Frequency and risk factors for naturally occurring Cushing’s syndrome in dogs attending UK primary-care practices

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Objectives: To estimate the frequency and risk factors for Cushing’s syndrome in dogs under UK primary veterinary care.

Materials and Methods: Dogs with Cushing’s syndrome were identified by searching electronic patient records of primary-care veterinary practices. Pre-existing and incident cases of Cushing’s syndrome during 2016 were included to estimate the 1-year period prevalence. Incident cases were used to estimate the annual incidence and to identify demographic risk factors for the diagnosis of Cushing’s syndrome in dogs, through multivariable logistic regression.

Results: Analysis included 970 pre-existing and 557 incident cases of Cushing’s syndrome from a population of 905,544 dogs. The estimated 1-year period prevalence for Cushing’s syndrome in dogs under veterinary care was 0.17% (95% confidence interval 0.16 to 0.18) and incidence was 0.06% (95% confidence interval 0.05 to 0.07). In multivariable logistic regression modelling, the Bichon frise (odds ratio=6.17, 95% confidence interval 4.22 to 9.00), Border terrier (5.40, 95% confidence interval 3.66 to 7.97) and Miniature schnauzer (3.05, 95% confidence interval 1.67 to 5.57) had the highest odds of Cushing’s syndrome. The Golden retriever (0.24, 95% confidence interval 0.06 to 0.98) and Labrador retriever (0.30, 95% confidence interval 0.17 to 0.54) were the most protected breeds. Increasing age, bodyweight greater than the breed-sex mean and being insured also showed increased odds of Cushing’s syndrome.

Clinical Significance: As Cushing’s syndrome is predominately diagnosed and managed in primary-care practice, this study provides valuable new information of its epidemiology in this setting. Demographics reported are supportive of previous work and additional novel associations identified, such as the Border terrier, could enhance the index of suspicion for veterinarians.

Introduction

Naturally occurring Cushing’s syndrome, hereby referred to as Cushing’s syndrome, is an endocrine disorder that results from chronic excessive production of glucocorticoids, due to an adrenocorticotropic hormone (ACTH) secreting pituitary mass, a glucocorticoid secreting adrenal tumour, or other rarer aetiologies (Behrend et al. 2013, Nelson & Couto 2014). The excessive circulating glucocorticoids, most commonly cortisol, result in the typically recognised clinical signs and are associated with increased risk for several other diseases including diabetes mellitus, hypertension and urolithiasis (Cook et al. 1993, Hess
et al. 2000, Ramsey et al. 2005, Fracassi et al. 2015, Miceli et al. 2017).

Cushing’s syndrome is reported to occur in approximately 0.20 to 0.28% of dogs attending primary-care practice (O’Neill et al. 2016, Carotenuto et al. 2019). Previously reported estimates have examined the prevalence over varying time periods and across a limited number of practices therefore their wider generalisability is uncertain. A number of risk factors have been reported to be associated with Cushing’s syndrome. Sex predisposition is still a contentious risk factor with a number of studies reporting an association with female dogs (Gallelli et al. 2010, Hoffman et al. 2018, Carotenuto et al. 2019). However, these studies are limited by either applying univariable analyses or examining dogs attending referral practices. One study examining primary-care practice and taking other risk factors into account failed to identify a sex association with Cushing’s syndrome (O’Neill et al. 2016). Many breeds have been associated with Cushing’s syndrome, most notably for the UK primary-care population, the Bichon frise (O’Neill et al. 2016), Yorkshire terrier, Jack Russell terrier (O’Neill et al. 2016, Carotenuto et al. 2019) and Dachshund (O’Neill et al. 2016, Hoffman et al. 2018). Other breeds that have been strongly associated with Cushing’s syndrome include, but are not limited to, the Schnauzer, Fox terrier, Cavalier King Charles Spaniel, Boxer, Shih-tzu (Carotenuto et al. 2019), Poodle, Irish Setter and Bassett Hound (Hoffman et al. 2018). However, some over-represented breeds reported in the literature are based on very small numbers, or referral dog populations that would likely be a biased subgroup of the general dog population (Bartlett et al. 2010). Also, not all published studies took the underlying breed population into account (Ling et al. 1979). Few breeds have been reported with decreased risk of having Cushing’s syndrome; the Border Collie and Labrador retriever had decreased odds when compared to crossbreeds in one study (O’Neill et al. 2016) and a lower frequency of Cushing’s syndrome has been reported in the Border Collie, Rottweiler, Great Dane and Doberman Pinscher in another (Hoffman et al. 2018). Further investigation into predisposed and lower risk breeds is warranted to assist primary-care practitioners in their index of suspicion for Cushing’s syndrome and to inform future research, such as genetic studies. Other previously associated risk factors include older age and a greater weight for their breed (O’Neill et al. 2016). Before undertaking this study, the authors completed a narrative review of the published literature surrounding the diagnosis of Cushing’s syndrome in dogs. Key words in PubMed included Cushing’s OR hyperadrenocorticism OR hypercortisolism AND canine OR dog for publications before April 2020. Relevant textbooks were also examined (Feldman & Nelson 2004, Nelson & Couto 2014, Ettinger et al. 2017).

The objectives of this study were (1) to estimate the 1-year period prevalence and incidence for Cushing’s syndrome in dogs under UK primary veterinary care and (2) to investigate risk factors for Cushing’s syndrome. A further objective was to report data for Cushing’s syndrome in dogs under primary veterinary care, which could be used as clinical benchmarks.

Based on the literature examined, the hypotheses of this study were (1) the Bichon frise, Yorkshire terrier, Jack Russell Terrier and Dachshunds would have the highest odds of Cushing’s syndrome diagnosis among purebred dogs in the UK primary-care population and (2) there would be no difference in odds of Cushing’s syndrome diagnosis between male and female dogs.

**METHODS**

This study used routinely recorded anonymised electronic patient records (EPR) from UK primary-care veterinary practices collaborating within the VetCompass programme. A retrospective cohort analysis of all dogs under veterinary care at collaborating practices in 2016 was used to report the frequency and to examine the risk factors for dogs diagnosed with Cushing’s syndrome. Dogs under veterinary care were defined as having either (1) at least one EPR documented during 2016 or (2) at least one EPR documented during 2015 and 2017. Search terms were applied to the study population to identify candidate dogs with increased probability of Cushing’s syndrome: ‘hypera, hyperadr*, hac, cushin*, cussions-1, triols*, vetor*’. The clinical records of all candidate dogs were manually reviewed to identify dogs eligible for inclusion. A Cushing’s syndrome case was included if a pre-existing (first diagnosed before 2016) or incident (first diagnosed within 2016) diagnosis of Cushing’s syndrome was recorded within the EPR between 1 January 2016 and 31 December 2016. Incident cases were additionally required to have a record of a low-dose dexamethasone suppression test (LDDST) or an ACTH stimulation test being performed within the EPR before diagnosis. Dogs were excluded as a case if the condition was considered iatrogenic or the dog had a record of glucocorticoid administration in the 30 days before first suspicion. All dogs that were not identified by the search terms as candidate cases during the initial screening were included as non-cases for Cushing’s syndrome in the risk factor analysis.

Data were cleaned in Excel (Microsoft Corp.) and uploaded into Stata 15 (Stata, TX, USA) for statistical analysis. Sample size calculations estimated that 187,200 dogs would need to be sampled to provide a prevalence estimate for a disorder expected to occur in 0.2% of the overall UK dog population (estimated at 8 million in 2016), with a 0.02% acceptable margin of absolute error at a 95% confidence level (Asher et al. 2011, OpenEpi 2018). Ethical approval was granted by the Royal Veterinary College Ethics and Welfare Committee (SR2018-1652).

Available demographic data for study dogs included date of birth, sex, neuter status, insurance status, breed, mean lifetime bodyweight above 18 months, veterinary group and veterinary clinic ID. Age (years) was calculated using the date of birth and the date of initial diagnosis for cases, or at the end of the study period (31 December 2016) for non-cases. Individual purebred and designer breeds were included in the risk factor analysis if there were either (1) greater than or equal to 15 Cushing’s syndrome case dogs of that breed or (2) greater than or equal to 5000 non-case dogs of that breed. All other breeds were grouped as either (1) ‘purebred other’ if they were a recognised breed...
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VeNom Coding Group (2018) or (2) ‘crossbred’ if they were recorded as a crossbreed or a designer breed-cross (e.g. Labrador-poodle or labradoodle). Bodyweight (kg) described the mean from all bodyweight data recorded for dogs aged over 18 months and was split into six categories: less than 10, 10 to less than 20, 20 to less than 30, 30 to less than 40, greater than or equal to 40 and unrecorded. Mean adult bodyweight was calculated for both sexes of each breed with at least 100 dogs in the overall study population to create a variable called ‘bodyweight to breed-sex mean.’ Dogs were categorised as ‘above’ (over 15% of breed-sex bodyweight mean), ‘within’ (within 15% of breed-sex bodyweight mean), ‘below’ (under 15% of breed-sex bodyweight mean) or ‘unknown’. Neuter and insurance status were recorded at the end of the study period for cases and non-cases. Individual veterinary clinics attended were assigned identification (ID) numbers. Veterinary groups consisted of clinics that were part of the same group of consolidated clinics and were assigned identification numbers from 1 to 5. Additional descriptive data were extracted by manual revision of the case EPRs, including date of first diagnosis, date of death, referral for Cushing’s syndrome, diagnostic testing performed, initial treatment method and recorded underlying aetiology of disease.

Categorical data were presented showing the count and corresponding percentage. Quantitative data were assessed for normality using Shapiro–Wilk testing and graphically; normally distributed data were summarised using the mean [standard deviation (SD)] and non-normally distributed data using the median [interquartile range (IQR) and range]. A Kaplan–Meier plot described the all-cause mortality trend of incident cases of Cushing’s syndrome from the date of diagnosis. Median survival time (MST) was defined as the number of days for the cumulative percentage of dogs surviving from the date of diagnosis to reach 50% (Dohoo et al. 2012). The end date was recorded as the date of death for dogs that were recorded to have died before 30 June 2020. Dogs were censoring at the date of the last clinical record for those that were lost to follow.

RESULTS

The study population included 905,544 dogs under primary veterinary care across 886 VetCompass participating practices in 2016. Search terms identified 12,141 candidate dogs with evidence of consideration of Cushing’s syndrome in the EPRs. All candidate dogs were manually examined and 1527 Cushing’s syndrome cases were identified; 970 pre-existing cases to 2016 and 557 incident cases in 2016.

Of the 557 incident cases, 51.4% (n=286) were female, 66.1% (368) were neutered and 28.2% (157) were insured. The median age at diagnosis was 10.9 years (IQR 9.0 to 12.7, range 3.9 to 16.1) and median weight was 11.6 kg (IQR 8.8 to 20.0, range 3.6 to 47.7). The most frequently reported breeds were the Jack Russell terrier (n=54/557, 9.7%), Staffordshire Bull terrier (50, 9.0%), Bichon frise (37, 6.7%) and Border terrier (35, 6.3%). Diagnosis was supported using an ACTH stimulation test in 78.6% of incident cases (438/557) and/or 28.9% (161) with a LDDST. Additional tests recorded in the EPRs included the urine cortisol-to-creatinine ratio (64, 11.5%), endogenous ACTH assay (2, 0.4%), 17-OH-Progesterone (10, 1.8%) and a high dose dexamethasone suppression test (4, 0.7%). Referral was recorded in 14 (2.5%) cases and the underlying aetiology of disease was recorded in 31 (5.6%) cases; 22 (70.1%) had pituitary dependent hypercortisolism (PDH) and 9 (29.9%) had adrenal dependent hypercortisolism (ADH). No other aetiologies for Cushing’s syndrome were described within the EPRs. Initial treatment recorded following diagnosis included trilostane (n=508, 91.0%) and adrenalectomy (2, 0.4%). No treatment was instigated in 48 (8.6%) cases. There were 333 (59.8%) cases that died within the study period, 166 (29.8%) were lost to follow-up.
and 58 were alive (10.4%) at study end-point. MST of cases from the date of diagnosis was 594 days (95% CI 519 to 661) (Fig 1). The cumulative proportion of all cases surviving to 1 year was 0.63 (95% CI 0.59 to 0.67) and 0.41 (95% CI 0.37 to 0.46) surviving to 2 years.

**Disease frequency**

The estimated 1-year period prevalence for Cushing’s syndrome in dogs in 2016 was 0.17% (95% CI 0.16 to 0.18). The 1-year incidence risk in 2016 was 0.06% (95% CI 0.05 to 0.07). The breeds with the highest breed prevalence’s were the Border terrier (1.02%; 95% CI 0.82 to 1.22), Bichon frise (0.97%; 95% CI 0.80 to 1.13) and Miniature schnauzer (0.42%; 95% CI 0.28 to 0.55) (Table 1).

**Risk factor analysis**

Univariable analysis identified breed, age at diagnosis, neutering status, sex combined with neutering status, bodyweight to breed-sex mean and insurance status as strongly associated with Cushing’s syndrome (<0.001). Sex alone was weakly associated (P=0.084) and was also taken forward for evaluation in the multivariable analysis (Table 2).

The final breed-focused multivariable model included four variables: breed, age at diagnosis, bodyweight to breed-sex mean and insurance status. Seven breeds were associated with increased odds of Cushing’s syndrome; the Bichon frise (OR=6.17, 95% CI 4.22 to 9.00), Border terrier (5.40, 95% CI 3.66 to 7.97), Miniature schnauzer (3.05, 95% CI 1.67 to 5.37), Lhasa apso (2.52, 95% CI 1.49 to 4.28), Yorkshire terrier (1.82, 95% CI 1.23 to 2.70), Staffordshire Bull terrier (1.52, 95% CI 1.08 to 2.13) and Jack Russell Terrier (1.50, 95% CI 1.07 to 2.08). Four breeds were at decreased odds of Cushing’s syndrome: the Golden retriever (0.24, 95% CI 0.06 to 0.98), Labrador retriever (0.3, 95% CI 0.17 to 0.54), Border Collie (0.32, 95% CI 0.13 to 0.78) and Cocker spaniel (0.44, 95% CI 0.21 to 0.90). Dogs with a bodyweight higher than their breed-sex mean had 1.44 times the odds of Cushing’s syndrome than those within their breed mean (95% CI 1.17 to 1.78; P<0.001). Dogs that were insured were associated with greater odds of Cushing’s syndrome compared to uninsured dogs (OR=2.46, 95% CI 1.98 to 3.04; P<0.001) (Table 3).

The non-linear association of age with Cushing’s syndrome was explored through visual interpretation of a smoothed line on the logit scale (Fig 2). Overall, the odds of Cushing’s syndrome increased with increasing age. The relationship demonstrated a rapid increase in the odds of developing Cushing’s syndrome up until the age to around 7 years of age. The increasing odds of Cushing’s syndrome then only increased very gradually from 7 years onwards. To account for the confounding effect of age in logistic regression modelling, age was included as a quadratic term as this best described the non-linear relationship.

Veterinary clinic ID was statistically significant and was included as a random effect indicating significant variation at the clinical level (LRT of rho P<0.001, rho=0.08). The final model demonstrated acceptable model fit (Hosmer lemeshow p=0.265) and model discrimination (AUROC=0.904; 95% CI 0.896 to 0.912). Sex-neuter was not retained in the multivariable model as the univariable effects were confounded fully by age and insurance status (P=0.302). No pair-wise interactions were identified.

**DISCUSSION**

This is the largest study to date to estimate the prevalence, incidence and risk factors for Cushing’s syndrome in dogs attending primary-care practice. One-year period prevalence for Cushing’s syndrome was 0.17% (95% CI 0.16 to 0.18).

**Table 1. Overall estimated prevalence of Cushing’s syndrome in dogs under primary veterinary care in the UK, by breed (cases n=1527; population n=905,544)**

| Category                | Prevalence (%) | 95% Confidence interval (%) |
|-------------------------|----------------|-------------------------------|
| Border Terrier          | 1.02           | 0.82 to 1.22                  |
| Bichon frise            | 0.97           | 0.80 to 1.13                  |
| Miniature schnauzer     | 0.42           | 0.28 to 0.55                  |
| West Highland White terrier | 0.38         | 0.29 to 0.46                  |
| Yorkshire terrier       | 0.34           | 0.27 to 0.41                  |
| Lhasa apso              | 0.33           | 0.23 to 0.44                  |
| Jack Russell terrier    | 0.30           | 0.25 to 0.34                  |
| Boxer                   | 0.26           | 0.16 to 0.37                  |
| Cavalier King Charles Spaniel | 0.19      | 0.12 to 0.25                  |
| Staffordshire Bull terrier | 0.19         | 0.15 to 0.23                  |
| Beagle                  | 0.16           | 0.07 to 0.25                  |
| Pomeranian              | 0.16           | 0.06 to 0.26                  |
| English springer spaniel| 0.13           | 0.08 to 0.18                  |
| Crossbreed              | 0.12           | 0.11 to 0.14                  |
| Shih-tzu                | 0.12           | 0.08 to 0.15                  |
| Cocker spaniel          | 0.09           | 0.06 to 0.12                  |
| Golden retriever        | 0.08           | 0.03 to 0.18                  |
| Rottweiler              | 0.08           | 0.02 to 0.15                  |
| Purebred other          | 0.07           | 0.06 to 0.08                  |
| Labrador retriever      | 0.07           | 0.05 to 0.09                  |
| Border Collie           | 0.05           | 0.02 to 0.08                  |
| Chihuahua               | 0.02           | 0.008 to 0.04                 |
| French Bulldog         | 0.01           | 0.00 to 0.03                  |
| German shepherd dog     | 0.01           | 0.00 to 0.03                  |
| Pug                     | 0.01           | 0.00 to 0.02                  |
| Cockapoo                | 0.01           | 0.00 to 0.02                  |
Cushing’s syndrome frequency and risk factors

The prevalence in the current study is slightly lower than those previously reported, however the CIs across the estimates within primary-care populations overlap and could be explained by the shorter time period observed in the current study. Studying prevalence across a longer time period provides dogs with a longer

### Table 2. Descriptive statistics and univariable logistic regression of associated risk factors for Cushing’s syndrome in dogs attending UK primary-care practice in 2016

| Variable | Cases | Non-cases | Odds ratio | 95% Confidence Interval | Category P-value | Variable P-value |
|----------|-------|-----------|------------|------------------------|------------------|------------------|
| Sex      |       |           |            |                        |                  |                  |
| Female   | 286   | 425,630   | -          | 0.86 to 1.02           | 0.084            |                  |
| Male     | 271   | 463,568   | 0.86       | 0.73 to 1.02           |                  |                  |
| Neuter status |       |           |            |                        |                  |                  |
| Entire   | 189   | 489,512   | -          | 2.21 to 2.65 <0.001    |                  |                  |
| Neutered | 368   | 399,688   | 2.15       | 1.85 to 2.65 <0.001    |                  |                  |
| Insurance status |       |           |            |                        |                  |                  |
| Insured  | 157   | 114,306   | 2.27       | 1.84 to 2.81 <0.001    |                  |                  |
| Uninsured| 400   | 779,096   | -          |                        |                  |                  |
| Breed    |       |           |            |                        |                  |                  |
| Crossbred| 117   | 225,304   | -          | 2.37 to 2.70 <0.001    |                  |                  |
| Border terrier |    | 35 (6.3) | 9317 (1.1)| 7.11                   | 4.86 to 10.39 <0.001 |
| Bichon frise |    | 37 (6.7) | 12,762 (1.4)| 7.11                   | 3.83 to 8.06 <0.001 |
| Lhasa apso |     | 16 (2.9) | 12,365 (1.4)| 7.11                   | 2.16 to 4.59 <0.001 |
| Miniature schnauzer | | 12 (2.2) | 8,133 (0.9)| 2.71                   | 1.49 to 4.92 <0.001 |
| West Highland White terrier | | 24 (4.3) | 18,136 (2.0)| 2.51                   | 1.62 to 3.91 <0.001 |
| Yorkshire terrier | | 32 (5.8) | 27,413 (3.1)| 2.25                   | 1.51 to 3.30 <0.001 |
| Jack Russell terrier | | 54 (9.7) | 47,641 (5.4)| 2.17                   | 1.57 to 3.00 <0.001 |
| Staffordshire Bull terrier | | 50 (9.0) | 52,285 (5.9)| 1.85                   | 1.33 to 2.58 <0.001 |
| Boxer |     | 8 (1.4)  | 9,293 (1.0)| 1.66                   | 0.81 to 3.40 0.167 |
| Cavalier King Charles Spaniel | | 14 (2.5) | 16,967 (1.9)| 1.55                   | 0.89 to 2.70 0.124 |
| Rottweiler |   | 5 (0.9)  | 7,233 (0.8)| 1.34                   | 0.55 to 3.27 0.526 |
| Purebred other | | 94 (16.9) | 114,406 (16.2)| 1.24                   | 0.94 to 1.62 0.129 |
| Beagle |     | 5 (0.9)  | 7,949 (0.9)| 1.22                   | 0.50 to 2.98 0.669 |
| English springer spaniel | | 8 (1.4)  | 19,987 (2.3)| 0.77                   | 0.38 to 1.58 0.477 |
| Shih-tzu |     | 11 (2.0) | 32,603 (3.7)| 0.68                   | 0.37 to 1.26 0.22 |
| Cocker spaniel | | 8 (1.4)  | 31,804 (3.6)| 0.47                   | 0.23 to 0.97 0.041 |
| Border Collie | | 5 (0.9)  | 22,178 (2.5)| 0.44                   | 0.18 to 1.08 0.075 |
| Labrador retriever | | 13 (2.3) | 59,279 (6.7)| 0.41                   | 0.23 to 0.73 0.002 |
| Golden retriever | | 2 (0.4)  | 9,467 (1.1)| 0.37                   | 0.09 to 1.49 0.16 |
| Pomeranian | | 1 (0.2)  | 6,147 (0.7)| 0.31                   | 0.04 to 2.21 0.241 |
| French Bulldog | | 1 (0.2)  | 16,337 (1.8)| 0.12                   | 0.02 to 0.87 0.036 |
| Pug |     | 1 (0.2)  | 16,153 (1.8)| 0.12                   | 0.02 to 0.88 0.037 |
| Cockapoo | | 1 (0.2)  | 18,234 (2.1)| 0.11                   | 0.01 to 0.76 0.025 |
| Chihuahua | | 1 (0.2)  | 36,671 (4.1)| 0.06                   | 0.01 to 0.40 0.004 |
| German shepherd dog | | 0 (0.0)  | 21,238 (2.4)| -                      | -                   |                  |
| Weight |       |           |            |                        |                  |                  |
| <10 |     | 178 (32.0) | 211,351 (23.7)| -                |                  | <0.001 |
| 10 to <20 | | 188 (33.8) | 162,797 (18.2)| 1.35               | 1.10 to 1.66 0.004 |
| 20 to <30 | | 76 (13.6)  | 116,972 (13.1)| 0.76               | 0.58 to 0.99 0.042 |
| 30 to <40 | | 31 (5.6)   | 67,514 (7.6)| 0.53                   | 0.36 to 0.78 0.001 |
| >40 |     | 14 (2.5)  | 25,786 (2.9)| 0.65                   | 0.36 to 1.08 0.093 |
| Missing |    | 70 (12.6) | 308,982 (34.6)| 0.15               | 0.10 to 0.21 <0.001 |
| Weight to breed-sex mean | |           |            |                        |                  |                  |
| Below |     | 104 (18.7) | 171,305 (19.2)| 0.80               | 0.63 to 1.01 0.062 |
| Within |   | 203 (36.5) | 265,045 (29.7)| -                 |                  | <0.001 |
| Above |     | 179 (32.1) | 145,962 (16.3)| 1.60               | 1.31 to 1.96 <0.001 |
| Missing | | 71 (12.8)  | 311,090 (34.8)| 0.17               | 0.11 to 0.24 <0.001 |
| Sex-neuter | |           |            |                        |                  |                  |
| Male entire | | 105 (18.9) | 257,400 (29.0)| -                 |                  | <0.001 |
| Male neutered | | 166 (29.8) | 206,188 (23.2)| 1.84               | 1.44 to 2.35 <0.001 |
| Female entire | | 84 (15.1)  | 232,110 (26.1)| 0.89               | 0.67 to 1.19 0.444 |
| Female neutered | | 202 (36.3) | 193,520 (21.7)| 2.38               | 1.88 to 3.02 <0.001 |
| Age median (IQR, years) | | 10.9 (9.0 to 12.7) | 4.4 (1.8 to 7.9) |                  | <0.001 |
| Linear term | | 4.18 | 3.44 to 5.07 <0.001 |                  |                  |
| Quadratic term | | 0.95 | 0.94 to 0.95 <0.001 |                  |                  |

Veterinary clinic ID was included as a random effect (cases n=557; non-cases n=893,403)

* Wald P-value

* Likelihood ratio test P-value

## Cushing’s syndrome frequency and risk factors

The prevalence in the current study is slightly lower than those previously reported, however the CIs across the estimates within primary-care populations overlap and could be explained by the shorter time period observed in the current study. Studying prevalence across a longer time period provides dogs with a longer
amount of time to become a case and therefore are likely to report higher prevalence than studies with a shorter time period (Ng et al. 2013, Ward 2013). Other published studies also utilising data from VetCompass have reported a 1-year period prevalence in 2016 therefore allowing direct comparison to other disorders (Heeley et al. 2020, Schofield et al. 2021). Prevalence estimates within referral level practice suggest a higher Cushing’s syndrome prevalence of 1.2 to 1.5% within a referral centre caseload (Bel-lacolomari et al. 2013, Carotenuto et al. 2019).

The annual incidence risk was estimated at 0.06% (95% CI 0.05 to 0.07). Incidence risk has been estimated for Cushing’s syndrome in two previous studies: 96 of 100,000 dogs/year (equivalent to 0.096%) in a UK study of insured dogs (Dobson et al. 2002) and one to two cases of 1000 dogs/year (0.1 to 0.2%) of pituitary dependent disease in USA veterinary hospitals (Willeberg & Priester 1982). Drawing direct comparisons across the studies is difficult due to the different source populations used; however, the present study is likely the most accurate

| Table 3. Multivariable logistic regression analysis to assess the risk factors for Cushing’s syndrome in dogs under primary veterinary care in the UK in 2016 |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Breed           | Odds ratio      | 95% CI          | Category P-value | Variable P-value |
| Crossbred       | -               | -               | -               | -               |
| Bichon frise    | 6.17            | 4.22 to 9.00    | <0.001          | -               |
| Border terrier  | 5.40            | 3.66 to 7.97    | <0.001          | -               |
| Miniature schnauzer | 3.05     | 1.67 to 5.57    | <0.001          | -               |
| Lhasa apso      | 2.52            | 1.49 to 4.28    | 0.001           | -               |
| Yorkshire terrier | 1.82             | 1.23 to 2.70    | 0.003           | -               |
| Beagle          | 1.77            | 0.72 to 4.36    | 0.214           | -               |
| Rottweiler      | 1.53            | 0.62 to 3.76    | 0.360           | -               |
| Staffordshire Bull terrier | 1.52       | 1.08 to 2.13    | 0.017           | -               |
| Jack Russell terrier | 1.50             | 1.07 to 2.08    | 0.016           | -               |
| Boxer           | 1.35            | 0.66 to 2.79    | 0.414           | -               |
| West Highland White terrier | 1.32        | 0.84 to 2.06    | 0.225           | -               |
| French Bulldog  | 1.30            | 0.21 to 10.87   | 0.686           | -               |
| Purebred other  | 1.26            | 0.95 to 1.66    | 0.112           | -               |
| Cavalier King Charles Spaniel | 1.24       | 0.71 to 2.17    | 0.450           | -               |
| Cockapoo        | 0.93            | 0.13 to 6.69    | 0.940           | -               |
| Shih-tzu        | 0.89            | 0.48 to 1.66    | 0.713           | -               |
| Pomeranian      | 0.63            | 0.09 to 4.54    | 0.649           | -               |
| English springer spaniel | 0.55       | 0.27 to 1.14    | 0.106           | -               |
| Cocker spaniel  | 0.44            | 0.21 to 0.90    | 0.024           | -               |
| Pug             | 0.37            | 0.21 to 10.87   | 0.318           | -               |
| Border Collie   | 0.32            | 0.13 to 0.78    | 0.012           | -               |
| Labrador        | 0.30            | 0.17 to 0.54    | <0.001          | -               |
| Golden retriever | 0.24             | 0.06 to 0.98    | 0.048           | -               |
| Chihuahua       | 0.15            | 0.02 to 1.10    | 0.062           | -               |
| German shepherd dog | -             | -               | -               | -               |
| Weight to breed-sex mean | - | - | - | - |
| Under           | 0.98            | 0.76 to 1.25    | 0.850           | -               |
| Within          | -               | -               | -               | -               |
| Over            | 1.44            | 1.17 to 1.78    | 0.001           | -               |
| Missing         | 0.40            | 0.27 to 0.58    | <0.001          | -               |
| Insurance status | -       | -               | -               | -               |
| Insured         | 2.46            | 1.98 to 3.04    | <0.001          | -               |
| Uninsured       | -               | -               | -               | -               |
| Age             | -               | -               | -               | -               |
| Linear term     | 4.10            | 3.35 to 5.01    | <0.001          | -               |
| Quadratic term  | 0.95            | 0.94 to 0.96    | <0.001          | -               |

Veterinary group included as a fixed effect and veterinary clinic as a random effect (cases n=557; non-cases n=853,704)
† Wald P-value
‡ Likelihood ratio test P-value
§ No data

FIG 2. Smoothed line on the logit scale presenting the non-linear association of age at diagnosis in dogs with Cushing’s syndrome under primary veterinary care in the UK (n=557)
Cushing's syndrome frequency and risk factors

current estimation of Cushing's syndrome incidence within UK primary-care practice. Based on the frequency estimates within the literature, it is clear that Cushing's syndrome is an infrequently diagnosed disease within primary-care veterinary practice and appears to be encountered less frequently for veterinarians in primary-care practice than for those within referral practices. Finally, prevalence may vary with geography, given that in human and veterinary medicine pituitary tumour aetio-pathogenesis has been associated with exposure to environmental factors (Diru et al. 2013, Cannavo et al. 2016).

Data that could be useful as clinical benchmarks were presented on the clinical approaches and survival characteristics of Cushing's syndrome in primary-care practice. The ACTH stimulation test was performed in 78.6% of incident cases and was used more than the LDDST in the present study. The ACTH stimulation test has previously been reported to be used in greater than 90% of cases within primary-care practice in the UK (O’Neill et al. 2016, Schofield et al. 2020). Other diagnostic tests for Cushing's syndrome were also used less frequently in the current study to previously reported benchmarking parameters (O’Neill et al. 2016). Previous studies examined earlier time periods (before 2013) and a smaller sample of UK veterinary practices, which could explain these differences. The commonly used diagnostic tests for Cushing's syndrome are not highly specific resulting in false positive results. The ACTH stimulation test has a likely specificity of 59 to 61% in dogs suspected of Cushing's syndrome (Monroe et al. 2012, Nivy et al. 2018), indicating a proportion of false positives in this study are likely. Equally, the ACTH stimulation test lacks sensitivity, estimates range from 80 to 88% for PDH cases to 57 to 63% for ADH cases (Peterson et al. 1982, Feldman 1983, Reusch & Feldman 1991, Kaplan et al. 1995, Monroe et al. 2012). Therefore, cases could be falsely excluded when using the ACTH stimulation. Specific aspects about the ACTH stimulation test protocols used by veterinarians in the current study were not known. The type of synthetic ACTH administered (Hill et al. 2004), the cortisol assay used (Behrend et al. 2013, Bennaim et al. 2019) and the sample collection method (Behrend et al. 1998, Schechter et al. 2020) can influence ACTH stimulation test cortisol concentrations. Further research into the ACTH stimulation test protocols used by primary-care veterinarians would be beneficial to be able to identify and address any factors that could improve interpretation of this preferred primary-care test. No diagnostic tests currently available for the diagnosis of Cushing's syndrome are highly accurate, however, alternative tests such as the LDGST and dynamic tests based on measuring UCCR are more sensitive than the ACTH stimulation test (Feldman 1983, Rijnberk & Mol 1988, Galac et al. 1997, Bennaim et al. 2018). Had the use of these alternative tests been greater in the current study population, prevalence estimates could have been higher. Generally, novel diagnostic methods are warranted to improve the diagnostic accuracy of Cushing’s syndrome.

Referral was recorded in 14 (2.5%) cases, indicating that Cushing's syndrome is a disease that is often diagnosed and managed completely within the primary-care setting. This highlights the importance of examining primary-care populations for this disease. The referral dog population are likely to consist of more complicated cases; therefore, assessment of diagnostic and monitoring test accuracy, and drug effectiveness for Cushing's syndrome using cases from within referral populations may not be applicable to the wider dog population. Further studies utilising cases of Cushing's syndrome from within primary-care populations are warranted to increase the generalisability of the evidence surrounding this disease. Differentiation into the underlying aetiology of Cushing's syndrome was rarely recorded, in only 5.6% of cases. This is lower than the 21.1% previously reported in a primary-care population in the UK (Schofield et al. 2019a).

Differences in the veterinary practices studied could describe some of this disparity, with variations in owner, veterinarian or practice demographics having potential effects. Cases that were differentiated were predominantly based on interpretation of ultrasonographic imaging of the adrenals or through interpretation of the LDGST. The LDGST is not a reliable method of identifying ADH (Feldman et al. 1996, Bennaim et al. 2018, van Bokhorst et al. 2019) and adrenal measurement via ultrasonography is considered difficult (Grooters et al. 1996); therefore, there is a possibility of incorrect reporting of the underlying aetiology under primary veterinary care. Reasons for infrequent differentiation could be explained by 91% of dogs receiving medication with trilostane following diagnosis, regardless of the underlying aetiology and surgical treatment rarely undertaken. The long-term management of cases in this study was not followed up over time; therefore, the number of dogs receiving surgical treatment at some point within their clinical records could have been slightly higher.

The MST in the current study of 594 days (95% CI 519 to 661) is in line with previous estimates within the literature in dogs treated with trilostane (Barker et al. 2005, Clemente et al. 2007, Arenas et al. 2014, Fracassi et al. 2015, Nagata et al. 2017, Schofield et al. 2019a). This shows reasonable survival in dogs with Cushing’s syndrome attending primary-care practice and the 1 and 2 year survival proportions indicated the over 60 and 40% survived to these time points respectively. This reflects a considerable amount of time for dogs to be living with Cushing’s syndrome and highlights the need to reduce the impact of the associated clinical signs and improve their quality-of-life during this time (Schofield et al. 2019b). This is also useful information to provide to owners, to support them following their dog’s diagnosis. Survival estimates for dogs managed with trilostane from referral populations are slightly more optimistic; however, differences may exist in the dog populations, such as mean age, breed differences and other comorbidities that could account for the differences observed. Survival estimates in the current study include 48 (8.6%) dogs that did not receive treatment and could have shortened the median survival (Nagata et al. 2017, Schofield et al. 2019a). Additionally, survival estimates for ADH are inferior to PDH; therefore, differing proportions of ADH and PDH in these populations could account for encountered prevalence differences (Barker et al. 2005, Clemente et al. 2007, Helm et al. 2011, Arenas et al. 2014, Fracassi et al. 2015, Nagata et al. 2017).
Breed, age at diagnosis, bodyweight to breed-sex mean and insurance status were associated with the diagnosis of Cushing’s syndrome in dogs attending primary-care practice. A previous study reported the risk factors for combined caseload of incident and pre-existing cases, making interpretation difficult due to the incurred selection bias from including the pre-existing cases (O’Neill et al. 2016). The identified risk factors and effect measures reported by this prior study could describe the diagnosis and consequent survival for Cushing’s syndrome, rather than solely for diagnosis.

Among the breeds, the bichon frise had the highest odds of Cushing’s syndrome (OR=6.17), accounting for about one in every 12 incident cases of Cushing’s syndrome within primary-care practice. Six other breeds had increased odds of Cushing’s syndrome compared to crossbred dogs, with novel associations of increased odds of Cushing’s syndrome in the Border terrier, Lhasa apso and Staffordshire Bull terrier. Based on the literature examined, this is the first time these breeds have been reported. The Border terrier had the highest breed prevalence of Cushing’s syndrome and second highest odds in the current study (OR 5.40, 95% CI 3.66 to 7.97). Due to the strong association identified here, it is interesting the Border terrier has not previously been associated with the diagnosis of Cushing’s syndrome. The popularity of Border terriers has decreased in England between 2005 and 2014; therefore, this could suggest a more concentrated breeding population in this breed and may be important to monitor in the future (O’Neill et al. 2017).

Breeds with reduced odds of Cushing’s syndrome compared to crossbred dogs included the Golden retriever, Labrador retriever, Border Collie and Cocker spaniel. The Border Collie consistently appears to be at reduced risk of Cushing’s syndrome (O’Neill et al. 2016, Hoffman et al. 2018) and the Labrador retriever has also previously been identified (O’Neill et al. 2016). The Golden retriever and the Cocker spaniel, however, have not previously been reported at reduced odds. Interestingly, of the 21,238 German shepherd dog (GSD) in the underlying population, none were included as incident cases in this analysis. Prior GSD OR estimates vary in the literature from 0.30 (95% CI 0.10 to 1.00) (O’Neill et al. 2016) to 1.43 (95% CI 0.34 to 6.00) (Carotenuto et al. 2019). Variations in GSD associations could possibly reflect genetic differences within the breed across different countries or could suggest that owners of GSDs within the current study were less likely to pursue a diagnosis of Cushing’s syndrome than in other populations. Further research to investigate barriers to assigning a diagnosis of Cushing’s syndrome could be beneficial and could highlight possible confounding factors that have not been accounted for in the present study. Additionally the low numbers of Cockerpoos, French Bulldogs and Pugs with Cushing’s syndrome should be noted, even with large numbers of dogs included in the underlying population. These three breeds were not significant in the final model after accounting for age due to the rising popularity of these breeds and young populations. For understanding which breeds are predisposed to, and protected from, Cushing’s syndrome is important; for veterinarians in primary-care practice to consider when selecting dogs for specific diagnostic testing for Cushing’s syndrome and to guide future research, such as genetic analysis of Cushing’s syndrome in dogs (Denyer et al. 2020).

Increasing age was associated with increasing odds of Cushing’s syndrome in dogs and median age at diagnosis of 10.9 years was in line with other studies (Helm et al. 2011, O’Neill et al. 2016, Nagata et al. 2017, Carotenuto et al. 2019). The association with age was not linear, therefore was modelled as a non-linear term to best control for confounding effects of age on the other risk factors included in the model (Austin & Brunner 2004, Altman & Royston 2006, Royston et al. 2006). The quadratic term best described the non-linear relationship (Dohoo et al. 2012). A visual interpretation for age association with Cushing’s syndrome was included to aid interpretation (Harrell Jr 2015). The relationship demonstrated the highest odds of Cushing’s syndrome from 7 years onwards and can aid veterinarians when considering Cushing’s syndrome cases by helping to raise the index of suspicion in older dogs.

Dogs with a bodyweight higher than their breed-sex mean had 1.44 times the odds of Cushing’s syndrome that those within their breed mean. A similar association was reported previously in dogs (O’Neill et al. 2016) and the human medical literature, suggesting an association between obesity and increased risk of Cushing’s syndrome (Tiryakioglu et al. 2010). The mean body-weight in the current study was calculated across each dog’s lifetime from 18 months of age until 31 December 2016. Dogs with a weight greater than the breed-sex average might suggest obesity or larger examples of the breed as a possible risk factor for Cushing’s syndrome. The causal inference is difficult here due to the temporality of observation as a clinical feature of Cushing’s syndrome can be weight changes. A gain in weight can result from glucocorticoid impact on central hypothalamic appetite centres resulting in increased appetite and therefore increased calorie consumption (Tataranni et al. 1996, McGavin & Zachary 2006). However, excess glucocorticoids also have a catabolic effect on skeletal muscle leading to muscle wastage and weight loss (McGavin & Zachary 2006). Therefore further research is required to understand the temporal sequence of this association and to understand the impact of Cushing’s syndrome on body-weight measurements.

Insured dogs were associated with 2.46 times greater odds of Cushing’s syndrome compared to uninsured dogs. The reason for this association could be that the financial benefit of pet insurance might make reaching a diagnosis more likely (Egenvall et al. 2009). The higher odds in the insured population also suggest that there may be many uninsured dogs with Cushing’s syndrome not identified in the current study. Veterinary group attended was forced into the model as a fixed effect to adjust for variation between groups, but was only weakly associated with Cushing’s syndrome in the final model. After taking breed and age into account, the larger effects in the univariable analysis were diluted suggesting variations in pet demographics across the different veterinary groups. Combined sex-neuter status variable was not associated with Cushing’s syndrome in the final model (P=0.302). Studies vary in demonstrating a sex predisposition to Cushing’s syndrome. No sex predisposition in dogs was indicated in a study of UK dogs attending primary-care practice in a
multivariable model (O’Neill et al. 2016). Female dogs have been associated with Cushing’s syndrome in other studies but these all were examining univariable associations; therefore, findings may have reflected confounding rather than true effects (Gallelli et al. 2010, Hoffman et al. 2018, Carotenuto et al. 2019). The current study adds further evidence to there being no major sex association with Cushing’s syndrome in dogs. Other factors associated with Cushing’s syndrome have been reported but were not assessed in the present study, including concurrent diseases such as diabetes mellitus, biliary mucoceles and systemic hypertension (Kim et al. 2017, Miceli et al. 2017, Hoffman et al. 2018, García San José et al. 2020). The direct causal relationships between Cushing’s syndrome and these associated diseases are not well understood. Additional studies utilising primary-care data could provide further insight into these associations and gain additional understanding of the risk factors for Cushing’s syndrome diagnosis. There were some limitations to this study. The data were retrospective and not primarily recorded for research purposes. There was some missing data in this study and misclassification of Cushing’s syndrome was possible; some dogs with Cushing’s syndrome might have been included within the denominator population, as a diagnosis could have been missed in primary-care practice or a diagnosis not sought by an owner. The association of a Cushing’s syndrome diagnosis with insurance status highlights this. Dogs with a recorded suspicion of Cushing’s in the EPRs were included in the candidate search terms and were excluded from analysis, to minimise this bias. Additionally, there is a risk of dogs being incorrectly diagnosed with Cushing’s syndrome in the EPRs and included as a case in this study. For both the ACTH stimulation test and the LDDST, specificity estimates not highly accurate indicating that some falsely diagnosed cases of Cushing’s syndrome were likely included in the present study (Van Liew et al. 1997, Monroe et al. 2012, Bennaim et al. 2018, Nivy et al. 2018). As misclassification was likely to have occurred for both cases and non-cases, it was assumed that any incurring bias would likely have resulted in diluting the effect estimates (Dohoo et al. 2012).

In conclusion, this study examined a large sample of dogs with Cushing’s syndrome diagnosed in 2016 under primary-care veterinary practices from across the UK. Findings can help veterinarians during diagnosis of Cushing’s syndrome by raising awareness of key breed and age associations. Identification of protected breeds offers new options for research into genetic mechanisms. Additionally, owners can be reassured by the promising median survival times of dogs treated with mitotane or bilateral adrenalectomy. Findings can help veterinarians during diagnosis of Cushing’s syndrome by raising awareness of key breed and age associations. Identification of protected breeds offers new options for research into genetic mechanisms. Additionally, owners can be reassured by the promising median survival times of dogs treated with mitotane or bilateral adrenalectomy. Findings can help veterinarians during diagnosis of Cushing’s syndrome.

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