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Feline diabetes mellitus in the UK: the prevalence within an insured cat population and a questionnaire-based putative risk factor analysis

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Prevalence and risk factors for the development of diabetes mellitus (DM) in cats in the United Kingdom have not previously been reported. The prevalence of DM was evaluated in a large insured population and was found to be 1 in 230 cats. In this insured cat population Burmese cats were 3.7 times more likely to develop DM than non-pedigree cats. A convenience-sampling questionnaire-based study was used in order to identify putative risk factors for the development of DM. The univariate risk factor analysis identified being male, neutered, inactive, weighing $\geq$5 kg and having a history of corticosteroid treatment as significant risk factors for the development of DM in these cats. In addition, male cats treated with megestrol acetate had a significantly increased risk of developing DM compared to females. In contrast, there was no difference in DM occurrence between male and female Burmese cats. A multivariate classification tree-based model on the questionnaire data looking for interactions between risk factors, identified gender as the most important overall risk factor for the development of DM with low physical activity being the next most important risk factor for female cats and breed the next most important for male cats.

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Diabetes mellitus (DM) is defined as a group of metabolic disorders characterised by hyperglycaemia as a result of defects in insulin secretion, insulin action or both (American Diabetes Association: Expert Committee 2003). When known risk factors, clinical behaviour and islet histopathology of DM in cats are compared to humans then 85–95% of cats are reported to have type 2 DM (Rand et al 2004); a disease characterised by inadequate insulin secretion and impaired insulin action. In America, the reported prevalence of feline DM has increased over the past 30 years from 1 in 1250 in 1970 to 1 in 81 cats affected by the disease in 1999 (Prahl et al 2003). The prevalence of feline DM in Australia and North America over the past 10 years is reported to be between 1 in 179 and 1 in 81 (Panciera et al 1990, Rand et al 1997, Baral et al 2003). Despite the importance of DM in feline practice the prevalence of feline DM in the UK has not been reported.

A number of studies have looked at potential risk factors for the development of DM, and advancing age has been reported to be the most important of them (Panciera et al 1990). Risk factors also include being male, with neutered males reported to be at greater risk than entire males (Panciera et al 1990, Crenshaw and Peterson 1996). More equivocal evidence is present for female cats, with Crenshaw and Peterson (1996) reporting equal risk for the development of DM in entire and neutered female cats whilst Panciera et al (1990) showed that neutered females were at increased risk compared to entire females. Obesity is also reported to be a risk factor for the development of DM with overweight cats being 4.6 times (95% CI 1.7–12.4) more likely to develop DM than cats in an ideal body condition (Scarlett and Donoghue 1998).

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In North America, no particular breed of cat appears to be associated with an increased risk for the development of DM (Panciera et al 1990, Crenshaw and Peterson 1996). In contrast, in Australia, an increased incidence of DM in Burmese cats has been reported (Rand et al 1997, Baral et al 2003). It should be noted that Burmese breeders in Australia, New Zealand and the UK have not accepted Burmese cats from America for over 20 years; therefore, the Burmese cats in these countries are quite different from those in America. Risk factors reported for the development of DM in Burmese cats in Australia include advancing age (Rand et al 1997), chronic or recurring medical problems, dental disease, repeated corticosteroid treatment, confinement indoors, lower physical activity and a trend towards greater body weight (Lederer et al 2003). It has also been reported that male and female Burmese cats are equally likely to develop DM (Rand et al 1997, Lederer et al 2003).

Only one report of 33 Burmese cats in Australia has assessed the use of corticosteroids as a risk factor for the development of DM (Lederer et al 2003). Despite not being reported as a risk factor in the general cat population for the development of DM, both corticosteroids and megestrol acetate have been associated with the development of DM in clinical cases and in feline models of DM (Peterson 1987, Nelson et al 1999, Hoenig et al 2000).

Despite the importance of DM, the prevalence and risk factors for its development in cats in the UK has not been reported. Unfortunately, it is not possible to easily obtain information from an unbiased sample of domestic cats in the UK. Therefore, we have adopted a two phase approach; firstly to determine the prevalence of DM in an insured population of cats and secondly to elucidate putative risk factors for the development of DM from a convenience-sampling questionnaire.

Materials and methods

Insured cat population prevalence study

The prevalence of DM in pet cats in the UK would ideally be obtained by assessing a properly stratified randomised sample of the entire domestic pet cat population. Unfortunately, there are no robust data available on this population from which an unbiased sample could be taken, therefore in order to try and obtain a measure of the prevalence of DM in the UK a large insured population was assessed. Information was obtained about cats insured with Pet Protect (www.petprotect.co.uk) in 2003; it included the total number of cats insured in that year, the number of cats diagnosed with DM, and breed details.

Questionnaire-based risk factor study

Putative risk factors for the development of feline DM were assessed via a convenience-sampling questionnaire that was included in the Feline Advisory Bureau (FAB) Journal, spring 2002 issue, which is distributed to approximately 2000 readers in the UK. A case report of a Burmese cat with concurrent DM and chronic pancreatitis was published in the same issue to stimulate interest and encourage replies; no mention was made of a suspected increased occurrence of DM in Burmese cats. The questionnaire requested the following information; breed, sex, date of birth, weight at birth and adult weight. Owners were also asked about breeding history; number of litters and kittens born; adult activity level with choices of 'sleeps most of the time', 'fairly active', 'active' and 'hyperactive'; vaccination status for cat flu, enteritis, chlamydia and feline leukaemia virus; previous or current treatment with megestrol acetate or corticosteroids and whether lipaemia of the aqueous humour had ever been detected. Dietary information regarding type of food fed and feeding frequency (ad lib, on request or meal fed either one, two, three or four times daily) was assessed for three different age groups, 1–3 months, 3–6 months and adult cats. Finally, owners were asked if the cat had ever been diagnosed with DM. A copy of the questionnaire is available from the authors on request.

Statistical analysis

Standard logistic regression with odds ratios (OR) and 95% confidence intervals (CI) were calculated to evaluate the differences in DM occurrence in different breeds from the insured population.

For the questionnaire data, activity level was divided into inactive for those cats with responses of 'sleeps most of the time' and 'fairly active', and active for those cats that were 'active' or 'hyperactive'. Feeding patterns were simplified to meal fed (including on request feeding) or ad lib. The large range of diets were further classified based on water content as wet, dry or a mixture of wet and dry food. As 36 breeds were represented in the questionnaire database, for the statistical analysis this was simplified to the following breed categories; Birman, British

Shorthair, Burmese, Cornish Rex, Devon Rex, Domestic Shorthair/Domestic longhair (DSH/DLH), Maine Coon, Persian, Siamese, and other. Breeds with less than 15 cats were classified as 'other'. The weight of the cats was known for 590 cats. In addition, whether the cat was $<$ or $\geq$5 kg was noted in a further six cats. Therefore, adult weight data were divided into two groups based on this weight division. For male cats, data regarding the number of litters and kittens born were excluded as it was felt that the number of litters sired and kittens born did not place a direct metabolic demand on male cats.

A Spearman rank correlation test was used to test the association between the prevalence of DM and the number of cats in a household. Almost 25% of cats were in single cat households, and over 60% had three or less cats thereby preventing the use of mixed-effect statistical methodologies in order to take into account that some owners have many cats, for which some of the 'management' risk factors (eg, diet) might be expected to be confounded. Therefore, the questionnaire data analysis was carried out using standard logistic regression. Preliminary analyses involved univariate logistic regression of all variables of interest, with OR and 95% CIs also calculated.

The high level of imbalance in the data (eg, there are no entire Maine Coon cats in the questionnaire database, and only three of the 21 Birman cats where activity status was reported were active), meant standard multivariate analytical techniques were not possible for many two-way comparisons, and certainly not for anything beyond two-way comparisons. A relatively underutilised but powerful multivariate technique was used to look at multi-factorial comparisons: classification tree-based statistical models (hereafter 'tree models') (Shaw and Dobson 1995, Clark and Pregibon 1997). The analysis consists of determining a binary division of the data, between groups of categories (eg, male vs female or Burmese vs all other breeds), such that there is the largest difference in terms of DM prevalence for those two subsets of data. One subset is then considered (eg, male only) and which binary division in terms of any of the other factors results in the largest difference in DM prevalence is determined. The other subset is then considered (eg, female only) and again which factor a binary division gives the largest difference in DM is determined. Different factors can be selected for different subsets of the data. This binary partitioning is continued for smaller and smaller subsets of data until no differentiation in terms of prevalence is possible. The analysis is produced in graphical form allowing easy comprehension of the grouping of prevalence in the data, and permitting explicit post hoc statistical comparison of particular subsets of data using χ^2 analyses.

All analyses were carried out in S-Plus (Insightful Corp, Seattle, WA), and $P < 0.05$ was taken to indicate statistical significance with the appropriate degrees of freedom quoted with the test statistic.

Results

Insured cat population prevalence study

This population consisted of 14,030 cats, 61 of which were diabetic (Table 1) giving a prevalence of 0.43% (95% CI 0.3–0.6). In this insured population the Burmese cats were significantly more likely to be diabetic (OR 3.7 (2.2–6.3)) than DSH/DLH cats ($\chi^2_1 = 4.5$, $P = 0.034$).

Risk factor study

A total of 249 questionnaires were returned with information about 761 cats, with the number of cats per owner ranging from one (24% of questionnaires) to 18 (with 6% of questionnaires relating to households with over five cats). Of these 761 cats, 45 had DM, giving a frequency of occurrence of 5.9% (95% CI: 4.3–7.9). There was a highly significant negative correlation between

Table 1. Summary of information collected from the Pet Protect population, with the number of cats of a particular breed (total number of cats that were pedigree = 2245), the number of cats with DM, and the percentage (+95% CIs) this represents

Breed	Total	With DM	%
All cats	14,030	61	0.4 (0.3–0.6)
DSH/DLH	10,912	52	0.5 (0.4–4.5)
Burmese	228	4	1.8 (0.02–4.3)
British Shorthair	129	1	0.7 (0.3–5.1)
Birman	108	1	0.9 (0.02–5.1)
Persian	372	1	0.3 (0.01–0.7)
Siamese	276	1	0.4 (0.01–2.0)
Other*	2005	1	0.05 (0–0.3)

*The information on breed was unknown for 1991 of the cats so these have been included in the 'other' group.

the occurrence of DM and the number of cats an owner had ($r_s = -0.254$, $P < 0.001$).

Information from all replies was recorded although not all questions were answered for every cat. An overview of the information obtained is shown in Table 2. The breed was known for 742 (97.5%) of the cats with 36 breeds in total; 86% of the cats were from just 10 breeds (Fig 1). There were 408 female cats (321 neutered) and 344 male cats (310 neutered). Of the 45 diabetic cats, 29 were male neutered, 14 were female neutered and one male entire, the gender of the other DM cat was unknown. None of the female entire cats were diabetic. Two-hundred and eighty-eight cats were classified as active and 392 as inactive. For the 45 diabetic cats, 10 were active, 28 inactive and activity level was unknown for seven. Of the 653 cats where corticosteroid usage was reported, 72 had been treated with corticosteroids, and of the diabetic cats eight were known to have received corticosteroids; for 14 of the diabetic cats it was not known whether corticosteroid treatment had been administered. Megestrol acetate treatment information was available for 655 cats, with 93 of these cats having received megestrol acetate, six of which were diabetic (five male neutered); however, for 13 of the diabetic cats megestrol acetate treatment information was unknown (Table 2).

Univariate risk factor analysis

Univariate analyses of the risk factors (Table 2) revealed significant associations between the presence of DM and the breed of cat ($\chi^2_9 = 24.5$, $P = 0.004$). Excluding those four breeds with no reported diabetics and the breeds with less than 15 cats (Table 2) did not change this result ($\chi^2_4 = 11.8$, $P = 0.019$). The Burmese cats had a significantly greater frequency of occurrence of DM compared to DSH/DLH cats (OR 3.3 (95% CI:1.5–6.8)) and Persian cats (OR 7.8 (1.10–60.3)); no other breed's diabetes prevalence was significantly different (Table 2). Male cats were significantly more likely to be diabetic than females and neutered cats were more likely than entire ones (both $P = 0.002$; Table 2). There was also a significant increase in the frequency of occurrence of DM with actual weight of the cat and whether the weight was $\geq$5 kg ($P < 0.010$; Table 2). The frequency of occurrence of DM was also significantly increased in cats having received corticosteroids, cats that were inactive compared to active cats, and adult cats on dry or wet diets more than those on mixed diets (all $P < 0.035$; Table 2). In contrast, weight at birth, adult feeding frequency, kitten feeding frequency or diet type, breeding status, or vaccination status for cat flu, enteritis, chlamydia, or feline leukaemia virus, and megestrol acetate treatment were not significantly associated with DM (all $P > 0.092$; Table 2). Only three owners reported that one of their cats had experienced lipaemia of the aqueous humour, none of which were diabetic, and the number of litters born to a particular cat was known for only one female DM cat and the number of kittens born to a particular cat was unknown for all the female diabetics, preventing any analyses.

Univariate risk factor analysis for the Burmese cats

Due to the significantly increased risk of DM in the Burmese cat group univariate analyses of the risk factors was repeated for this group of cats alone. In contrast to the whole questionnaire population, gender was not a significant risk factor for the development of DM in these cats ($\chi^2_1 = 0.5$, $P = 0.490$, OR = 1.5 (0.4–4.8)). There were no entire diabetic Burmese cats precluding any analysis of neuter status. These cats remained significantly more likely to be diabetic if they were $\geq$5 kg and inactive ($\chi^2_1 > 8.3$, $P < 0.001$, OR > 6.3). Breeding status, weight at birth, adult weight, type of diet or feeding frequency, previous or current treatment with megestrol acetate and cat flu, enteritis or feline leukaemia virus vaccination status were not significantly associated with the risk of developing DM (all $P > 0.128$), but treatment with corticosteroids and chlamydia vaccination approached statistical significance, despite the low number of cats with DM for these two factors ($\chi^2_1 = 3.8$, $P = 0.05$).

Multivariate risk factor analysis

Only 61.4% (467/761) of questionnaires had all the information on risk factors sufficiently completed (hereafter 'minimum data set'), so for much of the multivariate analyses 47% (21/45) of the DM cats could not be considered. Despite the fact that no entire females ($n = 87$) had DM and 9.2% of neutered male cats did ($n = 304$), there was no statistically significant interactions between the sex of the cat and the neutered status in terms of DM occurrence ($\chi^2_1 = 1.5$, $P = 0.218$). The only statistically significant interactions between any of the risk factors were between gender and megestrol acetate treatment

Table 2. Summary of questionnaire data, with the number of cats for which data were provided for a particular factor, the number of cats with DM in a particular category, the percentage (+95% CIs) this represents, the associated univariate statistical results (χ^2 test statistic and statistical significance) and the univariate OR (+95% CI)

	Total	With DM	%	χ^2 and P value	OR
Number of cats	761	45	5.9 (4.3−7.9)		
Breed*,†					
DSH/DLH	366	21	5.7 (3.5−8.7)	$\chi^2_9 = 24.5$, $P = 0.004$	−
Burmese	84	14	16.7 (9.4−26.4)		3.3 (1.5−6.8)
British Shorthair	34	2	5.9 (0.7−19.7)		1.0 (0.2−4.6)
Birman	23	1	4.3 (0.1−22.0)		0.7 (0.09−5.9)
Persian	40	1	2.5 (0.06−13.2)		0.4 (0.05−3.2)
Cornish Rex	20	0	0 (0−16.9)		NA‡
Devon Rex	19	0	0 (0.17.7)		NA‡
Maine Coon	16	0	0 (0−20.6)		NA‡
Siamese	36	0	0 (0−9.8)		NA‡
Other	123	6	4.9 (1.8−10.4)		0.8 (0.3−2.2)
Sex†					
Female	408	14	3.4 (1.8−5.7)	$\chi^2_1 = 9.6$, $P = 0.002$	−
Male	344	30	8.7 (5.9−12.2)		2.7 (1.4−5.2)
Neutered YN†					
Entire	120	1	0.8 (0.02−4.6)	$\chi^2_1 = 9.5$, $P = 0.002$	−
Neutered	631	43	6.8 (4.9−9.1)		8.7 (1.1−64.0)
Weight group†					
< 5 kg	375	14	3.7 (2.0−6.2)	$\chi^2_1 = 12.5$, $P < 0.001$	−
> 5 kg	221	25	11.3 (7.4−16.3)		3.3 (1.6−6.5)
Breeding†					
No	600	32	5.3 (3.6−7.5)	$\chi^2_1 = 2.8$, $P = 0.092$	−
Yes	136	3	2.2 (0.4−6.4)		0.4 (0.1−1.3)
Adult diet†					
Dry	143	13	9.1 (4.9−15.1)	$\chi^2_2 = 7.8$, $P = 0.020$	2.2 (1.08−4.5)
Mixed	526	23	4.4 (2.7−6.5)		−
Wet	58	7	12.1 (4.9−23.3)		3.0 (1.2−7.4)
Adult feeding†					
Ad lib	416	27	6.4 (4.3−9.3)	$\chi^2_1 = 0.6$, $P = 0.432$	−
Meal	331	17	5.1 (3.2−8.1)		0.7 (0.4−1.5)
Activity†					
Active	288	10	3.5 (1.6−6.3)	$\chi^2_1 = 4.5$, $P = 0.035$	−
Inactive	392	28	7.1 (4.7−10.2)		2.1 (1.02−4.5)
Corticosteroids†					
No	581	23	4.0 (2.5−5.9)	$\chi^2_1 = 5.6$, $P = 0.018$	−
Yes	72	8	11.1 (4.9−20.8)		3.0 (1.3−7.1)
Megestrol acetate†					
No	562	26	4.6 (3.0−6.7)	$\chi^2_1 = 0.5$, $P = 0.466$	−
Yes	93	6	6.5 (2.4−13.6)		1.4 (0.5−3.6)
Cat flu vaccination†					
No	8	1	12. 5 (0.3−52.7)	$\chi^2_1 = 0.8$, $P = 0.302$	−
Yes	725	32	4.4 (3.0−6.2)		0.3 (0.03−2.7)
Enteritis vaccination†					
No	19	1	5.3 (0.1−26.0)	$\chi^2_1 < 0.1$, $P = 0.938$	−
Yes	720	35	4.9 (3.4−6.7)		0.9 (0.1−7.1)

(*continued on next page*)

Table 2 (*continued*)

	Total	With DM	%	χ^2 and P value	OR
Chlamydia vaccination[†]					
No	59	5	8.5 (2.8−18.7)	$\chi^2_1 = 2.8$, $P = 0.096$	−
Yes	196	6	3.1 (1.1−6.6)		0.3 (0.1−1.2)
Leukaemia vaccination[†]					
No	66	2	3.0 (0.3−10.5)	$\chi^2_1 = 0.5$, $P = 0.482$	−
Yes	514	25	4.9 (3.1−7.1)		1.6 (0.3−7.1)
				χ^2 and P value	Slope (SE)
Weight[†]	590			$\chi^2_1 = 6.6$, $P = 0.010$	0.241 (0.09)
Weight at birth[†]	107			$\chi^2_1 < 0.1$, $P = 0.939$	−0.002 (0.03)

[*] 'Other' included 25 breeds including cross breed cats four of which were Burmese crosses, one of these Burmese crosses had DM.
[†] Information was missing in terms of breed ($n = 19$), sex ($n = 9$), neutered status ($n = 10$), breeding status ($n = 25$), weight group ($n = 171$), adult cat diet ($n = 34$), feeding frequency ($n = 14$), activity level ($n = 81$), corticosteroid ($n = 108$), megestrol acetate administration ($n = 106$), cat flu ($n = 28$), enteritis ($n = 22$), chlamydia ($n = 506$) and feline leukaemia virus ($n = 181$) vaccinations, weight ($n = 165$) and weight at birth ($n = 654$).
[‡] NA = OR and CIs not applicable due to none of the breed having DM.

($\chi^2_1 = 4.1$, $P = 0.043$) and DM occurrence, with 25% of megestrol acetate treated male cats having DM, compared to only 1.4% of megestrol acetate treated female cats.

An initial tree-model analysis carried out on the minimum data set of all the statistically significant univariate risk factors as well as megestrol acetate usage identified sex, neuter status, breed group, activity status and corticosteroid usage as the most important factors for the development of DM (data not shown). Therefore, a final tree-model analysis was carried out on the 584 cats for which the information on these five factors was complete (Fig 2). The tree analysis revealed that of the five variables the clearest division for occurrence of DM is by gender ($\chi^2_1 = 14.7$, $P < 0.001$; OR: 4.3 (1.5−11.9)). For the female cats, 3% of inactive cats had DM whilst none of the active cats were diabetic (Fig 2A). For the male cats, the clearest discrimination of the DM data was a division of the breeds, with all the negative breeds in Table 2 plus British Shorthair and Birman cats having no DM (the positive British Shorthair/Birman cats were from incomplete questionnaires and are therefore excluded) and the DSH/DLH, Burmese, British Shorthair and 'other' breeds having a frequency of occurrence of 10% (Fig 2B). A further increase in the occurrence of DM was seen in male DSH/DLH, Burmese, Persian and other cats that had corticosteroid treatment (26%) compared to those that had not (8%) (Fig 2C; $\chi^2_1 = 6.9$, $P = 0.008$; OR: 5.5 (2.0−14.8)). For those male cats not receiving corticosteroids, no entire cats had DM compared to 8% of neutered cats (Fig 2D). Finally, the tree analyses revealed that a further division of breed could be made for those male cats that had been treated with corticosteroids, with 37% of DSH/DLH and Burmese cats being diabetic compared to 0% of the male Persian and 'other' breed cats treated with corticosteroids.

Discussion

This paper is the first report of the prevalence of DM in a population of cats in the UK. The initial population studied was a large group of insured cats and the prevalence of DM was 1 in 230 cats. Whilst there are no robust data available it is believed that in 2003−2004, of the estimated 6−9.6 million domestic pet cats in the UK (Pet Food Manufacturers Association (PFMA) 2004, Euromonitor 2004, www.euromonitor.com) 8−12% were from pedigree breeds (PFMA 2004, Ross Tiffin Onswitch Insight Ltd 2006, personal communication). This insured population compares favourably with these estimates as 16% of the cats in this group were from pedigree breeds. The second part of the study, whilst being a convenience-sampling questionnaire rather than a true randomised cross-sectional, prospective study, represents the largest study of the putative risk factors for the development of DM in cats in Europe and adds considerably to the information generated by previous studies. This study suggests that the occurrence of DM is increased in

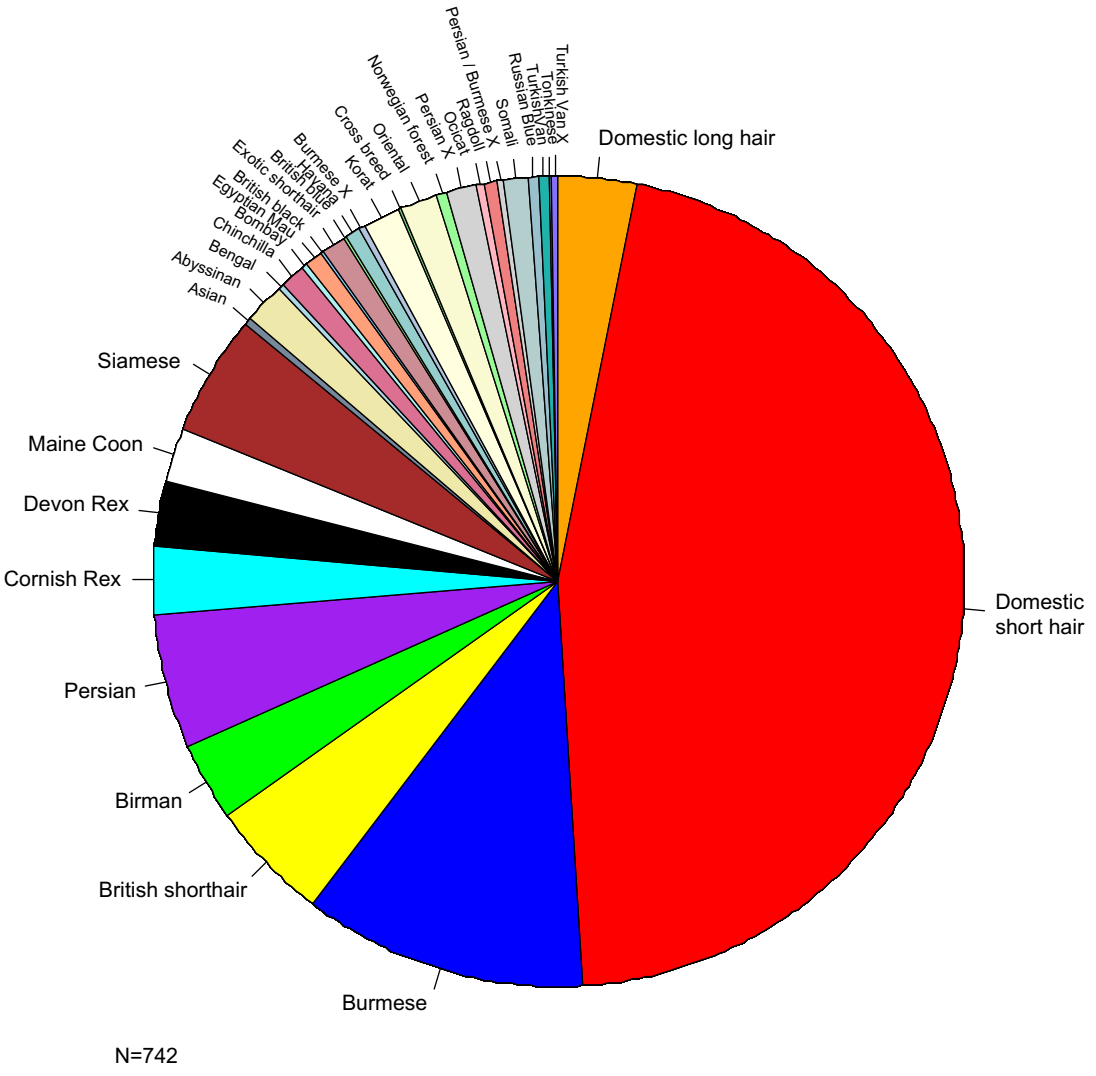

Fig 1. Pie chart of the 36 cat breeds recorded from questionnaire data on 742 cats, with the 10 most common breeds first.

Burmese cats and it is of interest that the risk factor analysis also highlighted an increased occurrence of DM in Burmese cats despite the limitations of a convenience-sampling questionnaire study. The Burmese cats comprised 10.1% of the pedigree cats in the insured population which is similar to the proportion of Burmese cats registered with the Governing Council of the Cat Fancy between 1988 and 2003 (11.1%; source: www.gccf.org). Further evaluation of breed as a putative risk factor would ideally use prospective studies (randomised cluster analysis) or evaluation of multiple insured populations.

In the current study, gender was shown to be a significant (and for the tree models the most significant) putative risk factor for the development of DM in the questionnaire data. Hoenig and Ferguson (2002) showed that insulin sensitivity in male cats prior to neutering was lower than in female cats. Appleton et al (2001) also reported a tendency towards lower insulin sensitivity in male compared to female cats when in lean body condition, and lean cats with reduced insulin sensitivity are at increased risk of developing glucose intolerance after weight gain. This may in part explain the increased risk of DM observed in this group of male cats.

The current study also identified neutering as being an important potential risk factor. It has been shown that neutered cats fed ad lib gain significantly more weight than entire cats (Fettman et al 1997) and that weight gain to the level of obesity results in reduced insulin sensitivity (Biourge et al 1997, Appleton et al 2001). Hoenig and Ferguson (2002) showed that female cats that had their weight controlled by diet restriction

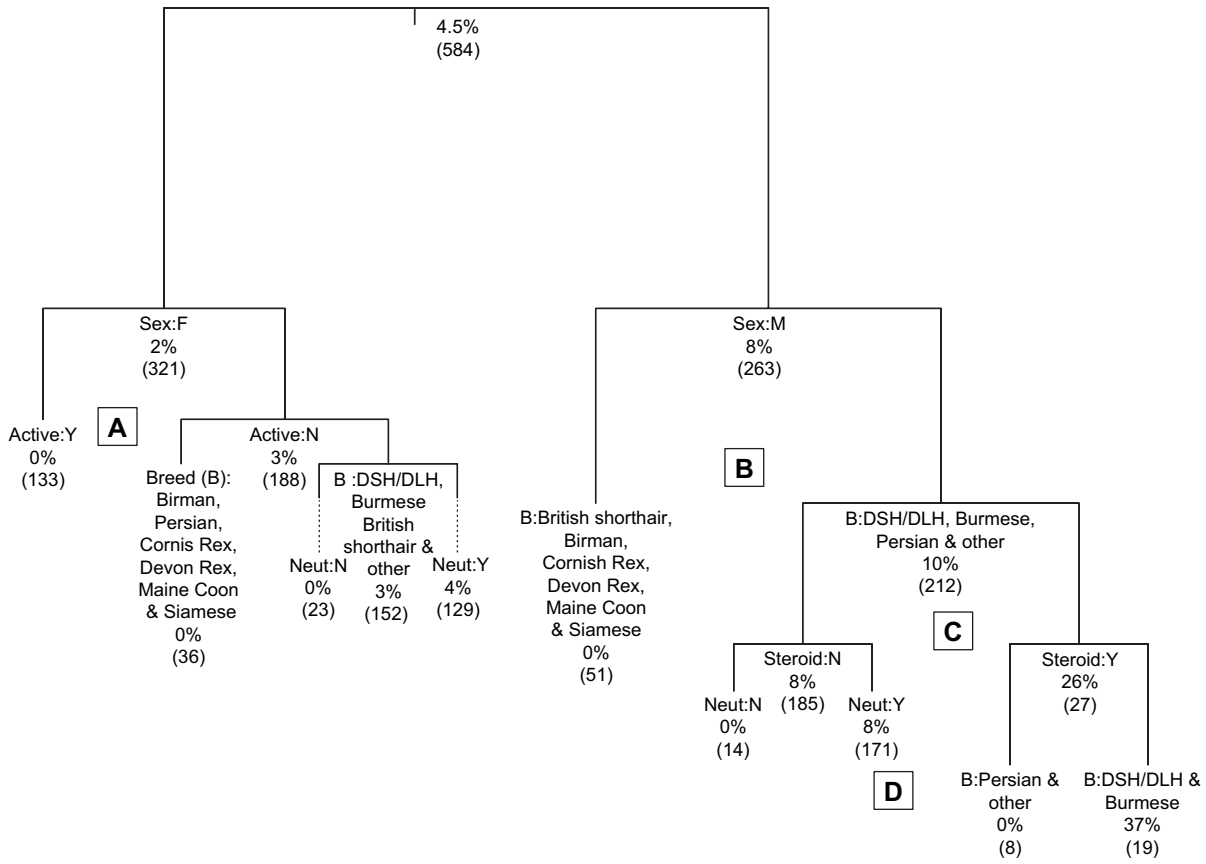

Fig 2. Tree diagram of the occurrence of DM for different combinations of risk factors. Data consist of the 584 questionnaires for which information on breed (B), sex, neutered status (Neut), activity level, and steroid usage. The percentage values at the end of each branch are the occurrence rates of DM in those particular cats with that particular combination of risk factors, and the values in brackets the number of cats of that particular combination of risk factors. (A−D) Please refer to the main text.

after neutering initially developed reduced insulin sensitivity but not glucose intolerance. In addition, insulin sensitivity returned to the same level as entire cats after 16 weeks. In the same study no reduction in insulin sensitivity occurred in neutered male cats. This suggests that neutering alone does not reduce insulin sensitivity. Therefore, it is the increased risk of obesity after neutering, rather than the neutering per se, which appears to be an important contributing factor to the increased occurrence of DM in the neutered cats in this study.

Advancing age has previously been identified as an important risk factor for the development of DM (Panciera et al 1990, Crenshaw and Peterson 1996, Rand et al 1997). However, because of the inaccuracy of owner's recollection on the onset of their cat's clinical signs it was not possible to obtain information about the age of onset of DM from this study.

The high degree of imbalance (missing combinations of factors) in the data meant that standard multivariate techniques to explore the interactions between factors were not appropriate. Therefore, a powerful yet relatively underutilised multivariate statistical technique was employed to consider the interactions between different potential risk factors in terms of DM prevalence: Classification tree-based models (Clark and Pregibon 1997). Such statistical models may appear complicated − but they merely show partitioning of data into groups based on combinations of parameters. The advantages of tree-based models are that they can deal with data imbalance, the order the factors are put into the model does not matter; and partitioning is objective − different factors can be considered important for different subsets of the data set. In addition, as Fig 2 demonstrates, the analysis is output in graphical form allowing easy comprehension of the grouping of occurrence rates in the data. If the data were more balanced then all the information presented in Fig 2 would be found by traditional statistical techniques; however, it is unlikely that such clear

graphical patterns would readily emerge from a series of statistical models of all the possible combinations in the database, with issues relating to the subjectivity in the choice of combinations. Therefore, we would encourage such tree-model based analyses to be used with other, potentially unwieldy databases.

The tree model showed that the importance of the putative risk factors in the questionnaire data can be ranked differently for male and female cats. However, the reason why breed may be more important in these male cats and activity in the female cats is uncertain and this ranking of potential risk factors between the sexes deserves further investigation. In humans physical inactivity has been shown to be an important risk factor for the development of type 2 DM by directly reducing insulin sensitivity with further decreases in insulin sensitivity occurring due to weight gain (LaMonte et al 2005). Despite obesity being proposed as a common interacting factor that may contribute to the increased risk of DM in many situations (eg, neutering, inactivity), and the univariate analyses indicating that increasing weight and weight $\geq$5 kg was an apparent risk factor in the questionnaire cat population, weight was not included in the final tree analysis due to its poor discriminatory value in terms of frequency of occurrence of DM. This either indicates that the importance of obesity has been over-emphasised or, more likely, that increasing weight in our study was not a good indicator of obesity.

The tree model also identified some potentially more subtle effects with higher DM occurrence in those corticosteroid treated male DSH/DLH, Burmese and British Shorthair cats compared to the untreated group. Increased fasting glucose levels and reduced clearance of an intravenous glucose load have been shown to occur in cats treated with either prednisolone or megestrol acetate (Middleton and Watson 1985, Peterson 1987). Polyphagia and obesity have also been reported as side effects of corticosteroid treatment (Behrend and Kemppainen 1997). Side effects of megestrol acetate treatment include increased appetite and lethargy (Henik et al 1985). These side effects, as well as direct drug effects on glucose homeostasis, may further contribute to the increased risk of DM in cats treated with steroids or megestrol acetate. However, in our study treatment with megestrol acetate was only a risk factor for the development of DM in male cats when these two factors were considered in isolation and did not emerge from the tree-model analysis. In this study, many of the female cats treated with megestrol acetate were breeding queens with the drug presumably being given intermittently for short periods to prevent oestrus. In male cats, the drug is most commonly used for behavioural modification, especially spraying behaviour, therefore long term use of the drug is more likely. It is suspected that length of treatment, and possibly the doses given, rather than gender determined the increased risk of DM in male cats treated with megestrol acetate although this hypothesis deserves further investigation.

The proportion of pedigree cats that were of Burmese breed in our questionnaire data (23.2%) is higher than reported for other populations (eg, 11.1% GCCF:www.gccf.org), this may be due to a long association between the FAB and the Burmese Cat Club (FAB 2006, wwwfabcat.org) and/or the concurrent publication of a case report of a Burmese cat with DM. However, the increased occurrence of DM in the Burmese cats in both this insured population and the convenience-based questionnaire study concurs with results previously reported in Australia (Rand et al 1997, Baral et al 2003). The cause of this increased prevalence is at present unknown. In New Zealand, a genetic predisposition to the development of DM in Burmese cats has been reported (Wade et al 1999) with some cats having more than 10% of their offspring developing DM. The mechanism of inheritance is unknown but is not thought to be sex linked and dominant inheritance was also thought to be unlikely. Lederer et al (2004) have investigated pancreatic histopathology and found that the only difference between diabetic Burmese and diabetic non-Burmese cats was a significantly lower frequency of pancreatitis in the Burmese cats.

Humans with central (abdominal) fat distribution are at greater risk of DM than those with peripheral fat distribution (Harris 1995). Burmese cats are solidly built individuals that typically have abdominal rather than inguinal fat (Rand et al 2004). However, no evaluation of fat distribution was made in the questionnaire, and therefore further evaluation of fat distribution in Burmese cats compared to non-Burmese cats would be useful in evaluating abdominal obesity as a contributing factor in the increased prevalence of DM in Burmese cats. Changes in fat distribution in diabetic cats treated with corticosteroids may also deserve further investigation as cats with both iatrogenic (Ferasin 2001) and naturally occurring (Watson and Herrtage 1998)

hyperadrenocorticism are reported to have increased abdominal fat.

In the Burmese questionnaire group there was no significant difference between the number of male and female cats that were affected by DM. This is again in agreement with the results from Australia, where male and female Burmese cats were equally likely to develop DM (Rand et al 1997, Lederer et al 2003). In contrast, there was a significant difference in the occurrence of DM in male compared to female DSH/DLH cats in the questionnaire study ($\chi^2_1 = 8.6$, $P = 0.003$). The reason for this difference between breeds is uncertain, however, in humans the prevalence of DM between males and females varies between ethnic populations (King and Rewers 1993) reflecting a genetic diversity of disease.

The reason for the negative correlation between DM and the number of cats in the household is uncertain. The questionnaire data were highly skewed in terms of cats per household with 40% of the 249 households having four or more cats. These larger households may be more likely to be breeding catteries, if so; they may contain predominantly female cats which are at reduced risk of developing DM compared to male cats. In addition, many breeders re-home older cats that are no longer breeding thereby reducing the average age of the cats in their household.

There were a number of limitations incurred by the use of a questionnaire-based study. The questions were designed around previous knowledge of the potential risk factors for the development of DM in cats (and humans) with type 2 DM. Most of the questions were designed to be broad based to enable completion by all of the owners. This may have incurred a degree of error resulting from subjectivity as is likely in any study of this type; for example, asking owner's to assess their cat's activity level. We also asked some questions that may have required a level of knowledge greater than that held by some pet cat owners, for example, kitten birth weight. Despite concerns these questions were included as it was felt that the information elicited could have advanced our understanding of the potential pathogenesis of DM in cats. Where many respondents were unable to provide replies to individual questions, these questions were then excluded from statistical analysis. Prospective studies with objective assessment of parameters would be necessary to reduce owner subjectivity and to gain more detailed replies. This would lead to the collection of more accurate information, for example, including objective assessment of body condition in addition to body weight.

Despite these limitations the questionnaire-based study has provided invaluable information about putative risk factors for the development of DM in cats in the UK and the tree-model analysis has highlighted the complex interactions of the risk factors indicating that future studies may need to take more account of the importance of combinations of risk factors, particularly based on the gender of the cat.

Conclusion

The prevalence of DM in this insured UK population of cats was 1 in 230, with Burmese cats at increased risk of developing DM (1 in 57). While the questionnaire analysis identified male gender, neutered status and inactivity as important putative risk factors for the development of DM, the male and female Burmese cats were at apparent equal risk. Additional potential risk factors for the development of DM not previously reported include corticosteroid treatment and, for male cats, treatment with megestrol acetate. The use of classification tree-based models has highlighted the fact that DM is a complex disease with multiple factors interacting to result in increased risk of disease. In addition, this model shows that the importance of the potential risk factors is different for male and female cats, with inactivity apparently important in females, and corticosteroid usage in males. Finally, this current work provides a framework for future prospective and stratified randomised studies where the importance of the putative risk factors outlined here can be considered.

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