**Title**

Feline hyperthyroidism reported in primary-care veterinary practices in England: Prevalence, risk factors and spatial distribution

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**Abstract**

Feline hyperthyroidism is a commonly diagnosed endocrinopathy that can have a substantial deleterious welfare impact in cats. This study aimed to estimate the prevalence, risk factors and geographical distribution for feline hyperthyroidism in England, using primary-care veterinary practice clinical data from the VetCompass Animal Surveillance Project. Prevalence was estimated from the overall owned cat cohort. Risk factor analysis used an age-matched, nested case-control design with multivariable logistic regression. There were 2,276 feline hyperthyroidism cases identified from 95,629 cats attending 84 practices from September 2009 to December 2011. Cases were aged 6-25 years, 3.7% were purebred, 56.4% were female and 88.1% were neutered. The apparent prevalence was 2.4% (95%CI: 2.3-2.5%) overall and 8.7% (95%CI: 8.3-9.0%) in cats aged 10 or above. Burmese (OR 0.15, 95%CI: 0.07-0.32, P<0.0001), Persian (OR 0.17, 95%CI: 0.08-0.33, P<0.0001), Siamese (OR 0.4, 95%CI: 0.21-0.75, P=0.004) and purebred cats overall (OR 0.33, 95%CI: 0.25-0.42, P<0.0001) had lower odds of feline hyperthyroidism than non-purebred cats. Insured cats had increased odds (OR 1.78, 95%CI: 1.56-2.03, P<0.001). There was little evidence of spatial variation. This study highlights feline hyperthyroidism as a high prevalence disease in England and reports reduced odds of diagnosis in certain breeds and in purebred cats overall.

## Introduction

Feline hyperthyroidism (FHT) is a commonly diagnosed endocrinopathy. Affected cats can present with signs including weight loss and poor body condition, polyphagia, tachycardia, hyperactivity and nervousness and are frequently diagnosed with associated diseases including renal insufficiency and cardiac hypertrophy (Scarlett 1994). FHT is thus a disease which can have a marked detrimental effect on the welfare of affected cats. Prompt diagnosis and treatment of FHT cases can improve quality of life (Birchard 2006, Peterson 2006, Trepanier 2006). Estimation of the prevalence of FHT is important to facilitate disease prioritisation and to assist clinicians in ranking the disorder among differential diagnoses. A FHT prevalence of 3.93% (95%CI: 2.05 – 6.77%) was estimated in cats aged over 10 years that attended several primary-care practices in Hong-Kong (De Wet et al., 2008). The prevalence of FHT among cats aged over 6 years referred to teaching hospitals in the USA between 1978 and 1986 ranged from approximately 0.01 to 0.28 per 1000 (Scarlett et al., 1988) and was estimated at 21.05/1000 visits in cats of all ages (measured between 1978 and 1997) in another study (Edinboro et al., 2004). At referral-based hospitals in Japan, the FHT prevalence was 8.9% in cats aged over nine (Miyamoto et al., 2002). However, prevalence estimates from a referral population may be less generalisable to the overall population than estimates from primary-care practice because the range and frequency of diseases seen in referral hospital settings differs substantially to those seen in the overall population (Bartlett et al., 2010).

The pathophysiological changes seen with FHT are well documented (Peter et al., 1987, Gerber et al., 1994, Scarlett et al., 1994), but the underlying causes of the disease remain unclear. Reported dietary and environmental associated factors for FHT include the consumption of canned food (Kass et al., 1999, Edinboro et al., 2004, Wakeling et al., 2009), the use of a litter tray (Kass et al., 1999, Wakeling et al., 2009) and living in an indoor environment (Scarlett et al., 1988). Host factors reported as associated with FHT are breed and sex (Scarlett et al., 1988, Kass et al., 1999, Edinboro et al., 2004, Olczak et al., 2004, Wakeling et al., 2009, de Wet et al., 2009), although the findings have not always been consistent. Some studies have reported increased odds of diagnosis of FHT in females compared with males (Edinboro et al., 2004 and Olczak et al., 2004), whereas others found no sex predisposition (Martin et al., 2000, De Wet et al., 2008, Wakeling et al., 2009). It has been reported that Siamese cats were at reduced

odds of diagnosis with FHT compared to non-Siamese (Scarlett et al., 1988), that Siamese and Himalayan cats (grouped together) were at reduced odds compared to other breeds combined (Kass et al., 1999) and that purebred cats were at reduced odds compared to non-purebred cats (Wakeling et al., 2009). Conversely, one study found that domestic shorthair cats were at lower odds than other breeds in Hong Kong (De Wet et al., 2009). There is limited evidence for neutering status as an associated factor for diagnosis with FHT because many studies included only neutered cats or too few neutered cats to permit investigation (Edinboro., Martin..). Two studies (Kass et al., 1999, Olczak et al., 2004) did examine for an association and did not find one, although sample size and low numbers of neutered cats in these studies may have resulted in a low power to detect assocaition.

Geographical location as an associated factor was investigated in parts of the USA (Scarlett et al., 1988) by examining differences in the numbers of cases reported by US veterinary teaching hospitals between 1979 and 1986. The study identified that FHT was diagnosed least commonly in the mid-sections of the country and most commonly in California.

In summary, the current literature includes sparse data regarding neutering status and geographic location and equivocal data regarding sex and breed as factors associated with FHT. As some of the studies were relatively small, these studies may have had insufficient power to detect differences in factors with low intrinsic variability (e.g. breed, in which the majority of cats tend to be non-purebred). The use of a large primary-care practice database to further evaluate these factors is therefore merited.

This study aimed to estimate the prevalence of FHT, examine for differences in breed, sex and neutering status in cats with FHT compared to those without and to look for geographic patterns for the disease in a large population of cats attending primary-care veterinary practice in England. It was hypothesised that there would be differences in the sex, neutering status and breed of those diagnosed with FHT compared to those not..

**Materials and Methods**

The study used the database of the VetCompass Animal Surveillance Project (VetCompass, 2013). Practices were enrolled into VetCompass on a convenience basis. The study dataset included all electronic patient records (EPRs) spanning September 2009 to December 2011 for cats attending 84 primary-care practices located mainly in central and south-west England. The VeNom Code data dictionary (VeNom coding group 2012) was embedded within practices' practice management systems (PMSs) to allow veterinarians to select summary diagnosis terms at the time of consultation. Practice EPR data were uploaded to the secure VetCompass structured query language (SQL) database held at the Royal Veterinary College. Ethics approval was granted by the Royal Veterinary College Ethics & Welfare Committee (URN 2010 1076e).

The overall cohort of practice-attending cats was used to estimate the period prevalence of diagnosis of FHT during the study period. A nested case-control design with frequency matching by age was used to investigate associations between the exposure variables of primary interest for the current study (those hypothesised to be associated with a diagnosis of FHT)- 'purebred' (whether or not a cat was recorded as a single specified recognisable breed), 'breed', 'sex' and 'neutering status' - and a diagnosis of FHT. Exposure variables studied to account for confounding effects included 'insurance status' and 'practice ID'. Cats were deemed to have received a diagnosis of FHT if the EPR recorded i) a veterinary diagnosis of FHT or ii) prescription or dispensation of a medical treatment specific to FHT (Thiamazole/Carbimazole) (NOAH 2012) or iii) surgery to remove one or both thyroid glands (thyroidectomy) with clinical text to support a diagnosis of FHT.

Sample size calculation estimated that approximately 2,000 cases and 4,000 controls would be needed to detect an odds ratio for diagnosis of FHT of 0.33 for a given breed, relative to a baseline non-purebred cat group (1% prevalence of breed in controls, 1:2 case to control ratio, power 80%, confidence-level 95%) (Epi-info 7, Centers for Disease Control and Prevention, GA, USA 2012).

The age of each cat in the cohort was derived from the date at the final clinical record. The age distribution of cases was substantially older than a random selection of non-cases, so a frequency matched by age group (1:2 case: control per strata) design was

used to select the controls, aimed at maintaining precision of effect estimates following stratification by age group. The list of control cats required for each age group was generated using an online random number sequencer (Haahr 2012). Internal validation for diagnosis reliability involved a detailed examination of the EPRs of a random sample of 200 cases and 200 controls.

Data were cleaned in Microsoft Excel 2007 (Microsoft Corp.) and exported to STATA Version 12 (Stata Corporation, TX, USA, 2012) for analysis. The variables 'age group', 'purebred', 'breed', 'neutering status', 'sex', 'insurance status' and 'practice ID' were selected for analysis; 'age group' (frequency matched) was forced into the model, the insurance status of an animal was considered a potential confounder *a priori* and the practice ID was included to evaluate clustering within practices. The variable 'purebred' was binary. Cats recorded as being of a single specified recognisable breed were labelled 'yes' and all others were labelled 'no'. For the variable 'breed', cats that were unspecified as being of a given breed were categorised as 'non-purebred' and cats with at least one purebred progenitor were categorised as 'purebred-cross' (e.g. Siamese cross).

The apparent prevalence was estimated using the number of FHT cases as a proportion of the overall number of study animals. Univariable logistic regression and then multivariable logistic regression analyses were performed. During multivariable logistic regression, analyses were conducted for each of the exposure variables of primary interest. Models containing a variable of primary interest and age group (base model) were compared to a model containing all exposure variables (maximum model). Exposure variables were dropped from the maximum model if they caused instability, for example due to sparse data or collinearity, but were not confounders. Confounders were evaluated using the change-in-estimate approach (Rothman 2008, Dohoo 2010). A change in the odds ratio for a primary exposure variable of more than 10% was considered to represent important confounding. All two-way interaction terms were evaluated between final model variables with likelihood ratio tests for homogeneity of odds. Clinic ID was tested in the final model as a random effect to evaluate clustering, with significance set at the 5% level. Finally, model fit was evaluated with the Hosmer Lemeshow goodness-of-fit test statistic (Hosmer and Lemeshow 2000).

For the spatial analysis, British National Grid co-ordinates were derived from case and control partial postcodes (excluding the last two letters of the postcode). The coordinates obtained were estimates of the centroid locations for each partial postcode (the average easting and northing of all the full postcodes within that area) (O'Neill 2011, unpublished). A geographic information system, ArcMap 10.1, (Environmental Systems Research Institute, CA, USA) was used to display case and control locations. An extraction map (Lawson and Williams 1993) was produced to display the ratio of densities of cases to controls. SaTScan (Kulldorff 2005) software was used to investigate potential clusters of higher and lower than expected numbers of hyperthyroid cats using a spatial scan statistic proposed by Kulldorff and Nagarwalla (1995) and Kulldorff (1997). Statistical significance was set at the 5% level.

**Results**

From the clinical records, 2,276 cats had a recorded diagnosis of FHT from a total of 95,629 cats attending the participating practices, resulting in an overall apparent prevalence of 2.38% (95%CI: 2.28-2.48%). Prevalence in cats that were 9 years of age and older (2221/28463) was 7.80% (95%CI: 7.49-8.12%) and in cats 10 years of age and older (2187/25262) was 8.66% (95%CI: 8.31-9.01%).

The 2,276 cases were compared to 4,524 controls. The median age of cases was 15.4 years (interquartile range 13.4-17.2, range 6-25). The number of cats in each breed category ranged from 52 (0.77%) in the purebred-cross group to 6,206 (91.43%) in the non-purebred group (Table 1). There was marked variation between the proportion of cases and controls by breed with a number of purebred cat breeds appearing at reduced odds of disease. Similar proportions of cases and controls were female (56.4 versus 56.5% respectively) and neutered (88.1% versus 86.0% respectively), although a higher proportion of cases were insured compared with controls (27.0% versus 17.9%). There were 411 (6.0%), 12 (0.0018 %), 20 (0.0029%), and 13 (0.0019%) missing values from the variables 'insurance status', 'breed', 'sex' and 'age group', respectively. Of 200 randomly selected cases evaluated to estimate diagnostic reliability, one case did not meet the case inclusion criteria. The 95% confidence interval suggested that up to 34 false positives could have been included in the 2,276 cases (1.5%). None of the 200 cats from the random list of controls met the case inclusion criteria for FTH.

In the univariable logistic analysis, Burmese, Persian and Siamese purebreds along with purebred-crosses and purebred cats overall had reduced odds of diagnosis with FHT compared to non-purebred cats (Table 1). Neutered cats and insured cats had increased odds of being diagnosed with FHT compared to unneutered and uninsured cats respectively. No significant association was detected between sex and diagnosis of hyperthyroidism.

In the multivariable logistic analysis, confidence intervals for odds ratios for each of the exposures of primary interest were stable in the maximum model and so this was used. Burmese cats had 0.15 (95% CI: 0.07-0.32) times, Persians 0.17 (95% CI: 0.08-0.33) times and Siamese 0.4 (95%CI: 0.21-0.75) times the odds of a diagnosis of FHT compared with non-purebred cats, after adjustment for age group, sex, neutering status and insurance status (Table 2). There was some evidence that purebred-crosses (OR 0.45, 95%CI: 0.23-0.88, P=0.020) and weak evidence that British Shorthair cats (OR 0.64, 95%CI: 0.38-1.07, P=0.091) were less likely to be diagnosed with FHT compared with non-purebred cats. Overall, purebred cats (separate model in which the variable 'purebred' was included instead of 'breed') had 0.33 (95% CI: 0.25-0.42, P<0.001) times the odds of a diagnosis of FHT compared with non-purebred cats. Neither neutering status (OR 1.03, 95%CI: 0.85-1.26, P=0.733) nor sex (OR 1.00, 95%CI: 0.90-1.11, P=0.995) were associated with a diagnosis of FHT once adjustments for the other variables in the model had been made. Insured cats had 1.78 (95%CI: 1.56-2.03) times the odds of diagnosis of FHT compared to uninsured cats. No significant final model interactions were detected. Model fit (Hosmer and Lemeshow 2000) was good (Hosmer-Lemeshow test statistic, P=0.419). Significant clustering was identified within practices, so practice identification number was retained as a random effect (rho= 0.012, P<0.0001).

In the spatial analysis, geographic coordinates were identified for 2,109 (92.7%) cases and 4,099 (90.6%) controls, spanning 882 locations. Map 1a describes the relative density of cases and Map 1b describes that of controls. The extraction map dividing density of cases by that of controls did not identify substantial variation in the ratio of densities across the study area. The spatial scan statistic highlighted one significant (P=0.0013) higher than expected odds cluster, centred in Battersea, London, with

radius 26.9km and an estimated odds ratio of 1.21 and one significant (P=0.00017) lower than expected odds cluster, centred in Spalding, Lincolnshire, with radius 50.8km and an estimated odds ratio of 0.62.

**Discussion**

The overall prevalence of diagnosis of FHT in the current study was 2.38%. Prevalence in cats aged 9 years or more was 7.80%, slightly lower than reported in cats of that age range in Japan (Miyamoto et al., 2002). Prevalence in cats 10 years of age or older was 8.66%, considerably higher than reported in cats of that age range in Hong Kong (De Wet et al., 2008). However, it is noted that these previous prevalence studies used different case definitions, inclusion/exclusion criteria and study populations.

Burmese, Persian and Siamese cats showed reduced odds of diagnosis of FHT compared to non-purebred cats. This concurs with US studies that showed reduced odds for Siamese (Scarlett et al., 1988, Kass et al., 1999), but this is the first report to the authors' knowledge to provide evidence regarding Persian and Burmese cats. There was scope for misclassification of breeds as the study relied on secondary data. However, breed was unlikely to be misclassified on the basis of disease presence and hence the misclassification was likely to be non-differential. Breeds represented by small numbers were grouped into the category 'other purebred' to permit examination of interactions. The study also compared non-purebred to purebred cats and, like a previous study (Wakeling et al., 2009), identified that purebred cats were at reduced odd of diagnosis with FHT than non-purebred cats. It is unclear as to why certain breeds appear to be protected and the results contradict the general notion that the cross breeding of animals tends to decrease predisposition to disease. Perhaps there are certain genes which predispose to the development of FHT which are not present in certain purebred populations. An alternative hypothesis would be that the breeds which appear protected tend to live with the disease for less time (for instance by developing the disease later in life or surviving for less time once they have the disease) than non-purebreds.

Insured cats showed increased odds of diagnosis with FHT compared with uninsured cats. This finding confirms the importance of including insurance status within

epidemiological analyses as a proxy for the multiple owner, veterinarian and animal-related differences that exist between insured and uninsured patients. Insured animals are likely to be observed by veterinarians more frequently and undergo more diagnostic procedures than uninsured animals (Egenvall et al., 2009).

In agreement with several other studies (Martin et al. 2000, De Wet et al. 2008, Wakeling et al., 2009), the current study did not detect evidence that sex was associated with FHT diagnosis. There was also no evidence in the final model that neutered cats were more likely to be diagnosed with FHT than unneutered cats, which concurs with previous findings (Kass et al., 1999 and Olczak et al., 2004). It should be noted that sex and neutering status were retained in the final model because they were of primary interest to the study. It is, however, emphasised that their inclusion did not alter the point estimates and confidence intervals for the other variables in the model.

The distribution and density of cases and controls across the geographic study area were very similar (Maps 1a and 1b). The spatial study was designed to be descriptive and potentially hypothesis generating. No high magnitude risk ratios were detected, although the study may have been underpowered in regions populated with only low numbers of cases and controls. This study highlights the potential for future, larger studies of primary-care national data to evaluate geographical risk factors.

There were some limitations in this study. The data were derived from veterinarians in primary-care practice; the veterinarians themselves were not collecting the data for research purposes, but simply to accurately record cases for clinical care. It is therefore possible that some variables for some animals may be more likely to have been misclassified compared to data collected primarily to address a research question. Due to the nature of the dataset, the case definition centred on a veterinary diagnosis FHT and not, as has been the case in some previous studies, on serum thyroxine levels. However, it is considered unlikely that many veterinarians would diagnose and initiate treatment for FHT without such blood sampling. Indeed, the recognised approach for diagnosing FHT involves the careful consideration of several factors including history, physical examination and blood sampling. Frequency matching by age improved precision of estimates but prevented investigation of age as an associated factor within the analyses. However, it was considered more important to avoid problems related to

separation of data due to substantially differing age distributions in the cases and controls than to include age as an independent factor (Hosmer and Lemeshow, 2001). Data regarding some dietary and environmental factors recorded as associated with FHT in previous studies were unavailable in the clinical records, so important residual confounding may have been present. In other words, some of the associations reported may in part reflect associations between unmeasured variables and a diagnosis of FHT. Cats that had undergone thyroidectomy or radioiodine treatment prior to data collection may not have been identified as cases unless there was subsequent comment on these procedures. Although many locations were represented in the study, these cats were mainly in the south-eastern and central parts of England. There may be associated factors that are not highly variable over this area, but are elsewhere. Finally, the spatial study was equivalent to a univariable or 'crude' analysis. As such, the explanations for the high and low odds areas may be straightforward such as certain practices/clinicians being particularly good at identifying cases of FHT.

In summary, this study estimated a clinically relevant prevalence (2.38%) for diagnoses of FHT in a large cohort of cats attending primary-care practices in England. Burmese, Persian and Siamese cats, as well as purebred cats overall, were at reduced odds of diagnosis while insured cats showed increased odds of diagnosis of hyperthyroidism. Further work to explore why certain breeds are at lower odds of diagnosis than others is warranted.

**Table 1: Univariable logistic regression analysis results for factors associated with a diagnosis with feline hyperthyroidism among cats attending primary-care practices in England**

| Risk Factor | Category | Case Number (%) | Control Number (%) | Crude Odds Ratio | 95% Confidence Interval | P-Value* |
|---|---|---|---|---|---|---|
| Purebred | No | 2190 (96.31) | 4068 (90.12) | 1 | | |
| | Yes | 84 (3.69) | 446 (9.88) | 0.35 | 0.28-0.44 | <0.001 |
| Breed | Non-purebred | 2179 (95.82) | 4027 (89.21) | 1 | | |
| | British shorthair | 22 (0.97) | 60 (1.33) | 0.68 | 0.42-1.11 | 0.127 |
| | Burmese | 7 (0.31) | 82 (1.82) | 0.16 | 0.07-0.34 | <0.001 |
| | Persian | 11 (0.48) | 101 (2.24) | 0.20 | 0.11-0.38 | <0.001 |
| | Siamese | 12 (0.53) | 55 (1.22) | 0.41 | 0.22-0.76 | 0.005 |
| | Other purebred | 32 (1.41) | 148 (3.28) | 0.40 | 0.27-0.59 | <0.001 |
| | Purebred cross | 11 (0.48) | 41 (0.91) | 0.50 | 0.26-0.97 | 0.041 |
| Sex | Male | 989 (43.57) | 1960 (43.46) | 1 | | |
| | Female | 1281 (56.43) | 2550 (56.54) | 0.99 | 0.90-1.10 | 0.911^ |
| Neutering Status | Unneutered | 270 (11.86) | 632 (13.97) | 1 | | |
| | Neutered | 2006 (88.14) | 3892 (86.03) | 1.22 | 1.05-1.42 | 0.011^ |
| Insurance status | Uninsured | 1585 (73.01) | 3465 (82.15) | 1 | | |
| | Insured | 580 (26.99) | 753 (17.85) | 1.73 | 1.53-1.96 | <0.001^ |
| Age Group[1] (years) | 17-25 | 645 (28.50) | 1290 (28.51) | 1 | | |
| | 14-17 | 919 (40.61) | 1838 (40.63) | 1.00 | 0.88-1.13 | 1.000 |
| | 11-14 | 542 (23.95) | 1082 (23.92) | 1.00 | 0.87-1.15 | 0.979 |
| | 6-11 | 157 (6.94) | 314 (6.94) | 1.00 | 0.81-1.24 | 1.000 |

*Wald test P-values unless denoted ^ (LRT)

[1]Frequency matched in the study design

**Table 2: Final multivariable logistic regression model results for factors associated with a diagnosis with feline hyperthyroidism among cats attending primary-care practices in England**

| Associated Factor | Category | Odds Ratio | 95% Confidence Interval | P-value* |
|---|---|---|---|---|
| **Breed** | Non-purebred | 1 | | |
| | British shorthair | 0.64 | 0.38-1.07 | 0.091 |
| | Burmese | 0.15 | 0.07-0.32 | <0.001 |
| | Persian | 0.17 | 0.08-0.33 | <0.001 |
| | Siamese | 0.40 | 0.21-0.75 | 0.004 |
| | Other purebred | 0.37 | 0.25-0.56 | <0.001 |
| | Purebred cross | 0.45 | 0.23-0.88 | 0.020 |
| **Sex** | Male | 1 | | |
| | Female | 1.00 | 0.90-1.11 | 0.995^ |
| **Neutering Status** | Unneutered | 1 | | |
| | Neutered | 1.03 | 0.85-1.26 | 0.733^ |
| **Insurance Status** | Uninsured | 1 | | |
| | Insured | 1.78 | 1.56-2.03 | <0.001^ |
| **Age Group[1]** | 17-25 | 1 | | |
| | 14-17 | 0.94 | 0.83-1.07 | 0.359 |
| | 11-14 | 0.90 | 0.78-1.05 | 0.169 |
| | 6-11 | 0.83 | 0.66-1.04 | 0.102 |

*Wald test P-values unless denoted ^ (LRT)

[1]Frequency matched in the study design

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