them are pathognomonic and it can sometimes be subclinical. If a cat presents with any of these clinical signs and they are middle to old age, FHT could be a differential diagnosis and the next step would be to take a blood sample and do a complete blood count, T_4 assay and serum chemistry. In addition to this, urinalysis could be beneficial to rule out any underlying kidney diseases (Taylor, 2017). Reference ranges of normal blood T_4 levels vary based on the lab.

Unfortunately, it is often difficult to come to a definitive diagnosis due to the presence of other comorbidities which are more likely to occur in an older cat, an example of one of these comorbidities is kidney disease (Pap & Cristina, 2017). Some cases are easy to diagnose, and others are much trickier due to a lack of clinical signs, complications from another disease or inconclusive lab results. When faced with an inconclusive result, it is often difficult to make the decision to do further tests as it is dependent on the welfare on the animal as well as the finances of the owner (Taylor, 2017). The AAFP feline hyperthyroidism guidelines (2016) outlined six different groups, based on case presentations, in order to aid diagnosis of hyperthyroidism. *Figure 1* is a diagram from the AAFP guidelines that summarises their methods of diagnosis (Carney *et al.*, 2016).

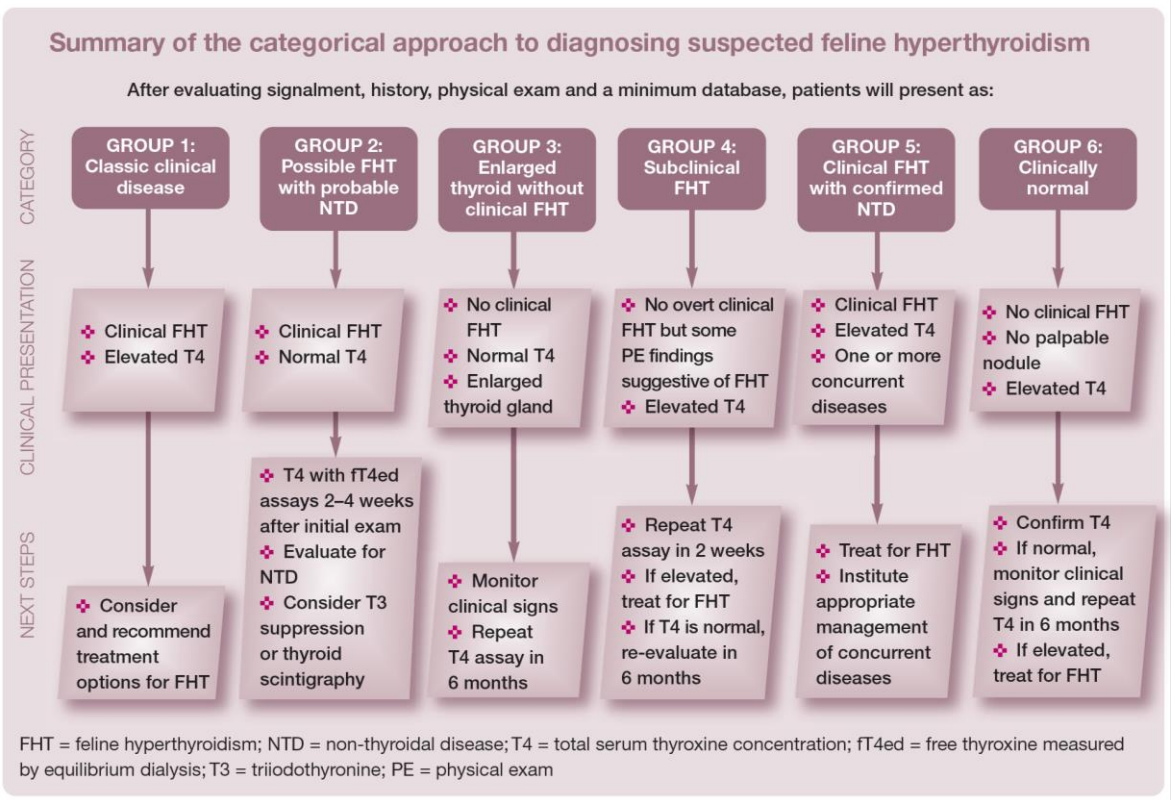

Figure 1. Summary of diagnosing suspected FHT from the AAFP guidelines (Carney *et al.*, 2016).

Often the symptoms of FHT go unnoticed by owners for some time. As hyperthyroidism commonly occurs in older cats, the clinical signs of weight loss, an unkempt hair coat and a change in behaviour can often be attributed to their increasing age rather than that they are in fact ill. In a report from the journal 'Veterinary Record', reviewing the discussions and presentations about FHT at a symposium in Barcelona in 2012, it stated that "cats could lose 10% of their body weight without owners noticing", highlighting how easy it could be for cats to be undiagnosed or diagnosed too late (No authors listed, 2012).

Alternatively, at a general check-up or routine vaccination, owners may mention that that their cats are healthier than they were previously because their appetite has increased, they are more active and have also lost a little excess weight, but, as previously mentioned, these could all be clinical signs of the disease. Perhaps this proves that as cats age, they should go for more regular check-ups and have geriatric screening panels containing T_4, in order to diagnose and treat FHT as soon as possible.

2.3. Consequences of hyperthyroidism

The increased level of circulating thyroid hormones in the body can affect the metabolic function of many other organs therefore leading to several secondary complications (Kornreich, 2017). A document by Mooney (2003) summarises the complications and consequences of FHT discussed in the literature. Some of her findings are as follows. FHT can have an impact on routine clinicopathological analyses. An example of this is the increased levels of liver enzymes (ALT, ALKP), which could result in misdiagnosis of liver abnormalities even though studies have found little to no changes in the liver. FHT can also affect the kidneys resulting in an increase in glomerular filtration rate and decreased serum creatinine concentration, for example. Sometimes, more seriously, it can completely disguise a cats underlying kidney disease. Finally, FHT can have a severe effect on the cardiovascular system. Clinical signs of tachycardia, murmurs, arrhythmias and cardiomegaly are common. Hyperthyroid cats can become hypertensive resulting in abnormalities of the eyes such as retinal detachment and sudden loss of vision. It is not clear what the cause of this hypertension is but it is thought to be related to increased beta adrenergic activity (Mooney, 2003). If left untreated, FHT can result in heart failure and even death of the animal (UC Davis School of Veterinary Medicine, 2018).

3. Own Investigation

3.1. Aim of the study

This study aims to look at the prevalence of FHT and aspects that are associated with the incidence of hyperthyroidism in cats at the University of Veterinary Medicine in Budapest, Hungary. Data such as the age, breed, sex and weight of the cats will be assessed to see whether there are certain factors that are significant in relation to the incidence of this disease.

Previous studies have suggested trends in the data (covered in the literature review) therefore the following hypotheses were tested:

1) The incidence of FHT is greater in females than males.
2) The different incidences of FHT between the two sexes is changing over time.
3) The incidence of FHT increases with time.
4) The incidence of FHT increases with age.
5) The incidence of FHT is greater in cats with a low body weight.
6) The incidence of FHT is greater in non-purebred cats.

3.2. Material and methods

Data was collected using the Doki For Vets^{TM} database at the University of Veterinary Medicine, Small Animal Clinic in Budapest, Hungary. Data of all cats that visited the university clinic between 2008 and 2018 were assessed. Those cats with a diagnosis of FHT on the database were investigated further to ensure that the diagnosis was correctly entered into the database. Methods to confirm the hyperthyroid diagnosis are as follows:

1) Blood T_4 levels were above the reference ranges.
    a. Over the 10 year period, different labs were used by the university to test T_4 levels of the blood therefore there were different reference ranges to take into account.
    b. Also, some cats arrived with an already confirmed FHT diagnosis based on previous examinations. T_4 levels were accepted when measured in well-known veterinary laboratories in Hungary, but these, of course, also had different reference ranges.

2) The cat was being treated with a brand of methimazole such as Felimazole®
    a. Methimazole is a drug used to prevent the thyroid gland from overproducing thyroid hormones. Treatment with this drug can cause the blood T_4 values to be within the reference range or only slightly high. If a cat was seen to be treated with this drug in their history, and still had elevated levels of thyroxine, it was concluded that they were hyperthyroid and so included in the study.
3) Veterinarian's notes discussed their clinical signs, treatment schedule and detailed information about further blood tests to ensure that the T_4 levels remained stable.
    a. Some potential candidates did not have very high T_4 levels, however, this was most likely because they were already diagnosed previously with FHT and their T_4 levels had been normalised through provision of Methimazole. In these cases, the vet's notes were used to confirm the diagnosis and include the animal in the study.
    b. Information provided in the history in order to aid diagnosis included presence of a goitre, tachycardia, polyphagia, polydipsia, polyuria, weight loss.
4) The cat had surgical removal of the thyroid gland.
    a. A thyroidectomy can be a cure for FHT and is sometimes used to treat hyperthyroid cats. If there were no T_4 values but it was described in the history that the cat had a thyroidectomy then it was confirmation that they had FHT and so they were included in the study.
5) The cat was treated with radioactive iodine.
    a. Radioactive iodine is usually a curative method of treatment for hyperthyroid cats. Therefore, a history of radioactive iodine treatment, despite there being no blood T_4 values, was used as confirmation of FHT, allowing that animal to be included in the study.

Based on the above criteria, 50 cats over the 10-year period had a confirmed hyperthyroidism diagnosis. Further information of each hyperthyroid cat was gathered from the database, including breed, sex, date of birth, date when diagnosed, body weight, body condition score (BCS), living conditions and finally additional information such as diet and other health issues that could be obtained from the veterinarians' notes. The age (in years)

when diagnosed was also calculated by subtracting the date of birth from the date of diagnosis.

The total number of cats that attended the clinic over the 10-year period was also gathered. The sex of all cats without FHT that came to the clinic between 2008 and 2018 was also obtained to create a control group. This number totalled 35,165; 12,061 males and 23,104 females.

3.3. Statistical analysis

A binomial logistic regression was used to analyse the change in the incidence rate of FHT between 2008 and 2018. The dependent variable was the relative frequency, the independent variables were the year, the sex and their interaction.

Fisher's exact test was also used to determine if there were non-random associations between two categorical variables. The variables tested were the sex and the incidence of hyperthyroidism as well as the year diagnosed and the incidence of FHT. The R statistical program was used to conduct this test (R Core Team, 2019).

The data collected of hyperthyroid cats was also analysed to find the mean and median values for age and body weight using Microsoft™ Excel. Finally, the prevalence of FHT in this study (as a representative of Budapest, Hungary) was also calculated using Microsoft™ Excel in the following way: total number of hyperthyroid cats from 2008-2018/total number of cats that came to the clinic from 2008-2018 x 100.

3.4. Results

The results of the binomial logistic regression can be seen below (*Tables 2 & 3).*

Year	Total number of cats	Hyperthyroid cats	Frequency	Prediction
2008	1494	3	2.0080321	1.3865632
2009	1222	1	0.8183306	1.5380051
2010	1076	0	0.0000000	1.7059594
2011	941	4	4.2507970	1.8922200
2012	1055	0	0.0000000	2.0987742
2013	1075	2	1.8604651	2.3278232
2014	1122	6	5.3475936	2.5818047
2015	1089	3	2.7548209	2.8634178
2016	1075	4	3.7209302	3.1756504
2017	964	4	4.1493776	3.5218091
2018	977	2	2.0470829	3.9055527

Table 2. Original model of binomial logistic regression for male cats.

Year	Total number of cats	Hyperthyroid cats	Frequency	Prediction
2008	4428	1	0.2258356	0.1498988
2009	3567	1	0.2803476	0.2141927
2010	3192	1	0.3132832	0.3060547
2011	2867	1	0.3487967	0.4372970
2012	3022	1	0.3309067	0.6247833
2013	936	2	2.1367521	0.8925805
2014	1176	2	1.7006803	1.2750156
2015	1027	0	0.0000000	1.8210104
2016	1042	3	2.8790787	2.6002054
2017	891	2	2.2446689	3.7115717
2018	977	7	7.1647902	5.2954306

Table 3. Original model of binomial logistic regression for female cats.

The raw data above can be visualised better in *Figure 2* below.

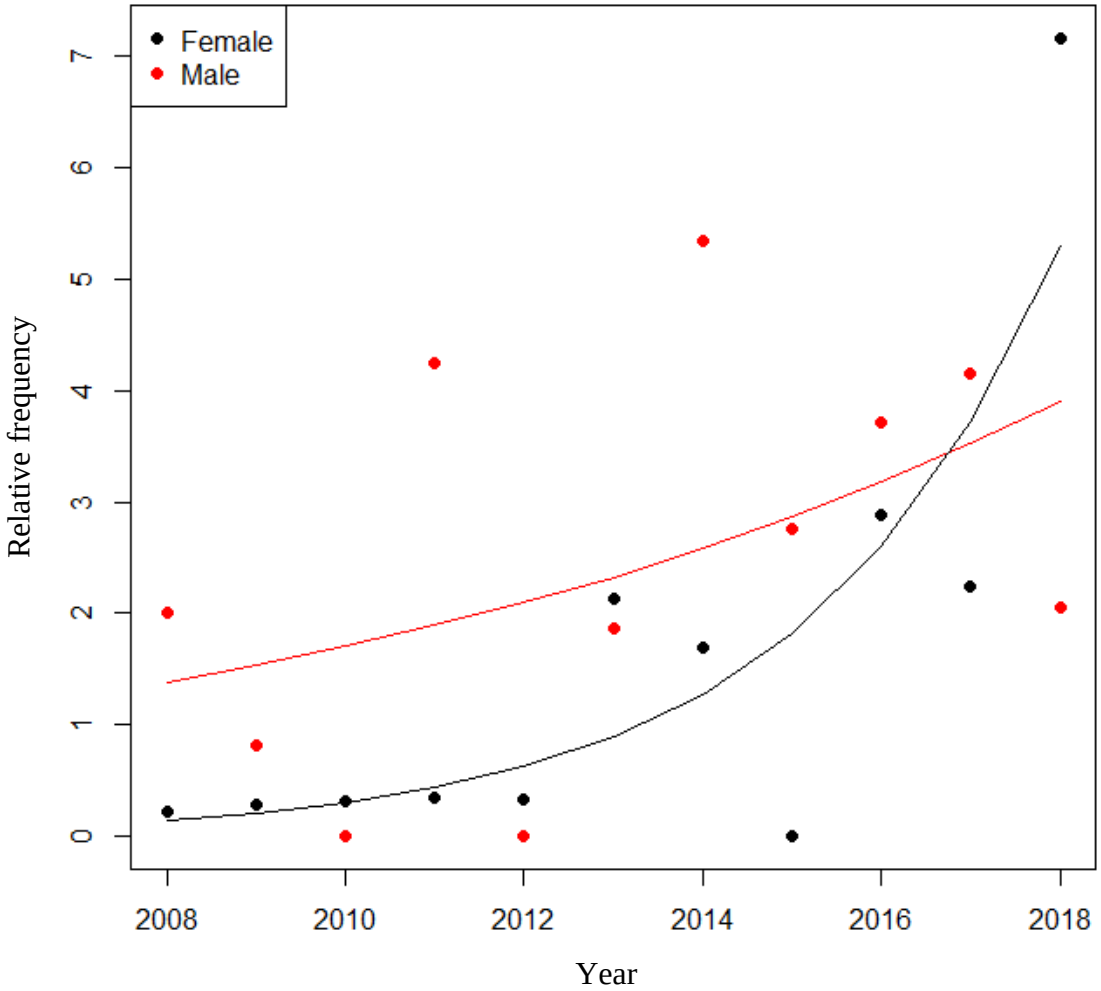

Figure 2. Binomial logistic regression for male and female hyperthyroid cats (model 1).

There was a significant difference (p=0.007) between the yearly average increase rate of FHT for male and female cats. Therefore, the incidence of females with FHT is growing while the incidence of males with FHT is not. Using a contrast matrix the odds ratio for males and females were expressed as follows: time effect for females: OR=1.4290, 95% confidence interval=(1.2142, 1.6818), p<0.0001; time effect for males: OR=1.1094, 95% confidence interval=(0.9718, 1.2664), p=0.153.

Despite this significant result, it appears that the female value for 2018 is an outlier and, as it is at the end of the period, it is an influential point. Therefore, a sensitivity analysis was conducted, removing both the female and male values for 2018. The results of the second model are as follows (*Tables 4 & 5).* It could also be argued that the value of 2014

for male cats is also an outlier but perhaps it is less influential as it is not at the end of the period.

Year	Total number of cats	Hyperthyroid cats	Frequency	Prediction
2008	1494	3	2.0080321	0.8870300
2009	1222	1	0.8183306	1.0804769
2010	1076	0	0.0000000	1.3160559
2011	941	4	4.2507970	1.6029163
2012	1055	0	0.0000000	1.9521813
2013	1075	2	1.8604651	2.3773677
2014	1122	6	5.3475936	2.8948914
2015	1089	3	2.7548209	3.5246755
2016	1075	4	3.7209302	4.2908798
2017	964	4	4.1493776	5.2227707

Table 4. Second model for binomial logistic regression for male cats.

Year	Total number of cats	Hyperthyroid cats	Frequency	Prediction
2008	4428	1	0.2258356	0.3033552
2009	3567	1	0.2803476	0.3695591
2010	3192	1	0.3132832	0.4502049
2011	2867	1	0.3487967	0.5484395
2012	3022	1	0.3309067	0.6680947
2013	936	2	2.1367521	0.8138342
2014	1176	2	1.7006803	0.9913341
2015	1027	0	0.0000000	1.2075006
2016	1042	3	2.8790787	1.4707340
2017	891	2	2.2446689	1.7912491

Table 5. Second model for binomial logistic regression for female cats.

The raw data above can be visualised better in *Figure 3* below.

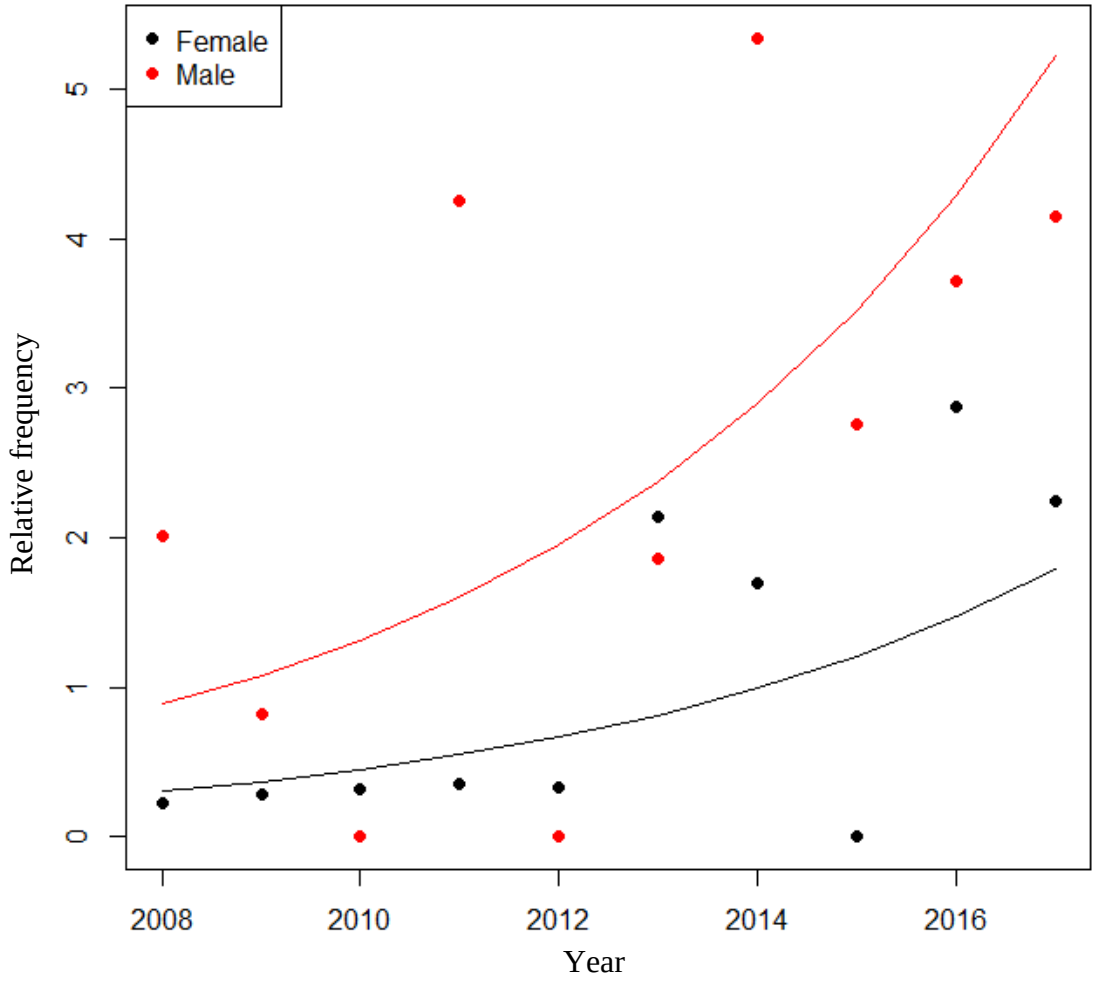

Figure 3. Binomial logistic regression for male and female hyperthyroid cats (model 2).

There is no significant interaction between year and gender (p=0.21) therefore, there is no difference between the yearly average increase rate of FHT for male and female cats. After removing this interaction between year and gender, it results in there being a significant increase in time and a significant difference between genders (Time effect: OR=1.2183, 95% confidence interval=(1.0924, 1.3647), p=0.0005; Male effect: OR=2.9258, 95% confidence interval=(1.531, 5.8344), p=0.0015). This therefore means that there is an increase in the incidence of FHT in time, which is the same for both genders, but males are at a higher risk than females.

The results of the Fisher's exact test are as follows: OR=0.378, 95% confidence interval=(0.2048, 0.6866), p=0.0008, which was obtained from the data in *Table 6*. Statistically the data does prove dependence of sex and the incidence of FHT.

	Control	Hyperthyroid cats	Frequency (%)
Male	12061	29	0.24
Female	23104	21	0.09

Table 6. Frequency of male and female hyperthyroid cats in the total population.

The mean age (years) of cats with FHT was 13.5 and the median was 13.2 (*Table 7*).

Age (years)	Number of cats
<7	0
7-14	37
>14	13
Total	50

Table 7. Age of hyperthyroid cats.

The mean weight (kg) of cats with FHT was 3.7 and the median was 4 (*Table 8*).

Weight (kg)	Number of cats
<3.5	14
3.5-4.5	20
>4.5	10
No data	6
Total:	50

Table 8. Weight of hyperthyroid cats.

The below table (*Table 9*) shows the frequency of hyperthyroid cases according to the year group. The greatest frequency of diagnoses was between 2016 and 2018 (Fishers test: p=0.0000019).

Year diagnosed	Control	Hyperthyroid cats	Frequency (%)
2008-2011	19008	12	0.06
2012-2015	10561	16	0.15
2016-2018	5972	22	0.37

Table 9. Frequency of hyperthyroid cases according to the year group they were diagnosed.

Of the 50 diagnosed hyperthyroid cats, 5 were not European Shorthair breed. The five cats were the following breeds: Persian, British Shorthair, Ragdoll and two Siamese.

Finally, the prevalence of FHT in Budapest, Hungary was: 0.14% rounded to two decimal places.

4. Discussion

4.1. Incidence

There was a significant increase in the incidence of FHT over the 10-year period in both sexes (p=0.0005). This also coincides with the fact that a greater number of cats were diagnosed in the final 2 years of this study when compared to the previous 8 years (p=0.0000019). The increased incidence of the disease could be due to several factors. It could be that there has been a genuine increase in the number of hyperthyroid cases, alternatively it could be due to an increased awareness of the disease and therefore a greater number of cats being diagnosed. Perhaps the method of diagnosis has also improved and therefore fewer cats are receiving a misdiagnosis.

The increase in the incidence of the disease could be related to environmental factors such as feed and environmental goitrogens, as discussed in the literature review. However, it was not possible to investigate whether these environmental factors were important in this study due to a lack of information provided in the animal's history. Ideally, if this study were to be conducted again, a questionnaire would be sent out to all hyperthyroid cat owners in order to gain further background information and to look at other factors affecting the incidence of FHT.

The following hypotheses: "the different incidences of FHT between the two sexes is changing over time" and "the incidence of FHT increases with time", outlined in the aims, have been supported by this study. However, it must be emphasized that this is only true for this relatively small sample of cats with FHT and could differ if the sample size were increased.

4.2. Sex

One of the hypotheses tested in this study was that the incidence of FHT was greater in female cats than male cats. The results, however, have shown that the risk was greater in male rather than female cats (p=0.0015). This result is the opposite of that stated in previous studies which have either found that the incidence of FHT is greater in females than males (Edinboro *et al.,* 2004; Olczak *et al.,* 2005) or that there is no significant relationship between sex and the incidence of FHT (Gójska-Zygner *et al.,* 2014; Bree *et al.,* 2018). This study did prove a dependence of sex and FHT (p=0.0008), but perhaps the variation in the results of

previous studies, or the small sample size does not definitively prove this dependence. If the sample size were to be increased, possibly there would be a different result.

A study by Skinner (1998) measured the thyroid hormone levels of healthy cats to see if there was a relationship between sex and the levels of T_4. Skinner discovered that sex was found to have a significant effect on thyroid hormone levels and that male cats had higher thyroid levels compared to female. It is not specifically known why this is, but it could, perhaps, be indicative of why the incidence of FHT in male cats was higher than females in this study.

Johnson (1994) also mentioned that the thyroid gland is suppressed by glucocorticoids. Perhaps female cats attending the clinic had higher production of glucocorticoids due to stress than male cats. This could influence the results of the blood test, therefore fewer female cats were diagnosed with FHT because of false negatives. Multiple studies have looked at the differences in corticosterone levels of male and female rodents to find that female rodents secrete greater amounts of corticosterone than male in response to stressors (Rincón-Cortés *et al.* 2019). A similar thing could occur in cats and therefore support the idea that the T_4 levels of female cats were affected by stress and glucocorticoid levels. This stress-related problem also occurs with the diagnosis/monitoring of glucose levels in diabetic animals. Therefore, a method of interstitial glucose monitoring, whilst the animal is at home, with no stress influences is used. The device is called "FreeStyle Libre", it was originally developed for humans but has since been utilised in veterinary medicine (Corradini *et al.*, 2016). Perhaps something similar could be developed in the future to monitor the levels of thyroid hormones in the blood, without the influence of stress. This, however, may be more difficult to do as it would likely require some sort of permanent venous catheter.

4.3. Age

The mean and median ages of cats in this study of 13.2 and 13.5 years old are reasonably similar to the ages of the cats in the study done by Olczak *et al.* (2005) (mean: 13 years 1 month; median: 12 years 11 months). Also, the youngest cat diagnosed in their study was 7 years 1 month old which corresponds to this study where no cats were diagnosed below the age of 7 years. The ages of the control group, i.e. all cats that attended the clinic in the 10-year period, were not available, therefore it was not possible to analyse whether

these findings statistically differ from the whole population of cats submitted to the clinic. Therefore, the hypothesis “the incidence of FHT increases with age” cannot be evaluated.

4.4. Breed

Similarly to age, no data was available from the control group therefore a causal relationship between breed and FHT cannot be confirmed.

4.5. Body weight

The average body weight of cats with FHT was 3.7kg. This is within the normal body weight range for cats according to the pet obesity prevention guidelines who state that a body weight of 8-11lbs (~3.5-4.5kg) is normal for an adult domestic cat (Association for Pet Obesity Prevention, 2019). Of course, this value varies slightly with the breed. There were, however, six hyperthyroid cats that did not have their body weight recorded. If those six body weights were known and included in the study, it could alter the results quite dramatically. The body weight is not often a factor that is investigated in previous studies, this is likely because weight loss is usually a symptom of the disease, therefore it is hard to evaluate whether weight loss increases the incidence of FHT or whether the weight loss is due to the disease itself.

Cats in this study were not weighed every time they came to the clinic; therefore, it was hard to know whether their weight had significantly changed or not. The weights of hyperthyroid cats were often written into the vet’s notes rather than inputted into the body weight chart of the patient. Ideally cats should be weighed every time they come to the clinic in order to see if their weight loss or gain has any significance. This is especially important as the cat ages and often develops more complications (No authors listed, 2012).

It was also not possible to do the statistical analysis of this factor because the weights of all the control cats that came to the clinic over the 10-year period were not inputted into the system. This study has, however, highlighted the fact that body weight is not often recorded and therefore it should now be routinely included in every cats’ visit to the university clinic. Overall, it cannot be concluded that there is a causal relationship between decreased body weight and FHT.

4.6. Prevalence

This study has shown that the prevalence of FHT is very low when compared to other studies conducted elsewhere in the world. Only 0.14% of 35,215 cats between 2008 and 2018 were diagnosed with FHT in Budapest, Hungary. A paper by Peterson (2012) which looked at the causes of FHT, summarised a few prevalence rates from previous studies across the world. A study done between 2001 and 2003 described an annual incidence rate of 11.92% in the UK and 1.53% in Spain (Wakeling *et al.*, 2005). The study gathered data from 5 hospitals across Spain, not specifying whether they were city based or rural, and one hospital in London. A similar study completed in Japan noted a prevalence of 8.9% in 2002. Data for this study were collected from the Hong Kong society for the prevention of cruelty to animals (SPCA) in Wanchai, a busy commercial area of Hong Kong (De Wet *et al.*,2009). Finally, the prevalence rate in an urban population in Germany in 2006 was 11.4% (Sassnau, 2006). These numbers are all considerably higher than the results in Hungary suggesting that the prevalence of FHT is low in Budapest.

Although the result of this study could be perfectly valid, it could also be that the data collected from the university clinic may not be a representative sample of the entire population of cats in Budapest, or even Hungary. The university clinic is more often a referral clinic and therefore, as FHT is becoming more of a routine problem, perhaps more cats are being diagnosed elsewhere in Hungary's first opinion practices rather than being diagnosed at the more specialised university clinic. Bree *et al.* (2018) quite rightly stated that "direct comparisons are difficult because of differences in populations tested, inclusion and exclusion criteria used and thyroid hormone concentration cutoffs employed for diagnosing hyperthyroidism". This statement certainly applies to this study in comparing the results of other countries. Wakeling *et al*. (2005) also mentioned that there are "cultural differences in the willingness of clients to seek and pay for the care of their senior cats" which could perhaps be another factor that is lowering the incidence of FHT in Budapest.

Something else to bear in mind is that the previous studies have looked at the prevalence of FHT in cats above a certain age, and therefore the entire population is not analysed. If the entire population of cats were evaluated, those prevalence values would likely be lower in other countries.

Alternatively, perhaps the prevalence of FHT is genuinely low in Budapest and the next question to ask is why it is so. Could it be related to a consumption of cat foods low in

iodine or due to a lack of environmental goitrogens? If the study were to be repeated it would be worth investigating the environmental factors of the diagnosed hyperthyroid cats through the addition of a questionnaire in order to find an answer to these questions.

4.7. Limitations of the study

A definite drawback with this study was that the reference ranges for T_4 levels over the 10-year period varied due to the use of different laboratories processing the blood. It could be that some cats were classed as not hyperthyroid in one lab but could have been hyperthyroid at another lab with a different laboratory method and reference range. Ideally, if this investigation were to be done again, all the samples would be sent to the same lab with the same reference range to avoid any discrepancies. Further to this, the T_4 levels in some cats with FHT could be periodically in the upper half of the reference range making these cases difficult to diagnose. The true incidence of FHT in this study could therefore be higher. To resolve this issue, every cat with clinical suspicion, but normal total T_4 levels should be retested, possibly also with free T_4 equilibrium dialysis (fT_4ED) and/or scintigraphy to better diagnose.

There was a lack of data available for this study due to inappropriate documentation of data in the university software Doki for Vets™. This study has highlighted the need for better data documentation by vets/members of staff at the clinic. If the study were to be repeated to look at the incidence of FHT between 2020 and 2030, for example, it would be recommended that data such as date of birth/age, sex, breed, body weight, neuter status and BCS were all documented for every cat, every time it attended the clinic, with or without FHT. It would also be beneficial if the patient registration system would show the patient's age at the time of a particular examination. Provision of this data would aid statistical analysis.

A further difficulty with this study was that the computer system, vet's notes etc. were all in Hungarian making it more difficult for non-Hungarian speakers to interpret the data. Perhaps some data was missed due to the language barrier. If it could be made possible, English language students should have better access to collect statistical data about patients.

Currently, it is also difficult for any student (English speaking or Hungarian) to run data queries on groups of patients in Doki for Vets™ system. This year the system was also updates (hardware and software), which resulted in temporary malfunctions.

To keep this study in line with previous studies investigating FHT, it would be beneficial to give every owner of a recently diagnosed hyperthyroid cat a questionnaire for them to complete in their own time. For technologically savvy clients they could complete an online questionnaire, alternatively, a hand-written version could be completed and returned to the practice. This method of data collection is similar to Martin *et al.* (2000). The questionnaire would ask for details of the type (wet or dry) and flavour of food the cat consumed over its lifetime, whether it is an indoor or outdoor cat, the use of flea products on the cat or in the environment and whether it is vaccinated or not. It could also ask the owners what the cats maximum body weight was and whether their cat had recently lost a lot of weight and if so, since when. This would be a good way to decide whether weight loss is because of FHT or a cause of FHT. As soon as the cat is diagnosed with hyperthyroidism, the vet should also document its sex, age, breed, neuter status, BCS and any medical conditions in the computer system. This way, as much data as possible is provided for every hyperthyroid cat making the statistical analysis much more reliable. Perhaps this could also be implemented in other clinics across Hungary to get a better sample of the entire population.

5. Conclusions

According to the results, the following statements can be made:

1) The incidence of FHT increases between 2008 and 2018 for both male and female cats.
2) Male cats are at higher risk of developing FHT than female.
3) The greatest number of cats were diagnosed with FHT between 2016 and 2018.
4) The prevalence of FHT in Budapest, Hungary was low related to the data published in the literature.

It should be highlighted, however that these results are based on a small sample size and that an increase in the sample size could significantly alter the results.

The increased incidence of the disease and the greatest number of diagnoses between 2016 and 2018 is suggestive of better awareness of the disease and improved diagnostic methods. Alternatively, however, it could be due to increased environmental contaminants. It would be recommended that this was investigated further through the use of questionnaires to find out about feed and lifestyle, or, alternatively with the application of silicone pet tags to monitor the cat's environment.

The greater risk of developing FHT in male cats could be indicative of the need for owners of male cats to be more aware of the clinical signs of the disease and to take their cats for regular visits to the vets. Geriatric blood tests would also be recommended to ensure that the T_4 levels are within the normal range.

The low prevalence of the disease in Budapest compared to other urban areas published in the literature is likely to be due to a small sample size and poor representation of the entire population. Repeating the study and including data from multiple clinics across the city would both increase the sample size and be a better representation of the entire population.

6. Summary

It has become evident in small animal veterinary practices that there is an increasing incidence of feline hyperthyroidism (FHT). There has been a significant increase in the prevalence of the disease since the 1970s. It is unclear, however, whether this is specifically due to an increase in the number of cases or because there is a greater awareness of the disease amongst veterinarians. Hyperthyroidism is due to an increased production of thyroid hormones, T_3 (Triiodothyronine) and T_4 (Thyroxine), from one or both lobes of the thyroid gland which may be enlarged due to hyperplasia, a benign tumour, or rarely, a malignant tumour. There have been many studies over the past 40 years focusing on the potential causes of the rising incidence of FHT across the world.

The aetiology of FHT is not known but there are several factors that the literature suggests could be possible causes of the disease. Some reason it to be related to chemicals in the home such as sprays, flame retardants or anti-flea treatments; others believe the major cause to be iodine levels in manufactured cat food or the flavour/type of food fed to cats. Perhaps genetics and sex play an important role or even neuter status. It is believed that a combination of these factors, rather than just one alone, is likely to be associated with the incidence of FHT

This study aimed to look at the prevalence of FHT and aspects that are associated with the incidence of hyperthyroidism in cats in Budapest, Hungary. Data such as the sex, breed, age and body weight of the cats were assessed to see whether there are certain factors that are significant in relation to the incidence of the disease.

The results of this study are as follows:

1) The incidence of FHT increases between 2008 and 2018 for both male and female cats.
2) Male cats are at higher risk of developing FHT than female.
3) The greatest number of cats were diagnosed with FHT between 2016 and 2018.
4) The prevalence of FHT in Budapest, Hungary was low (0.14%) related to the data published in the literature.

It was not possible to evaluate the relationship between breed, age, body weight and FHT due to a lack of data available from the control group.

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