Title: An epidemiological study of diabetes mellitus in dogs attending first opinion practice in the UK

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Abstract

Objectives: To estimate the prevalence of canine diabetes mellitus (DM) in primary-care clinics in England, to identify risk factors associated with DM and to describe the survival of affected dogs.

Methods: Cases of DM were identified within the electronic patient records of 89 small-animal practices. A nested case-control study identified risk factors for the diagnosis of DM using logistic regression models. Cox proportional hazards models were used to analyse variables associated with survival.

Results: Four-hundred and thirty-nine canine DM cases were identified, giving an apparent prevalence of 0.34% (95% confidence interval 0.31 - 0.37%). Neutered males were at an increased risk of diabetes compared to entire males, whereas neutering was not associated with DM in females. Compared with crossbred dogs, Yorkshire terriers had increased odds, whereas German shepherd dogs and golden retrievers had lower odds of DM. Being classified as overweight and having a diagnosis of pancreatitis, hyperadrenocorticism or a urinary tract infection were positively associated with DM. Older dogs and those diagnosed with pancreatitis had a higher hazard of death, whereas insured and neutered dogs had a lower hazard.

Clinical significance: This study provides an objective assessment of canine DM using primary-care veterinary practice data and is a valuable benchmark against which future epidemiological trends in DM can be assessed and improvements in the management of DM in primary-care practice can be judged.

Introduction

Canine diabetes mellitus (DM) is a complex endocrinopathy that develops as a result of the interplay between environmental and genetic factors. Although the pathogenesis of the disease varies between individuals, similar clinical signs, including polyuria, polydipsia and weight loss, are commonly reported irrespective of the underlying aetiology (Catchpole and others 2013). New management strategies and therapies for canine DM are currently being developed (Wiedmeyer and DeClue 2011; Niessen and others 2012; Hess and Drobatz 2013), which may alter the outcome of affected animals and subsequently impact on the future epidemiology of the disease. Human type 1 DM, a disease with an autoimmune aetiology (Bluestone and others 2010), shares some characteristics with canine DM (Catchpole and others 2008), which may be influenced by environmental factors shared by both species. It is possible that an increasing incidence of human type 1 DM (Tuomilehto 2013) may be mirrored in the canine population. Recording baseline epidemiological data, such as prevalence and median survival times, provides a useful benchmark for observing future trends over time and for evaluating the impact of novel interventions or changes in underlying risk factors.

Prevalence estimates of canine DM from referral practice and insurance database populations range between 0.32% and 1.33% (Guptill and others 2003; Fracassi and others 2004; Davison and others 2005). The current prevalence within primary practice caseloads in the UK may differ from these existing estimates.

Factors associated with diagnosis of the disease include signalment. DM is generally diagnosed in dogs between 5 and 12 years old (Guptill and others 2003; Davison and others 2005; Fall and others 2007), although rare cases of familial DM in juvenile dogs have been reported (Kramer 1981; Davison and others 2005). Females were at a greater risk of DM in some studies (Foster 1975; Doxey and others 1985; Guptill and others 2003; Fall and others 2007), although this finding was not observed in a UK study (Davison and others 2005). Geographical or temporal variation in neutering practices may influence the sex pre-dispositions within a population, although associations identified between neutering and DM diagnosis have varied between studies. Doxey and others (1985) observed significantly more entire females in the diabetic population compared with the general dog population attending a veterinary hospital. However, Guptill and others (2003) reported that, although females were overall at increased risk of DM compared with males, there was no significant difference in risk between neutered and entire females. Conversely, neutered males had higher odds of DM than entire males (Guptill and others 2003).

Epidemiological studies have identified breed differences in the susceptibility to DM (Foster 1975; Doxey and others 1985; Hess and others 2000a; Guptill and others 2003; Fracassi and others 2004; Catchpole and others 2005; Fall and others 2007), suggesting a genetic component to this complex disease (Catchpole and others 2005). Samoyed and poodles are frequently reported to be predisposed breeds (Doxey and others 1985; Hess and others 2000a; Guptill and others 2003; Fracassi and others 2004; Catchpole and others 2005; Fall and others 2007), whereas German shepherd dogs and boxers are suggested to have a decreased risk of DM (Guptill and others 2003; Fracassi and others 2004; Catchpole and others 2005).

Co-morbidities with canine DM are frequent (Hess and others 2000b; Davison and others 2005; Hume and others 2006); some of which may contribute to the development of the disease. Destruction of insulin-secreting pancreatic beta cells due to immune-mediated disease or exocrine pancreatic disease may be part of the pathogenesis of canine DM in some cases (Watson and others, 2007). Insulin antagonism as a result of pathological (endocrine or iatrogenic) or physiological (gestation or dioestrus) processes is also thought to be a component of the development of the disorder (Watson and others 2007; Catchpole and others 2008; Fall and others 2010). Dogs are thought to be resistant to disease comparable to type-2 diabetes in humans (Verkest and others 2011). However, reversible insulin resistance and greater postprandial blood glucose concentrations were associated with canine obesity (German and others 2009; Verkest and others 2012). Two small studies reported an association between excess weight and canine DM (Klinkenberg and others 2006; Wejdmark and others 2011) but they should be viewed with some caution because body condition score was owner-perceived and recorded after DM diagnosis.

A winter peak in the diagnosis of both canine diabetes and human type-1 DM has been reported (Davison and others 2005; Moltchanova and others 2009), although other studies found no seasonal incidence of canine DM (Guptill and others 2003; Fall and others 2007).

There are limited published survival data for canine DM. In a population of dogs treated for diabetic ketoacidosis (DKA) at a university hospital, 70% survived to discharge (Hume and others 2006). In a study of insured dogs in Sweden, the median survival time was 57 days after the first insurance claim, with significant differences in survival time between breeds (Fall and others 2007). Seventy per cent of diabetic dogs referred to a UK veterinary school between 1979 and 1983 were successfully stabilised on insulin; 64% of stabilised dogs survived for more than 1 year (Doxey and others 1985).

There are wide variations in study populations, methodology and analysis in the literature concerning the epidemiology of canine DM. Pet insurance or referral populations may be subject to selection bias (Egenvall and others 2009; Bartlett and others 2010). Moreover, the generalisability of studies conducted at other times or geographical locations may be limited; varying genetic pools or environmental influences may result in differing predispositions between countries. On-going analyses of large-scale primary practice data using electronic patient records (EPRs) would improve understanding of the epidemiology of DM in dogs.

The aims of the current study were to evaluate DM prevalence, risk factors for diagnosis and survival in dogs attending primary-care clinics in England.

Materials and methods

Electronic patient record data were uploaded from veterinary clinics in England, between August 2009 and June 2012, as part of the Veterinary Companion Animal Surveillance System project (VetCompass 2012). Veterinary surgeons coded clinical diagnoses at the time of consultation, by selecting appropriate summary terms from a standardised list of VeNom codes (Venom Coding Group 2012). In addition, routinely collected demographic data, clinical notes and details of prescribed treatments were

available for analysis. Data were available for all dogs attending the participating clinics during the study period.

Sample size calculations estimated that approximately 200 cases and 400 non-diabetic controls would be required to detect an odds ratio (OR) of two, for a variable to which 10% of controls were exposed in an unmatched case control study (95% significance level, 80% power, case-control ratio 1:2) (Epi Info 7 2012). Ethics approval was provided by the Royal Veterinary College's Ethics and Welfare Committee (URN 2010 1076C).

To identify diabetic cases, the VetCompass database was searched for dogs with coded summary diagnoses of "diabetes mellitus" or "diabetic ketoacidosis". Treatment notes were searched for generic and brand names of insulin and oral hypoglycaemic agents. Clinical notes were searched for "diab*", "insul*, "hypergl*" and "glucosu*" to allow for spelling errors. Further searches for "DM" or "ketones" together with "PTS" or "euth" were performed. Animal identification numbers from each search method were aggregated and duplicate records were removed. The case definition required at least one of the following criteria: a definitive veterinary diagnosis of DM documented in the clinical notes, summary diagnosis or insurance claims, prescribed insulin treatment or documented glucosuria and ketonuria (≥2+ on urine dipstick). Dogs with a tentative or differential summary diagnosis of DM but not otherwise satisfying the above case definition, and dogs receiving insulin to treat hyperkalaemia were excluded.

Prevalence estimate

Both pre-existing cases (diagnosed with DM before data collection began) and incident cases (newly diagnosed with DM during the data collection period) were included in the prevalence estimate. This was calculated by dividing the number of DM cases by the total number of dogs attending participating clinics during the study period. Standard methods were used to calculate the 95% confidence intervals (95% CI) to indicate the precision of the estimate (Kirkwood and Sterne 2003).

Case-control study

A nested case-control study was used to identify risk factors for DM diagnosis by comparing the characteristics of the incident DM cases to a sample of non-diabetic control dogs. Cases were categorised into four groups based on last recorded age (3.0 - <8.0 years, 8.0 - <11.0 years, 11.0 - <13.0 years and ≥13.0 years) and were frequency matched by age to controls at a 1:2 case-control ratio. A random sequence generator (Random.org) was used to select the controls for each age group within the population of non-diabetic dogs attending participating practices. The demographic data available for each dog included clinic ID, date of birth, VeNom breed term (Venom Coding Group 2012), sex, neuter status, bodyweight and insurance status. Dog breeds were further classified as purebred or crossbred and whether the breed was recognised by the UK Kennel Club (Kennel Club 2012). Breeds with greater than ten dogs were evaluated individually, whereas less popular breeds were combined as a 'Purebred others' category. Maximum weights for each animal were calculated from all recorded bodyweight entries and additionally categorised. The date of DM diagnosis was defined as the date the first confirmatory diagnostic sample was taken

and further grouped into month and season of diagnosis. To assess the seasonality of DM diagnosis, the month and season of the first recorded consultation for controls was used as a comparison group to account for any seasonal variation in veterinary consultations. Neuter status at DM diagnosis was determined for cases and the most recent neuter status was extracted for controls. A four-category sex-neuter variable was created which, included "neutered" and "entire" categories for both sexes. Clinical notes and treatment details were reviewed to determine whether a dog was diagnosed with the following co-morbidities or presenting signs at any time during data collection: hyperadrenocorticism, hypothyroidism, pancreatitis, exocrine pancreatic insufficiency, being overweight, haematuria and urinary tract infection. Dogs without these observations recorded were assumed to not have these disorders or abnormalities. Data were checked and cleaned in a spreadsheet (Microsoft Office Excel 2007, Microsoft Corp.) and exported to Stata 12.1 for further analysis (Stata Corp.).

Descriptive statistics were generated for the incident cases and non-diabetic control dogs to characterise the study population. Univariable logistic regression models were used to evaluate associations between each individual explanatory variable (potential risk factor) and being diagnosed with DM. Multivariable logistic regression models were used to identify demographic variables that had a statistically significant association (P-value ≤ 0.05) with DM after accounting for any confounding effects of other measured factors. Pairwise interactions between final model variables were assessed. Age was forced into the model to account for the frequency matching in the sampling strategy. "Clinic ID" was included as a random effect to assess for clustering at the practice level (Dohoo and others 2009). Co-morbidities and presenting signs were individually added to the multivariable logistic regression model to measure the associations of these variables with DM after adjusted for potential confounding effects of the other variables. Model fit was assessed with the Hosmer-Lemeshow test (Hosmer and Lemeshow 2000). Breed and the effect of sex and neuter status were of *a-priori* interest.

Survival analysis

For the survival analysis, the censoring status of incident DM cases was determined on the date of death (uncensored, all-cause mortality), the date that animals left the participating clinic (censored) or the last date of the study period (censored). The median survival time was defined as the time following DM diagnosis when the cumulative proportion of dogs surviving fell to 50% (Jager and others 2008). Clinic ID, breed, maximum bodyweight, sex, neuter status, insurance status and season of diagnosis were recorded as for the case-control study. The age at DM diagnosis was extracted and categorised into three groups (3.0 - <10.0 years, 10.0 - <12.0 years and $\geq$12.0 years) and dogs were classified as overweight for the survival analysis if this was noted on or before the date of DM diagnosis. When available, the presence of ketonuria and pancreatitis up to 7 days before or after DM diagnosis was recorded. Treatment records were examined for oral or parenteral corticosteroids or progestagens administered within 6 weeks preceding DM diagnosis. A time restriction was not applied to dogs with hyperadrenocorticism, as the date of diagnosis may be less likely to reflect onset of the disease; to avoid false positive results due to the physiological stress response to diabetes (Gilor and Graves 2011), adrenal function tests may be delayed in unstable diabetic patients.

Univariable and multivariable Cox regression models were used to assess whether each explanatory variable was associated with survival in diabetic dogs; both individually and after adjusting for the confounding effects of other variables respectively. Hazard ratios (HR) indicate whether the "hazard of death" is increased or decreased in dogs within different categories in a variable. Statistical significance was set at the 5% level. Evaluation of confounding and interaction were performed as for logistic regression. Including "clinic ID" as a frailty term assessed for clustering at the practice level. The proportional hazards assumption (that the HR is constant over time) was checked by statistical assessment using Schoenfeld residuals and graphical assessment of log cumulative hazard and Kaplan-Meier Cox plots (Dohoo and others 2009).

Results

Descriptive statistics and prevalence estimate

Data were available from 128,210 dogs attending 89 primary practice clinics, located mostly in central and south-east England. Four hundred and thirty-nine dogs diagnosed with DM were identified within the EPRs, giving an apparent prevalence of 0.34% (95%CI: 0.31-0.37%). Two hundred and nine diabetic dogs (47.6%) were incident cases (newly diagnosed with DM during the data collection period). Further analyses relate only to the incident cases. The median age of onset of DM was 9.9 years (range 3.3 – 17.4 years). There were 105 female and 104 male diabetic patients, of which 68 (64.8%) and 81 (77.9%) respectively were neutered at the time of DM diagnosis. A slightly higher proportion of female controls (68.5%) and a lower proportion of male controls (58.3%) were neutered compared to the diabetic patients. Most diabetic patients (70.4%) had a maximum weight of less than 20kg during the study period and 83.2% were purebred dogs. Twenty-four diabetic dogs (11.5%) were diagnosed with pancreatitis, two-thirds of which were diagnosed with DM and pancreatitis concurrently. Eighteen (8.6%) diabetic dogs were diagnosed with hyperadrenocorticism, either prior to or during the study period. No dogs were diagnosed with exocrine pancreatic insufficiency.

Case-control study

Although there was no evidence of an overall association between sex and a diagnosis of DM in univariable analysis (P = 0.572, Table 1), the combined sex-neuter variable was significantly associated with the odds of DM (P = 0.004). Entire males had lower odds of DM compared with neutered males and females. Neutered males had approximately 2.5 times the odds of DM compared with entire males (OR 2.52, 95%CI: 1.48 – 4.31) and a significant difference between neutered and entire females was not detected (OR 0.85, 95%CI: 0.51 – 1.39, P = 0.510). There were strong associations between both weight and breed and DM in univariable analysis. Lighter dogs were more likely to be diagnosed with DM than heavier dogs (P <0.001). Similarly, compared with crossbred dogs, small breeds tended to have higher odds, whereas large breeds generally had lower odds of DM (Table 1). There was no statistically significant association between DM diagnosis and insurance status, whether a dog was purebred or crossbred overall or whether a dog was of a UK Kennel Club recognised breed. Although there was a trend towards an association between season of diagnosis and

DM in univariable analysis, with lower proportions of dogs being diagnosed with DM in summer and autumn compared with winter and spring, the association failed to be significant (P = 0.080). There were strong associations between all of the selected co-morbidities and DM in univariable analyses, with the exception of hypothyroidism.

The multivariable logistic regression model contained observations for 627 animals and included the following variables: sex stratified by neuter status, the individual breed variable and age group (Table 2). Neutered males had more than twice the odds of a diagnosis of DM compared to entire males (OR 2.26, 95%CI: 1.29-3.96). Yorkshire terriers (OR 4.56, 95%CI: 1.79-11.64) had the highest odds of DM. Conversely, golden retrievers had 0.12 (95%CI: 0.02-0.96) times the odds and German shepherd dogs had 0.06 (95%CI: 0.00-1.00) times the odds of DM compared with crossbreds. The Hosmer-Lemeshow test indicated good model fit (P = 0.921). Clustering was not significant when "clinic ID" was included as a random effect (P = 0.339).

When added individually to the multivariable model, there were strong associations between DM diagnosis and being diagnosed with pancreatitis (OR 13.03, 95%CI: 4.25 - 39.94, P < 0.001), hyperadrenocorticism (OR 20.35, 95%CI: 4.45 - 93.20, P < 0.001), having a urinary tract infection (OR 5.35, 95%CI: 1.97 – 14.54, P = 0.001) and haematuria detected (OR 14.48, 95%CI: 6.91 – 33.85, P < 0.001) (Table 3). Being recorded as overweight within EPRs was associated with a diagnosis of DM (OR 3.26, 95%CI: 1.93 – 5.50, P < 0.001).

Survival analysis

There were 91 deaths (43.5%) from all-cause mortality during the study period, with most deaths occurring shortly after DM diagnosis (Figure 1). The median survival time was 17.3 months after DM diagnosis. Diabetic dogs that were insured, neutered and Kennel Club recognized breeds had lower hazards of death (longer survival times) in the univariable analysis. Dogs that were older and those diagnosed with pancreatitis and ketonuria at the time of DM diagnosis had increased hazards of death. There was a weak association between individual breeds and hazard of death in univariable analysis. There was insufficient evidence of survival differences associated with sex, weight, purebred status, season of DM diagnosis, hyperadrenocorticism, being overweight and prior glucocorticoid treatment in univariable analysis (Table 4).

Insurance status, neuter status, pancreatitis and age group remained statistically significant in the multivariable Cox model. Insured dogs had a hazard ratio of 0.60 (95%CI: 0.38-0.94, P = 0.023) compared with uninsured dogs. Dogs recorded as being neutered at the time of DM diagnosis had a hazard ratio of 0.56 (95%CI: 0.36-0.88, P = 0.014) compared with entire dogs. Dogs with a diagnosis of pancreatitis had a hazard ratio of 2.51 (95%CI 1.28-4.95, P = 0.016) compared with those without. Dogs aged 10 to less than 12 years had a hazard ratio of 1.38 (95%CI: 0.85-2.25) and dogs aged 12 years and above had a hazard ratio of 2.16 (95%CI: 1.28-3.63) compared to dogs aged 3 to less than 10 years old (Table 5). Breed and the presence of ketonuria were evaluated but not retained in the final multivariable Cox model. There was no evidence that the proportional hazards assumption was violated in the final model. Including clinic as a frailty term did not improve model fit (P = 0.499).

Discussion

The current study identified a prevalence of DM of 0.34% (95%CI: 0.31-0.37%) for dogs presenting to a large group of primary practices. Certain breeds and being neutered (in males) were factors associated with a diagnosis of DM. Diagnoses of pancreatitis, hyperadrenocorticism, urinary tract abnormalities, and being overweight were also associated with DM. Overall, median survival time was 17.3 months following DM diagnosis, although increasing age and a concurrent diagnosis of pancreatitis were associated with an increased hazard, whereas insured and neutered dogs had a decreased hazard of death.

The apparent prevalence of 0.34% (95%CI: 0.31-0.37%) is lower than the estimates reported by studies using referral populations in other countries (0.64% (Guptill and others 2003) and 1.33% (Fracassi and others 2004)). These differences may have resulted from selection bias or temporal, geographical or other population differences. However, the prevalence estimate in the present study is similar to that previously reported in a population of insured dogs in UK (0.32%) (Davison and others 2005). Further, the current study found no association between being insured and being diagnosed with DM, suggesting that both primary care and insurance data may be appropriate sources for estimating DM prevalence.

There was no evidence for a female predisposition to DM, as observed in another UK study (Davison and others 2005) but in contrast with other research (Foster 1975; Doxey and others 1985; Guptill and others 2003; Fall and others 2007). It has been suggested that the proportion of diabetics of each sex in study populations may be influenced by differences in neutering practices, as entire females may develop progesterone-induced DM (Fall and others 2010). However, neuter status did not have a significant effect on the odds of female dogs developing DM in the current study. It is possible that the lack of an association may result from confounding by obesity as neutered females had approximately twice the odds of being overweight than entire females (OR 2.15, 95%CI: 1.00-4.67, P = 0.040) in the case-control population. The increased risk of being overweight in neutered females and the subsequent likely impact of this on the odds of DM may counteract any increased risk in entire females due to progesterone effects. In male dogs the association was different, with neutered males being at increased odds of DM compared to entire males. One possible explanation is that male-sex hormones may have a protective effect against DM, although other factors associated with neutering in males may also influence this association. The interaction between neutering and sex on the effect of DM diagnosis identified here is consistent with a pattern reported in a population of dogs attending teaching hospitals in the USA (Guptill and others 2003).

Consistent with other studies (Hess and others 2000a; Guptill and others 2003; Fracassi and others 2004; Catchpole and others 2005), specific breeds were associated with DM in the current study, although our study lacked the power to detect differences between all but the most common breeds. These breed predispositions suggest that genetic components influence the susceptibility of some individuals to canine DM (Catchpole and others 2013). In addition, a strong association between bodyweight and DM diagnosis was identified in univariable analysis in the current study; with lighter dogs having higher odds of DM compared to heavier dogs. This may relate to the individual breeds associated with a diagnosis of DM. Further, all of

the dogs diagnosed with hyperadrenocorticism, a potential risk factor for DM, were less than 20 kg, which may be breed-related. A non-significant trend towards lighter dogs being associated with older age was also identified (P = 0.141). Although age group was included in the multivariable model, residual confounding is possible; if small breeds tend to live longer, they may be more likely to develop diseases afflicting geriatric animals, such as DM.

Being recorded as being overweight was associated with a diagnosis of DM, although weight classification was subjective and under-reporting was likely. Diabetic dogs may be more likely to be examined regularly and concerns regarding their weight may be more likely to be recorded. Consistent with other studies, being diagnosed with hyperadrenocorticism and pancreatitis were associated with DM (Hess and others 2000b; Davison and others 2005; Hume and others 2006; Blois and others 2011). Hyperadrenocorticism increases gluconeogenesis and can cause insulin resistance (Gilor and Graves 2011) and pancreatitis has been proposed to cause DM by damaging insulin-producing beta cells (Watson and others 2007). It is biologically plausible that these disorders preceded DM; although temporality could not be assessed in the case-control study and reverse causality could not be ruled out.

A strong association between being diagnosed with urinary tract abnormalities and DM was also identified. However, a causal relationship has not been established and urinary tract abnormalities are likely to be secondary to DM (Hess and others 2000b). In combination with other tools, urinalysis can be used to manage diabetic patients (Cook 2012). Urinary abnormalities may therefore be more likely to be detected in diabetic patients than non-diabetic dogs, biasing this result.

In the current study, median survival time was 17.3 months following diagnosis of DM. This was longer than the median survival time of 57 days reported for a population of insured diabetic dogs in Sweden (Fall and others 2007). This discrepancy may have been partly due to the popularity of hunting breeds in the Swedish population, which had lower survival rates than other breeds (Fall and others 2007).

Dogs diagnosed with pancreatitis within 7 days of DM diagnosis had an increased hazard of death. This finding contrasts with those of Hume and others (2006), who found an association between mortality and hyperadrenocorticism, but not pancreatitis, in a study of dogs with DKA. However, because these studies had different case definitions, methodology, veterinary facilities and geographical locations, they are not directly comparable.

Although being insured was not associated with DM diagnosis, it was associated with increased survival following diagnosis. This may reflect that DM is a low-cost condition to diagnose, whereas longer-term management requires a considerable financial and emotional commitment. Improved survival in diabetic dogs that are insured may result from inherent characteristics specific to owners who choose to insure, combined with reduced financial restrictions to potentially lengthy and expensive treatment protocols. This finding also suggests that using insurance data to evaluate survival may result in biased results and that primary practice data, that includes both insured and uninsured dogs, should better reflects the survival of the wider dog population. Overall, neutered diabetic patients had a hazard ratio of 0.56

(95%CI: 0.36-0.88) compared to entire animals. This survival difference may reflect either a biological advantage (due to low concentrations of sex steroids) or may be a proxy for owners who are more likely to treat and less likely to euthanase their pets.

There were some limitations to the current study. The data analysed were not primarily recorded for research purposes, so may have contained inconsistencies and errors. Veterinary surgeons were not blinded to the health status of dogs, so diabetic patients may have been more likely to undergo testing for co-morbidities. Similarly, dogs with other chronic diseases may have been more likely to be diagnosed as DM cases if they had been investigated more intensively than otherwise healthy dogs. It was not possible to ascertain dietary intake or exercise, which could confound the associations between DM and other variables. Finally, charity, mixed or non-corporate veterinary clinics may differ from this population of corporate owned companion animal clinics.

In conclusion, awareness of the associations between neutered males, specific breeds and diagnoses of pancreatitis or hyperadrenocorticism and DM could aid clinicians when considering DM as a differential diagnosis. Older dogs or those with pancreatitis at DM diagnosis may have a less favourable prognosis, whilst insured and neutered diabetics appeared to have a reduced hazard of death. On-going data collection within the VetCompass project will enable larger analyses of affected animals in subsequent years to generate epidemiological trends over time. This may be of particular value as clinical management evolves and new treatments for this complex, multifactorial disorder are introduced.

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Table 1: Descriptive statistics and univariable logistic regression analysis results for risk factors associated with canine diabetes mellitus in a case-control study nested within a population of 128,210 dogs attending primary practices in England.

Variable	Case (%)	Control (%)	OR[1]	95% CI[2]	P-value
Sex					
Female	105 (50.2)	200 (47.9)	Base		0.572
Male	104 (49.8)	218 (52.1)	0.91	(0.65 – 1.27)	
Neuter status					
Entire	60 (28.7)	154 (36.8)	Base		0.041
Neutered	149 (71.3)	264 (63.2)	1.45	(1.01 – 2.07)	
Sex-neuter					
Male-entire	23 (11.0)	91 (21.8)	Base		0.004
Male-neuter	81 (38.8)	127 (30.4)	2.52	(1.48 – 4.31)	
Female-entire	37 (17.7)	63 (15.1)	2.32	(1.26 – 4.28)	
Female-neuter	68 (32.5)	137 (32.8)	1.96	(1.14 – 3.38)	
Insurance status					
Not insured	122 (60.1)	245 (62.7)	Base		0.543
Insured	81 (39.9)	146 (37.3)	1.11	(0.79 – 1.58)	
Maximum weight (kg) during study period					
Below 10.0	63 (32.1)	75 (22.0)	Base		<0.001
10.0 to less than 20.0	75 (38.3)	89 (26.1)	0.67	(0.56 – 0.79)	
20.0 to less than 30.0	31 (15.8)	79 (23.2)			
30.0 and above	27 (13.8)	98 (28.7)			
Purebred status					
Crossbred	35 (16.8)	76 (18.2)	Base		0.656
Purebred	174 (83.2)	342 (81.8)	1.10	(0.71 – 1.72)	
UK Kennel Club recognised breed					
No	60 (28.7)	121 (29.0)	Base		0.950
Yes	149 (71.3)	297 (71.0)	1.01	(0.70 – 1.46)	
Season DM diagnosed (cases) or season of first veterinary consultation (controls)					
Winter	55 (26.3)	98 (23.4)	1.58	(0.97 – 2.59)	0.080
Spring	65 (31.1)	101 (24.2)	1.82	(1.12 – 2.93)	
Summer	39 (18.7)	110 (26.3)	Base		
Autumn	50 (23.9)	109 (26.1)	1.29	(0.79 – 2.12)	
Breed (≥10 dogs)					
Yorkshire terrier	18 (8.6)	8 (1.9)	4.77	(1.88 – 12.10)	<0.001
Border terrier	6 (2.9)	4 (1.0)	3.18	(0.84 – 12.04)	
Bichon frise	7 (3.4)	6 (1.4)	2.47	(0.77 – 7.94)	
CKCS[3]	9 (4.3)	8 (1.9)	2.39	(0.84 – 6.74)	
Border collie	11 (5.3)	11 (2.6)	2.12	(0.83 – 5.39)	
WHWT[4]	16 (7.7)	19 (4.6)	1.79	(0.82 – 3.91)	
Cocker spaniel	9 (4.3)	13 (3.1)	1.47	(0.57 – 3.78)	
Jack Russell terrier	24 (11.5)	44 (10.5)	1.16	(0.61 – 2.21)	
Crossbred	**33 (15.8)**	**70 (16.8)**	**Base**		

Purebred others		60 (28.7)	117 (28.0)	1.09	(0.65 – 1.83)	
Labrador retriever		11 (5.26)	48 (11.5)	0.49	(0.22 – 1.06)	
Staffordshire bull terrier		3 (1.44)	22 (5.3)	0.29	(0.08 – 1.03)	
Greyhound		1 (0.5)	11 (2.6)	0.19	(0.02 – 1.56)	
German shepherd dog[5]		0 (0)	18 (4.3)	0.06	(0.00 – 0.97)	
Golden retriever		1 (0.5)	19 (4.6)	0.11	(0.01 – 0.87)	
Co-morbidities and presenting signs						
Overweight	No	165 (78.9)	382 (91.4)	Base		
	Yes	44 (21.1)	36 (8.6)	2.83	(1.76 – 4.56)	<0.001
Pancreatitis	No	185 (88.5)	414 (99.0)	Base		<0.001
	Yes	24 (11.5)	4 (1.0)	13.43	(4.59 – 39.25)	
Hyperadrenocorticism	No	191 (91.4)	416 (99.5)	Base		<0.001
	Yes	18 (8.6)	2 (0.5)	19.60	(4.50 – 85-33)	
Hypothyroidism	No	207 (99.0)	412 (98.6)	Base		0.606
	Yes	2 (1.0)	6 (1.4)	0.66	(0.13 – 3.32)	
Haematuria	No	165 (79.0)	411 (98.3)	Base		<0.001
	Yes	44 (21.0)	7 (1.7)	15.66	(6.91 – 35.47)	
Urinary tract infection	No	193 (92.3)	411 (98.3)	Base		<0.001
	Yes	16 (7.7)	7 (1.7)	4.87	(1.97 – 12.03)	
Age group (frequency matched)						
3.0 to less than 8.0 years		41 (19.6)	82 (19.6)			1.000
8.0 to less than 11.0 years		85 (40.7)	170 (40.7)	1	(0.63 – 1.58)	
11.0 to less than 13.0 years		57 (27.3)	114 (27.3)	1	(0.61 – 1.63)	
13.0 years and above		26 (12.4)	52 (12.4)	1	(0.55 – 1.82)	

[1]OR = Odds ratio
[2]95% CI = 95% confidence interval
[3]Cavalier King Charles spaniel
[4]West Highland white terrier
[5]Values for German shepherd dog were derived by firth logit due to complete separation

Table 2: Multivariable logistic regression analysis results for risk factors associated with canine diabetes mellitus in a case-control study nested within a population of 128,210 dogs attending primary practices in England. Observations for 627 individuals.

Variable	OR[1]	95% CI[2]	P-value
Sex-neuter			
Male-entire	Base		0.031
Male-neuter	2.26	(1.29 – 3.96)	
Female-entire	2.00	(1.05 – 3.82)	
Female-neuter	1.81	(1.03 – 3.18)	
Breed (≥10 dogs)			
Yorkshire terrier	4.56	(1.79 – 11.64)	<0.001
Border terrier	3.49	(0.91 – 13.42)	
CKCS[3]	2.54	(0.88 – 7.29)	
Bichon frise	2.27	(0.70 – 7.35)	
Border collie	2.22	(0.87 – 5.72)	
WHWT[4]	1.99	(0.89 – 4.42)	
Cocker spaniel	1.48	(0.57 – 3.83)	
Jack Russell terrier	1.17	(0.61 – 2.26)	
Crossbred	**Base**		
Purebred others	1.14	(0.68 – 1.93)	
Labrador retriever	0.54	(0.25 – 1.18)	
Staffordshire bull terrier	0.31	(0.09 – 1.13)	
Greyhound	0.20	(0.02 – 1.63)	
Golden retriever	0.12	(0.02 – 0.96)	
German shepherd dog[5]	0.06	(0.00 – 1.00)	
Age group (frequency matched)			
3.0 to less than 8.0 years	Base		0.984
8.0 to less than 11.0 years	0.96	(0.59 – 1.55)	
11.0 to less than 13.0 years	1.04	(0.62 – 1.76)	
13.0 years and above	0.99	(0.53 – 1.85)	

[1]OR = Odds ratio
[2]95% CI = 95% confidence interval
[3]Cavalier King Charles spaniel
[4]West Highland white terrier
[5]Values for German shepherd dog were derived by firth logit due to complete separation

Table 3: Co-morbidities and presenting signs individually added to final multivariable logistic regression model for risk factors associated with canine diabetes mellitus in a nested case-control study from a population of 128,210 dogs attending primary practices in England.

Co-morbidity or presenting sign		**OR[1]**	**95% CI[2]**	**P-value**
Overweight	No	Base		<0.001
	Yes	3.26	(1.93 – 5.50)	
Pancreatitis	No	Base		<0.001
	Yes	13.03	(4.25 – 39.94)	
Hyperadrenocorticism	No	Base		<0.001
	Yes	20.35	(4.45 – 93.20)	
Hypothyroidism	No	Base		0.773
	Yes	1.29	(0.23 – 7.22)	
Haematuria	No	Base		<0.001
	Yes	14.48	(6.91 – 33.85)	
Urinary tract infection	No	Base		0.001
	Yes	5.35	(1.97 – 14.54)	

[1]OR = Odds ratio
[2]95% CI = 95% confidence interval

Table 4: Descriptive statistics and univariable Cox regression analysis of risk factors associated with survival in a population of 209 dogs diagnosed with diabetes mellitus in primary practice in England

Variable	Number (%)	HR[1]	95% CI[2]	P-value
Insurance status				
Not insured	131 (62.7)	Base		0.007
Insured	78 (37.3)	0.54	0.35 - 0.86	
Sex				
Female	105 (50.2)	Base		0.716
Male	104 (49.8)	0.93	0.61 – 1.40	
Neuter status				
Entire	60 (28.7)	Base		0.043
Neutered	149 (71.3)	0.64	0.41 – 0.98	
Sex-Neuter				
Male-entire	23 (11.0)	Base		0.140
Male-neuter	81 (38.8)	0.47	0.25 – 0.89	
Female-entire	37 (17.7)	0.70	0.35 – 1.41	
Female-neuter	68 (32.5)	0.57	0.30 - 1.07	
Age group (years)				
3.0 to less than 10.0	108 (51.7)	Base		0.013
10.0 to less than 12.0	64 (30.6)	1.40	0.89 – 2.34	
12.0 and above	37 (17.7)	2.20	1.32 – 3.67	
Maximum weight (kg)				
Below 10.0	63 (32.1)	Base		0.460
10.0 to less than 20.0	75 (38.3)	0.94	0.56 – 1.58	
20.0 to less than 30.0	31 (15.8)	0.62	0.29 – 1.32	
30.0 and above	27 (13.8)	1.18	0.62 –2.27	
Purebred status				
Crossbred	35 (16.8)	Base		0.389
Purebred	174 (83.2)	0.79	0.47 – 1.33	
Kennel club registered breed				
No	60 (28.7)	Base		0.050
Yes	149 (71.3)	0.65	0.42 – 0.99	
Season diabetes mellitus diagnosed				
Winter	55 (26.3)	0.97	0.51 – 1.84	0.894
Spring	65 (31.1)	1.19	0.65 – 2.16	
Summer	39 (18.7)	Base		
Autumn	50 (23.9)	1.10	0.59 – 2.06	
Breed ≥10 dogs				
Jack Russell terrier	24 (11.5)	1.51	0.75 – 3.16	0.081
Labrador retriever	11 (5.3)	1.23	0.48 – 3.24	
Crossbred	**33 (15.8)**	**Base**		
Yorkshire terrier	18 (8.6)	0.88	0.38 – 2.05	
Purebred other	96 (45.9)	0.87	0.49 – 1.55	
West Highland white terrier	16 (7.7)	0.35	0.10 – 1.22	
Border collie	11 (5.3)	0.30	0.07 – 1.32	

Co-morbidities and presenting signs					
Ketonuria	No	69 (46.0)	Base		0.053
	Yes	81 (54.0)	1.66	0.99 – 2.78	
Pancreatitis	No	193 (92.3)	Base		0.022
	Yes	16 (7.7)	2.36	1.22 – 4.59	
Hyperadreno - Corticism	No	191 (91.4)	Base		0.994
	Yes	18 (8.6)	1.00	0.48 – 2.06	
Overweight	No	171 (81.8)	Base		0.722
	Yes	38 (18.2)	1.10	0.65 – 1.87	
Prior glucocorticoid treatment	No	187 (89.5)	Base		0.362
	Yes	22 (10.5)	1.36	0.72 – 2.55	

[1]HR = Hazard ratio
[2]95% CI = 95% confidence interval

Table 5: Final multivariable Cox regression model for risk factors associated with survival in a population of 209 dogs diagnosed with diabetes mellitus in primary practice in England

Variable		HR[1]	95% CI[2]	P-value
Pancreatitis	No	Base		0.016
	Yes	2.51	1.28- 4.95	
Age group (years)	3.0 to less than 10.0	Base		0.019
	10 to less than 12.0	1.38	0.85 – 2.25	
	12.0 and above	2.16	1.28 – 3.63	
Insured	No	Base		0.023
	Yes	0.60	0.38 - 0.94	
Neutered	No	Base		0.014
	Yes	0.56	0.36 - 0.88	

[1]HR = Hazard ratio
[2]95% CI = 95% confidence interval

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