

Standard Article

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Environmental Risk Factors for Diabetes Mellitus in Cats

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Background: Diabetes in cats resembles type 2 diabetes in people. The etiology is not fully understood, but both genetic and environmental factors are believed to contribute.

Objectives: To assess the associations of environmental risk factors with diabetes in cats.

Animals: Cats with a diagnosis of diabetes ($n = 396$) insured by a Swedish insurance company during years 2009–2013, and a control group ($n = 1,670$) matched on birth year.

Methods: A web-based questionnaire was used in a case–control study. An invitation to participate was sent to owners of 1,369 diabetic cats and 5,363 control cats. The survey contained questions related to the cat's breed, age, sex, neutering status, body condition, housing, access to the outdoors, activity level, diet, eating behavior, feeding routine, general health, stressful events, other pets in the household, medications, and vaccination status. Data were analyzed by multiple logistic regression.

Results: Response rate was 35% for the diabetic group and 32% for the control group. Indoor confinement, being a greedy eater, and being overweight were associated with an increased risk of diabetes. In cats assessed by owners as being normal weight, there was an association between eating predominantly dry food and an increased risk of diabetes (Odds ratio 3.8; 95% confidence intervals 1.3–11.2).

Conclusions and Clinical Importance: Dry food is commonly fed to cats worldwide. The association found between dry food and an increased risk of diabetes in cats assessed as normal weight by owners warrants further attention.

Key words: Case–control study; Dry food; Logistic regression; Type 2 diabetes.

Diabetes mellitus (DM) in cats has an incidence of 11.6 cases per 10,000 cat-years at risk.¹ Most cats suffer from a type of DM similar to type 2 diabetes (T2DM) in people, characterized by a relative deficiency of insulin secretion combined with insulin resistance, in contrast to the primary beta-cell deficiency of type 1 diabetes. Similarities between type 2 diabetes in cats and people include common risk factors, such as obesity, age, and physical inactivity, as well as similar pathophysiological findings, including deposition of amyloid in islets.^{2–6} Other risk factors associated with increased risk of DM in cats include male sex, neutering, indoor confinement, and treatment with certain drugs.^{1,3,6,7}

Obesity is a growing global health problem,⁸ also for many cats, which often spend their lives as indoor pets, are fed commercial diets, often in abundance, with

Abbreviations:

CI	confidence interval
DM	diabetes mellitus
HR	hazard ratio
OR	odds ratio
SD	standard deviation
T2DM	type 2 diabetes mellitus

overweight as a common consequence.⁹ Obesity, together with physical inactivity, are believed to be the main contributors to the insulin resistance associated with diabetes in both cats and people.⁵

There are many studies on environmental risk factors for T2DM in people, but studies on the cat population are scarcer.³ Better knowledge on predisposing factors for feline DM is important to identify individuals at risk at an earlier stage and subsequently have a better possibility to prevent development of disease. The main aim of this study was to investigate the associations between DM in cats and environmental risk factors. We have previously reported on demographic risk factors for DM in Swedish cats, using data from the same insurance register.¹

Materials and Methods**Study Population**

All cats insured in Agria Pet Insurance^a at any time point during 2009–2013 were eligible for inclusion in the study. DM cases ($n = 1,369$) were identified based on 4 diagnostic codes (DM, DM without complication, DM with complication, and DM with ketoacidosis). When an insurance claim is made, a diagnosis is assigned by the attending veterinarian, based on a standardized system with approximately 8,000 diagnostic codes.¹⁰ The control group ($n = 5,363$) was recruited from the same database and time period, and control cats were matched on birth year with the diabetic cats. An invitation to participate in the study including a

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web address to the questionnaire was sent out to all cat owners by mail. Owners were briefly informed in the invitation letter that an extra set of questions would be provided if their cat had at some time point been diagnosed with diabetes.

Questionnaire

The web-based questionnaire (in Swedish) was available during a 4-month period through an online survey provider^b, and contained 48 questions. Questions included information about the age and sex of the respondent, number of adults in the household, the presence of children (<18 years) in the household, and the habitat, as well as questions on the cat's birth year, breed, sex, and neutering status. Owners were asked if their cat was still alive, and if it was not, the cause and year of death. A positive answer to the question "Has your cat ever been diagnosed with diabetes?" was used to verify case status. All questions on potential environmental risk factors referred to the year preceding a diagnosis of DM, or to the last year of the cat's life for controls. Owners were asked about the cat's general health, treatment with progestins or corticosteroids, vaccination status, type of diet, feeding regime, eating behavior, body condition, number of cats in the household, presence of other animals in the household, possibly major stressful events, activity level, and about indoor confinement or whether the cat had access to the outdoors. Respondents were given several answering options per question, including the alternative "I wish not to answer this question/I do not know," as well as space for free-text answers. For example, the question about the cat's eating behavior offered 5 different answering options: (1) greedy (finishes meals immediately); (2) finishes meals within hours; (3) nibbles several times daily; (4) picky (leaves food often); and (5) Other/I do not know. Answers were mandatory to proceed through the survey, and most often with only one possible answer. It was possible for respondents to return to previous questions and change their answers. Depending on the answer, some questions led the respondents to a set of extra questions. Questions on type of diet and medications allowed several answers. For diet, owners were asked to give only one answer if the cat's diet consisted mainly of 1 type of food ($\geq 75\%$), and 2 answers if the cat ate approximately 50% of each type of food. It was not possible to give more than 2 answers to this question. Medications asked for were previous use of progestins and corticosteroids.

Data Analysis

All answers from the questionnaire were thoroughly scrutinized, and all uncompleted answers were excluded. In case of conflicting answers (ie, birth year after time of death), contact with the respondent was made if possible, and answers were then corrected or excluded. All free-text answers were reviewed, and replies were corrected in case of obvious misinterpretation of the question (eg, a change of breed category to "domestic" if the owner stated that the cat was in fact a mix between 2 breeds). Purebred cats with <20 individuals within the breed were grouped as "other purebreds."

The cat's age at the time of the risk factor analysis was calculated from available information on birth year, and year of diagnosis of DM for the cases, and year of death, or time when answering the questionnaire for the controls.

Answers on type of diet were grouped according to following categories: "dry" if $\geq 75\%$ dry food, "mixed" if approximately 50% dry and wet food, and "wet" if $\geq 75\%$ wet food. Wet food included all types of canned food, raw and homemade diets (excluding table scraps), and mice and other prey.

Respondents estimated their cat's body condition with a 5-grade scale with illustrations and accompanying instructions.¹¹ Answers

were then grouped, with estimated body condition scores of 1–2 to "underweight," 3 to "normal weight," and 4–5 to "overweight."

Answering options to the question about indoor confinement versus access to the outdoors were as follows: strictly indoors, partly outdoors (indoor cats allowed access to enclosed outdoor space or leash walks, or access to being outdoors parts of the year), and outdoors (cats that can choose between indoors and outdoors, or strictly outdoors cats).

Univariable logistic regression was used to assess associations between a diagnosis of DM and all explanatory variables included in the questionnaire. Potential 2-way interactions were also to be assessed between all variables, but the answering option "I wish not to answer this question/I do not know" rendered very few replies per question, and made analysis of interactions impossible because there were too few respondents for all possible combinations of answers. Rather than excluding these answers as missing values, we decided to impute them if used by <2% of respondents, to the most commonly used answering alternative. Univariable analysis were then rerun on the imputed dataset, and variables and 2-way interactions were included in a multiple logistic regression model if $P < .15$. A backwards elimination approach with stepwise removal of nonsignificant interactions and main effects was then applied to the multiple logistic regression analysis, based on a lowered Akaike information criterion (AIC). Odds ratios (OR) were calculated with 95% confidence intervals (CI). The significance level was set at 5%.

Age at time of risk factor analysis was calculated as mean age \pm standard deviation (SD). Comparisons between groups were performed with an unpaired *t*-test for mean age in cases and controls, and a chi-square test for the proportions of cats alive in cases and controls at the time their owners took part in the survey. To investigate the extent of influence on the results of the difference in age span between the case and the control group found in the study (see 2nd paragraph results), we also created a smaller, age-span matched dataset used for sensitivity analysis. Controls were selected 1 : 1 randomly matched to the cases based on the cat's age at the time of the risk factor analysis (resulting in a smaller dataset, and 1 : 1, as opposed to 1 : n, matching was selected because of nonavailability of controls in some age-span strata). We tested the identified final model from the large dataset on this smaller dataset, using standard logistic regression analysis, and 2 conditional logistic regression analyses on both pair- and frequency-matched data (with each cat pair as strata and cat age in years as strata, respectively). Odds and hazard ratios (HR) were calculated with 95% CI. Data handling was performed by SAS (version 9.4).^c

Results

A total of 2,212 questionnaires were received, of which 2,175 were complete (484 diabetic cats, 1,691 controls). Response rate was 35% for the diabetic group and 32% for the control group. Median time to complete the survey was 12 minutes. Four cats were excluded from the study caused by conflicting answers. Twenty cats were excluded because the birth year was outside the selected range, and 85 cats were excluded because the year of a DM diagnosis was outside the study period. Questionnaires with data on 2,066 cats thus remained for analysis; 396 with DM and 1,670 controls. Cat owner characteristics did not differ between groups. Respondents comprised 84% females and 16% males. About half of the respondents (48%) lived in towns (200–200,000 inhabitants), 27% lived in larger cities and 26% in the countryside. Seventy-eight

percent of the cats lived in a household without children and 26% of the cats lived in a single-person household.

Most cats were domestic cats (81%), and 19% were purebreds. Fifty-six percent were males and 44% were females. There were 0.2% intact males, and 1.6% intact females, leaving 98% of cats neutered. Mean age at time of the risk factor analysis differed between cases (10.9 ± 3.1 years) and controls (13.9 ± 3.1 years) ($P < .0001$), because cats were matched on birth year, and owners of diabetic cats were asked about the time preceding diagnosis which in general was earlier than for the control cats, who replied from the last year of the cat's life. (In the smaller age-matched dataset [$n = 730$], mean age was 11.4 ± 2.7 years for both cases and controls.) Of the diabetic cats, 32% were alive at the time their owners took part in the survey. On the other hand, of the control cats, 59% were alive ($P < .0001$). Descriptive statistics are shown in Table 1.

In the univariable analysis, several of the variables were associated with a diagnosis of DM. Burmese and Norwegian forest cats had a higher risk of DM, whereas Birman and Persian cats had a lower risk of DM compared with domestic cats. Living in a rural environment, being female, having access to the outdoors, being underweight, living with a dog in the household, and being fed ad libitum were all factors associated with a reduced risk of DM. Being male, previous treatment with corticosteroid injections, eating predominantly dry food, being vaccinated, having a greedy eating behavior, being overweight, living with no other animal species, and living indoors were all factors associated with an increased risk of DM. The number of cats eating dry food, wet food, and mixed food was 779, 203, and 1,084, respectively. Cats were judged as being greedy eaters ($n = 334$), finishing meals within hours ($n = 203$), nibbling food

several times daily ($n = 1,379$), or being picky ($n = 150$).

In the multiple logistic regression, breed, sex, vaccination status, corticosteroid injections, eating behavior, and households with no other pets than cats remained associated with an increased risk of DM. The interactions between type of diet and body condition score, and between activity level and indoor confinement or access to the outdoors also remained in the final model. Overweight cats had an increased risk of DM compared with cats with a normal body condition for all available types of diet. On the other hand, when comparing cats with a normal body condition as assessed by owners, there was an increased risk of DM for cats eating predominantly dry food compared with wet food (OR 3.8; 95% CI 1.3–11.2). Similarly, the interaction between activity level and indoor confinement versus outdoor access resulted in separate interpretations for each group. For both moderately active and inactive cats, indoor confinement was associated with an increased risk of DM. For the inactive cats, partly outdoor access was associated with a reduced risk of DM compared with being strictly indoors. If cats were active, there were no differences in risk of DM with respect to indoor versus outdoor access. Odds ratios for DM for the different main effects and interactions are shown in Figures 1–4.

For the smaller dataset in the sensitivity analyses, 365 cats in the case group were paired with 365 cats in the control group (total $n = 730$). The standard logistic regression, and the conditional logistic regression analyses on pair-matched and frequency-matched data showed that no single variable significantly associated

Table 1. General information of diabetic cats ($n = 396$) and control cats ($n = 1,670$) with regard to breed, age, sex, neutering status, and whether the cat was dead or alive.

	Cases ($n = 396$)	Controls ($n = 1,670$)	All ($n = 2,066$)
Breed (n)			
Birman	4 (1%)	70 (4%)	74 (4%)
Burmese	16 (4%)	14 (1%)	30 (1%)
Domestic cats	308 (78%)	1,364 (82%)	1,642 (81%)
Maine coon	3 (1%)	20 (1%)	23 (1%)
Norwegian forest cat	29 (7%)	61 (4%)	90 (4%)
Other purebreds	30 (8%)	95 (6%)	125 (6%)
Persian	6 (2%)	46 (3%)	52 (3%)
Age (years)			
Mean (SD)	10.9 (± 3.1)	13.9 (± 3.1)	13.3 (± 3.3)
Sex (n)			
Male	278 (70%)	872 (52%)	1,150 (56%)
Neutering status (n)			
Neutered	393 (99%)	1,638 (98%)	2,031 (98%)
Dead or alive (n)			
Dead	268 (68%)	688 (41%)	956 (46%)

SD, standard deviation.

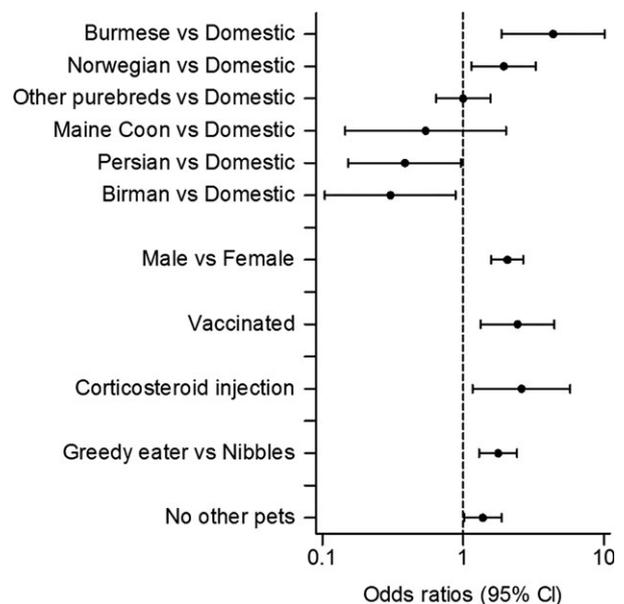


Fig 1. Odds ratios for diabetes mellitus (cases $n = 396$, controls $n = 1,670$) from the multiple logistic regression analysis depending on breed, sex, vaccination status, corticosteroid injections, eating behavior, and only cats as pets in a household. Error bars represent 95% confidence intervals (CI).

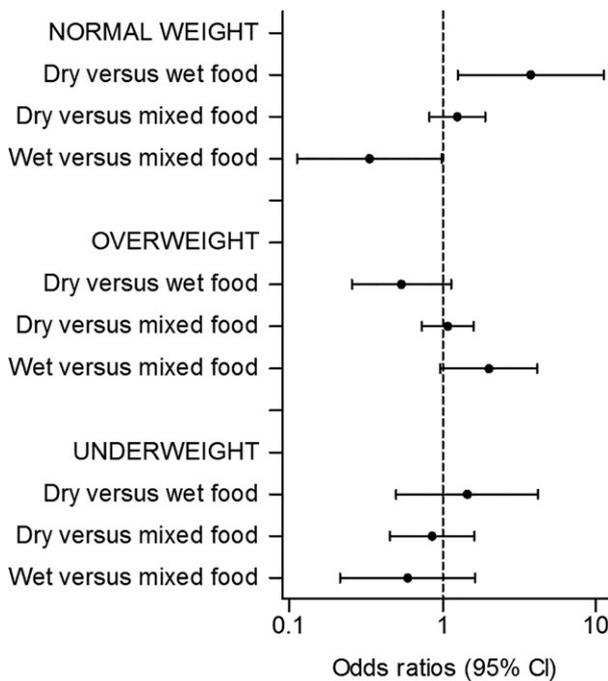


Fig 2. Odds ratios for diabetes mellitus (cases n = 396, controls n = 1,670) from the multiple logistic regression analysis for the interaction between diet and body condition. Comparisons within each body condition group. Error bars represent 95% confidence intervals (CI).

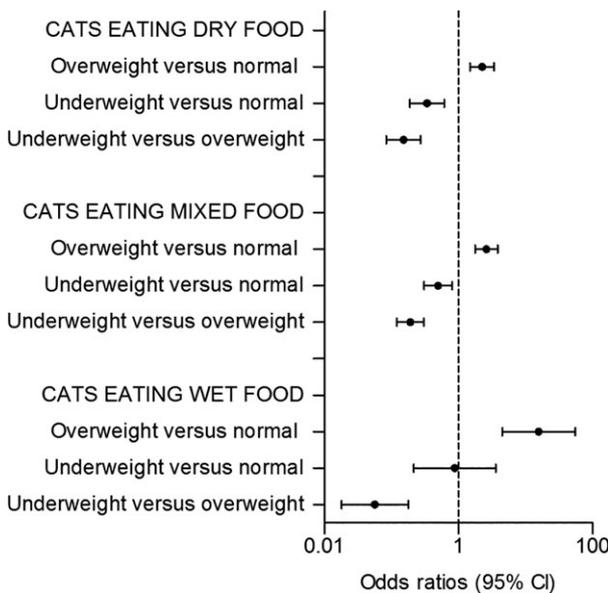


Fig 3. Odds ratios for diabetes mellitus (cases n = 396, controls n = 1,670) from the multiple logistic regression analysis for the interaction between diet and body condition. Comparisons within each diet group. Error bars represent 95% confidence intervals (CI).

with DM in the full model, changed from being a risk factor associated with disease to become a protective factor (associated with a decreased risk of DM), or vice versa, in the smaller data-set (see Table S1).

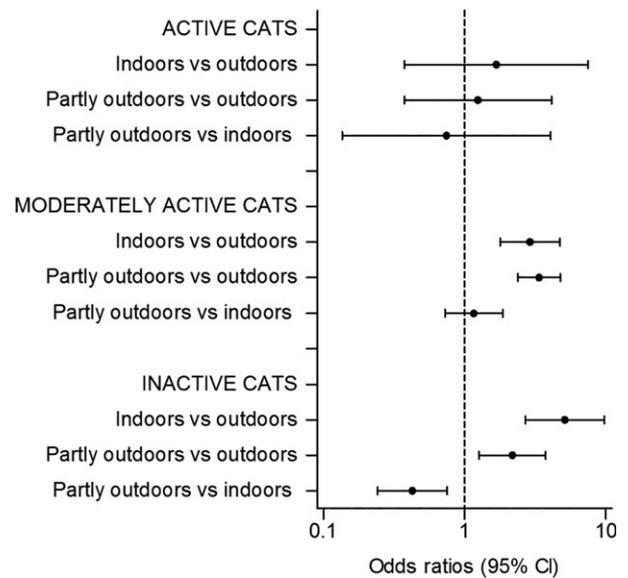


Fig 4. Odds ratios for diabetes mellitus (cases n = 396, controls n = 1,670) from the multiple logistic regression analysis for the interaction between activity level and indoor confinement or access to the outdoors. Error bars represent 95% confidence intervals (CI).

Discussion

To our knowledge, this survey is the largest case-control study on diabetic cats until now. Both new and known risk factors were shown to be associated with an increased or decreased risk of DM. We found an association between dry food and an increased risk of DM in cats in a normal body condition as assessed by owners. Indoor confinement, being a greedy eater, and being overweight were also associated with an increased risk of DM.

The association of DM risk with dry food diet in normal weight cats is to our knowledge previously not reported, and it has earlier been proposed that the proportion of dry food in the diet might not be a risk factor for DM.³ However, because cats are obligate carnivores, whose natural diet consists mainly of protein-rich animal prey, it has been hypothesized that a high-carbohydrate diet such as commercial dry food might put an increased demand on the cat's insulin secretion, thereby predisposing them to the development of DM.⁵ Further, cats lack several enzymes involved in carbohydrate metabolism, such as salivary amylase, and have low activities of intestinal amylase and disaccharidases, indicating that they are not adapted to using carbohydrates as an energy source.¹² For diabetic cats, the benefits of low-carbohydrate diets in the management of disease have been established,¹³⁻¹⁵ but the potential role in disease development has not been shown. Diets rich in carbohydrates lead to higher postprandial glucose and insulin concentrations in healthy cats.¹⁶ Chronic hyperglycemia and the subsequent hyperinsulinemia are associated with a prolonged and increased demand on the pancreatic β -cells, which together with the deleterious effects of glucose toxicity are believed to

be a major cause of beta-cell failure seen in the pathogenesis of DM in cats.¹⁷ In particular, if fed long-term, high-carbohydrate diets could therefore potentially lead to DM in susceptible cats, that is, cats with an underlying low insulin sensitivity.⁵ It can be hypothesized that normal weight cats developing diabetes could represent a group of cats with a higher susceptibility for DM, as they develop disease despite not being overweight. The interaction present between body condition and diet in our data enabled us to detect a difference between diets in the normal weight cats. Our results should be interpreted with caution, as the macronutrient content in food given to cats in our study is unknown, although a typical commercial dry diet generally contains more carbohydrates than a typical wet diet.¹⁸ It is also possible that the difference between dry and wet food detected in our study might relate to a protein effect rather than a carbohydrate effect, as it is not possible to alter one macronutrient without another.¹⁹

In our study, an effect of type of diet was found only in cats with a normal body condition, suggesting that for overweight cats, the risk of the obesity per se is more important than the type of diet. Being overweight has previously been reported as one of the most important risk factors for DM in both cats and people,^{4,8,9} and this is supported by our results. We showed that for overweight cats, there was an increased risk of DM when compared to cats in a normal body condition, and the type of diet did not affect these results. It has previously been shown that owners tend to underestimate the body condition of their pet, especially if the pet is overweight, which is a limitation of our study and might have led to underestimation of the measured effect.^{20–22} Moreover, possibly diabetic cat owners have gained more knowledge about their cat's body condition and about the risks with obesity, which could influence the answers. Furthermore, it is possible that some diabetic cats might have lost weight before diagnosis, which also could have led to an assessment of normal weight by the owners.

Being described as a greedy eater was associated with DM in cats in our study and is a new finding although it was previously mentioned to possibly be associated with an increased risk of DM in Burmese cats.²³ Eating quickly is a possible risk factor for DM in people,²⁴ and so-called emotional eating was associated with adverse outcomes in human patients with diabetes.²⁵ In people, eating slowly is associated with a lower caloric intake and enhanced satiety,²⁶ but this has to our knowledge not been evaluated in cats. Nevertheless, the finding that being greedy is associated with DM in cats is interesting and needs future consideration. It is unclear whether being greedy is associated with preferences for some types of food, or whether it is otherwise associated with an increased DM risk. It might also to some extent reflect a polyphagic state often seen in diabetic cats before diagnosis.

Indoor confinement has previously been described as a risk factor for DM in cats.³ Our study supports this finding and also found an interaction with the cats' reported activity level. For cats reported to be active,

we were not able to differentiate DM risks based on access to the outdoors or not. On the other hand, for cats reported as moderately active or inactive, indoor confinement was a risk factor. Limited outdoor access did not lower the risk of DM for active and moderately active cats, but for inactive cats, it was protective compared with strict indoor confinement. This indicates that more regular access to the outdoors, allowing the cat to roam freely, is protective against DM for most cats, but for the inactive cats, being partly outdoor might help lowering the risk of DM. Probably, muscle activity in cats allowed free access to the outdoors contributes to lowering the insulin resistance, similarly to what has been shown in people, where regular physical activity increases insulin sensitivity.²⁷ Physical inactivity in people increases the risk of T2DM both directly and indirectly, by lowering insulin sensitivity and also by increasing the risk of obesity.²⁸

There was a significant association between previous corticosteroid injections and the risk of developing DM. A recall bias among owners of diabetic cats can contribute to this finding. However, others have also found evidence for this association,^{3,23} and it has been shown in people that corticosteroids do decrease insulin sensitivity²⁹ and can cause hyperglycemia.³⁰ Administering corticosteroids to cats at risk of developing DM should be done cautiously, especially to middle-aged, overweight cats, where other factors causing insulin resistance are likely to be present.

The associations between demographic risk factors and DM were identified by our group previously using the same database, and similar findings were present also in this study.¹ Male cats were twice as likely to develop DM compared with females, and Burmese cats and Norwegian forest cats were identified as risk breeds. Almost all cats in this study were neutered and therefore, assessing whether neutering status was a risk factor for DM was not possible. An association between neutering and DM has been identified before,⁶ but it is not clear whether the neutering itself causes insulin resistance or whether it indirectly influences the risk of DM by increasing the risk of obesity. Neutering increases the risk of obesity in cats, probably because of both an increase in food intake and a decrease in the metabolic rate.^{31–33}

An association with an increased risk of DM was seen in fully vaccinated cats compared with unvaccinated cats, but the proportion of unvaccinated cats in the study population was low (7%). There are no supporting evidence that vaccines cause DM in cats, and the association detected in our study should not be interpreted to support a decision not to routinely vaccinate cats. The finding can be explained by diabetic cats having had more visits to a veterinarian than control cats, and can also refer to a recall bias because owners of diabetic cats could be more aware of their cat's health and vaccination status than owners of healthy cats.

Limitations of our study are mainly related to the study design, especially the problems with dietary recall bias and the difficulties for owners to accurately assess their cat's body condition. Owners of diabetic cats can

be more prone to remember events preceding the cat's diagnosis of DM because of a recall bias, causing a type I error. They can also have more knowledge about DM and be more aware of the risk factors for disease, which might influence their responses. For example, owners of diabetic cats are more likely to be aware of their cat's body condition, and also of the dangers of obesity. Moreover, owners of diabetic cats are asked about circumstances the year preceding their pet's diagnosis of DM, which can be several years back in time. This differs from the control group, whose replies refer to the last year in the cat's life, in general more recently. This also led to the fact that the age distribution differed between groups in a way we did not fully anticipate. To confirm our results, we performed a sensitivity analysis on a smaller subset of our data, where cases and controls were matched directly on age at the time of the risk factor analysis. Similar results were obtained in all these analyses although the substantially smaller number of included cats led to a failure to find significant associations for all variables significant in the larger dataset. We concluded that the results from the full dataset are valid despite the difference in age between cases and controls.

In conclusion, our study identified several novel potential risk factors and confirmed several previously reported factors associated with an increased, or decreased, risk of developing DM. The association between types of diet for cats with a normal body condition score, where dry food was associated with an increased risk of DM compared with wet food in normal weight cats, was a new finding which warrants further investigation, as dry food is a common food type fed cats worldwide. Access to being outdoors was also protective against DM and should be considered in light of the shift from a former mainly outdoors to today's indoor confinement of domestic cats; a change in lifestyle that has occurred during the last decades.

Footnotes

^a Agria Pet Insurance, Stockholm, Sweden

^b Netigate®, Stockholm, Sweden

^c SAS Institute Inc., Cary, NC

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Off-label Antimicrobial Declaration: Authors declare no off-label use of antimicrobials.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Table S1. Results from the full model (n = 2,066) compared to the results from the sensitivity analyses (n = 730).