Journal of Veterinary Internal Medicine

ACVIM
Open Access
American College of
Veterinary Internal Medicine

STANDARD ARTICLE

Seizure occurrence in dogs under primary veterinary care in the UK: prevalence and risk factors

Alexander Erlen[1] | Heidrun Potschka[2] | Holger A. Volk[3] | Carola Sauter-Louis[4] |
Dan G. O'Neill[5]

[1]Inst. of Pharmacology, Toxicology, and
Pharmacy, Ludwig-Maximilians-University,
Munich, Germany

[2]Inst. of Pharmacology, Toxicology, and
Pharmacy, Ludwig-Maximilians-University,
Munich, Germany

[3]Clinical Science and Services, The Royal
Veterinary College, Hatfield, UK

[4]Institute of Epidemiology, Friedrich-Loeffler-
Institut, Greifswald, Germany

[5]Pathobiology and Population Health, The
Royal Veterinary College, Hatfield, UK

Correspondence
Alexander Erlen, Address: Inst. of
Pharmacology, Toxicology, and Pharmacy,
Ludwig-Maximilians-University, Königinstr.
16, 80539 Munich, Germany,
Email: alexander.erlen@pharmtox.vetmed.uni-
muenchen.de

Background: Primary-care veterinary clinical records can offer data to determine generalizable epidemiological data on seizures occurrence in the dog population.

Objectives: To identify and examine epidemiologic characteristics of seizure occurrence in dogs under primary veterinary care in the UK participating in the VetCompass™ Programme.

Animals: 455,553 dogs in VetCompass™'.

Methods: A cross-sectional analysis estimated the 1-year period prevalence and risk factors for dogs with seizures during 2013.

Results: The overall 1-year period prevalence for dogs having at least one seizure during 2013 was 0.82% (95% CI 0.79-0.84). Multivariable modelling identified breeds with elevated odd ratios [OR] compared with the Labrador Retriever (e.g. Pug OR: 3.41 95% CI 2.71-4.28, P < 0.001). Males had higher risk for seizures (Male/Entire OR: 1.47 95% CI 1.30–1.66; Male/Neutered OR: 1.34 95% CI 1.19–1.51) compared to entire females. Age (3.00 - ≤ 6.00 OR: 2.13 95% CI 1.90-2.39, P < 0.001, compared to animals aged 0.50–≤ 3.00 years), and bodyweight (≥ 40.00kg, OR: 1.24 95% CI 1.08–1.41, P = 0.002, compared to animals weighing < 10.0 kg) were identified as risk factors for seizures.

Conclusion and clinical Importance: Seizures are a relatively common clinical finding in dogs. The results for breed, age, sex and bodyweight as risk factors can assist veterinarians in refining differential diagnosis lists for dogs reported with behaviors that may have been seizures. In addition, the prevalence values reported here can support pharmacovigilance with baseline data from the overall population.

KEYWORDS

Canine, Epilepsy, Convulsion, Frequency, First-opinion, Breed

1 | INTRODUCTION

Seizures in dogs are sudden, short lasting and transient events that are characterized by motor, autonomic or behavioral features.[1] They are considered common events in dogs.[2] Causes including genetic and insult-triggered brain diseases, peripheral diseases, electrolyte imbalances, intoxications and idiopathic.[3] Seizure activity can have substantial impact on quality of life[3-5] as well as causing emotional distress for owners.[6,7] To date, most studies have focused on the subset of cases that are classified as epileptic.[8,9]

Seizures are either epileptic or reactive according to the classification of the IVETF. Epileptic seizures are manifestations of excessive synchronous neuronal activity in the brain that is usually self-limiting and that are promoted by a predisposition of the brain for ictogenesis.[1,10] Epilepsy is usually defined as requiring at least two unprovoked epileptic seizures more than 24 hours apart[11] and reactive seizures (also called provoked seizures) are considered as natural

Abbreviations: CI, confidence interval; EPR, electronic patient record; IQR, interquartile range; OR, odds ratio; PMS, practice management system; ROC, receiver operating characteristic; RVC, Royal Veterinary College; UK, United Kingdom; CNS, central nervous system; DYAR, dog years at risk; IVETF, International Veterinary Epilepsy Task Force

responses from the normal brain to some transient disturbance in function (e.g. metabolic or toxic) which is reversible when the cause or disturbance is rectified.[1,3] Analysis of a large pet insurance database reported an epilepsy incidence of 18 per 10,000 dog years at risk (DYAR) in Sweden for either idiopathic epilepsy or epileptic convulsions.[8] A study using primary-care veterinary clinical data reported a prevalence of 0.62% for epilepsy in dogs in the UK.[9] A cross sectional study compared period prevalence of epileptic seizures in a 2.5-year observation period between first opinion practices (0.43%) and a referral clinic in southern Germany (1.78%).[12] Among the referral subset of dogs seen at a veterinary teaching hospital in Germany, 2.6% had a history of seizures reported.[13] Epidemiological studies using first opinion databases that explore seizures in general rather than relying on semi-arbitrary classification into various subsets might offer novel and more clinically pertinent insights into this disease in dogs. There are breed predispositions to various forms of epilepsy, but predisposition studies often fail to describe the prevalence of seizures either in dogs overall and in individual breeds.

This study aimed to identify and explore seizure occurrence in the general dog population under primary veterinary care in the UK. The specific objectives were to estimate the 1-year period prevalence for dogs that showed seizures and to also identify demographic risk factors associated with dogs that showed seizures, with breed as a risk factor of special interest. These results could be especially valuable for practitioners, insurance companies, pharmaceutical and nutrition manufacturers and pharmacovigilance agencies by providing a representative evidence-base that can be generalized to the wider dog population and fill the evidential data gap on seizure occurrence.

2 | MATERIALS AND METHODS

This study was based on data collected within the VetCompass™ Animal Surveillance System [14] at the Royal Veterinary College (RVC). VetCompass™ collates electronic patient record (EPR) data from hundreds of UK primary-care practices for epidemiological research. Demographic information collected included species, breed, date of birth, sex and neuter status, while clinical information includes free text notes, treatment data as well as summarized diagnosis terms from the VeNom Codes standardized lists.[15] Clinical data from participating practices are extracted from practice management systems (PMSs) using automated queries, uploaded securely to the RVC server and reformatted for entry into the VetCompass™ online database system.[16]

A cross-sectional analysis using cohort clinical data of dogs attending VetCompass™ practices was used to estimate the 1-year period prevalence and risk factors for dogs with at least one seizure during 2013.[17] The denominator population for the current study comprised all dogs that had at least one EPR (clinical note, bodyweight or treatment) recorded in VetCompass™ during 2013 or dogs that had 'at least one EPR before and one EPR after 2013'. These dogs were defined as being under veterinary care during 2013.

Sample size calculations estimated that a study with 149,698 dogs would be required to represent a disorder with 1% expected prevalence to a precision of 0.05% at a 95% confidence level from an estimated UK national population of 9.4 million dogs.[18,19] Ethical approval was granted by the RVC Ethics and Welfare Committee (reference number 2015 1369).

A two-step letter-string search process was used to identify seizure cases in the VetCompass™ dog population. In step one, all EPRs were initially screened for candidate seizure cases using a range of letter-string search terms including seiz*, siez*, convul*, tonic*, clonic*, myoclo*, "had fit", "had a fit", epil*, diaz*, clonaz*, midazol*, phenobarb*, gabapen*, levetira*, bromide, pregaba*, zonis*, imepit*, pexi*, keppr*, hypnov*, epiph*, phenolep*, librom*, lyric*, alpraz* and zoneg*. In step two, the EPRs of all candidate cases which had been identified as possible seizure cases were manually read and evaluated for inclusion as a seizure case according to the study case definition. A seizure case was defined as any dog with at least one seizure event occurring during 2013 recorded in the EPR. All dogs with reported seizure activity in 2013 were grouped as seizure cases and all remaining dogs were grouped as non-cases.

A "Purebred "variable classified all dogs of a recognizable breed as" purebred", all dogs recorded with a designer breed name as "designer" [20] and all remaining dogs as "crossbred" . A "Breeds" variable included the breed name of any individual purebred or designer breed types with 15 or more seizure cases during 2013 while all remaining purebred and designer types were grouped as "Other purebreds and designers breed types" and a general category of crossbred dogs was also included. A "Kennel Club Breed Group" variable defined all KC recognized breeds according to their relevant UK KC breed groups (Gundog, Terrier, Utility, Hound, Working, Toy and Pastoral) and included all remaining dogs as "Breed not-Kennel Club recognized". The age for all dogs described the age at 31st December 2013. An age variable "Age" contained 7 age categories in years (0.00 - ≤ 0.50, 0.50 - ≤ 3.00, 3.00 - ≤ 6.00, 6.00 - ≤ 9.00, 9.00 - ≤ 12.00, ≥ 12.00, unrecorded) according to the IVETF guidelines.[21] The "Neuter status" variable recorded the neutering status recorded at the final EPR. Sex and neuter status were also combined into a single variable (Sex-neuter) that reported the results across seven permutational categories. The variable "Adult (> 18 months) bodyweight" described the maximum bodyweight recorded during the study period for dogs older than 18 months and categorized adult bodyweight into 6 groups (< 10.00 kg, 10.00 - ≤ 20.00 kg, 20.00 - ≤ 30.00 kg, 30.00 - ≤ 40.00 kg, ≥ 40.00 kg, unrecorded). A "Bodyweight relative to breed and sex mean" variable characterized the adult bodyweight of individual dogs as either below or equal/above the mean adult bodyweight for their breed and sex within the overall study population. This variable allowed the effect of adult bodyweight to be assessed within each breed/sex combination.

After data checking and cleaning in Excel (Microsoft Office Excel 2013, Microsoft Corp.), statistical analyses were conducted with IBM SPSS Statistics 24®. The 1-year period prevalence with 95% confidence intervals (CI) described the probability for each dog of having at least one seizure at any time during the 1-year 2013 study period. The CI estimates were derived from standard errors, based on approximation to the normal distribution.[22] Descriptive statistics characterized the count and proportions of cases and non-case dogs for each of the study variables. Binary logistic regression modelling was used to evaluate univariable associations between risk factors and being a

seizure case. Because breed was a factor of primary interest for the study, purebred status and Kennel Club Breed group (highly correlated with breed), and adult (>18months) bodyweight (a defining characteristic of individual breeds) were excluded from the initial breed multivariable modelling. Instead, each of these variables individually replaced the breed variable in the main final breed model in order to evaluate their effects after taking account of the other variables and these results were reported. Risk factors with liberal associations in univariable modelling (P < 0.2) were taken forward for multivariable logistic regression modelling evaluation. Model development used automated backwards stepwise elimination. The area under the ROC curve was used to assess the quality of the model fit. Statistical significance was set at P < 0.05.

3 | RESULTS

The study population comprised 455,553 dogs attending primary care practices in the UK participating in VetCompass™. Initial screening identified 10,584 candidate cases. After manual review, 3,731 (35.25%) dogs met the seizure inclusion criteria giving an overall 1-year period prevalence of 0.82% (95% CI 0.79 - 0.84) for dogs having at least one seizure. Individual breeds with the highest seizure prevalence included Pug (1.88% of the breed affected, 95% CI 1.52 - 2.24), Boxer (1.77%, 95% CI 1.44 - 2.09), Basset Hound (1.74%, 95% CI 1.02 - 2.46), Border Terrier (1.67%, 95% CI 1.33 - 2.01) and Border Collie (1.45%, 95% CI 1.24 - 1.66) (Table 1).

The most common breeds among the non-case dogs were the Labrador Retriever 32,998 (7.3%), Staffordshire Bull Terrier 32,407 (7.2%), Jack Russell Terrier 27,473 (6.1%), Cocker Spaniel 15,765 (3.5%), Yorkshire Terrier 15,248 (3.4%) as well as 100,249 (22.2%) crossbreds and 13,768 (3.0%) designers (Table 2). Of the non-case dogs, 337,805 (74.8%) were purebred and 232,080 (51.4%) were male. Of the males, 91,692 (20.3%) were entire and 102,968 (22.8%) were neutered (neuter status was not available for the remainer). The median adult bodyweight for non-cases was 16.60 kg (interquartile range [IQR]: 9.00 - 28.00, range: 0.30 - 112.00) and the median age was 4.09 years (IQR: 1.70 - 7.58, range: 0.00 - 24.68) (Fig 1).

Of the seizure cases, 2,962 (79.4%) were purebred, 2,131 (57.1%) were male. Of the males 731 (19.6%) were entire and 934 (25.0%) were neutered (neuter status was not available for the remainer). Across both sexes combined, 1,767 (47.3%) dogs were neutered. Dogs with seizures had a median adult bodyweight of 18.20 kg (IQR: 9.30 - 30.45, range: 0.80 - 86.90) and median age of 7.27 years (IQR: 4.23 - 11.07, range: 0.11 - 23.23) (Fig 1). The most common breeds among the seizure cases were Labrador Retriever (323/3,731 cases, 8.7% of all cases), Staffordshire Bull Terrier (228/3,731, 6.1%), Jack Russell Terrier (218/3,731, 5.8%), Border Collie (178/3,731, 4.8%) and Yorkshire Terrier (178/3,731, 4.8%) as well as crossbreds (681/3,731, 18.3%) and designer dogs (78/3,731, 2.1%), (Table 2).

Data completeness varied between the variables assessed: breed 100.0%, age 98.6%, sex 99.5%, bodyweight (> 18 months) 72.8% and neuter 84.1%. Univariable logistic regression modelling identified five variables that were liberally associated with seizures and were further evaluated in the main multivariable logistic regression modelling:

breed, age, bodyweight relative to breed and sex mean, neuter status, sex and sex-neuter (Table 2). The final breed multivariable logistic regression model showed good discrimination (area under the ROC curve: 0.714). After accounting for the effects of the other variables evaluated, 11 breed types had significantly increased odds of seizures compared with Labrador Retriever dogs. The breeds with the highest odd ratios (OR) included the Pug (OR: 3.41 95% CI 2.71 - 4.28, P < 0.001), Basset Hound (OR: 2.13 95% CI 1.38 - 3.30, P < 0.001), Dogue de Bordeaux (OR: 2.10 95% CI 1.37 - 3.22, P < 0.001), Boxer (OR: 1.95 95% CI 1.57 - 2.42, P < 0.001) and Beagle (OR: 1.91 95% CI 1.40 - 2.59, P < 0.001). Breeds with a significant lower OR of seizures in comparison to Labrador Retrievers were the Shih-tzu (OR: 0.53, 95% CI 0.40 - 0.70, P < 0.001), West Highland White Terrier (OR: 0.52, 95% CI 0.40 - 0.67, P < 0.001), English Springer Spaniel (OR: 0.50, 95% CI 0.34 - 0.74, P < 0.001) and Cocker Spaniel (OR: 0.44, 95% CI 0.34 - 0.58, P < 0.001). Crossbred dogs presented as well significantly reduced odds for seizures in comparison to Labrador Retriever (OR: 0.75 95% CI 0.66 - 0.86 P < 0.001). Compared with dogs aged between 0.50 - ≤ 3.00 years, dogs aged 3.00 - ≤ 6.00 years had 2.13 times the odds (95% CI 1.90 - 2.39, P < 0.001) for seizures. Dogs younger than 0.50 years had reduced odds (OR: 0.30 95% CI 0.20 - 0.45, P < 0.001) for seizures. The results showed a general trend towards increasing odds with increasing age. Males, regardless of neuter status had higher odds of seizures compared with entire females (Table 3).

As described in the methods, three variables (Purebred status, Kennel Club Breed groups, Adult (> 18months) bodyweight individually replaced the breed variable in the final multivariable breed model. Purebred dogs had 1.28 times the odds (95% CI 1.18 - 1.39, P < 0.001) compared with crossbred dogs. Compared with "Breeds not Kennel Club recognized", the "Toy" Kennel Club Breed group showed 1.68 times the odds (95% CI 1.52 - 1.86 P < 0.001), the "Working" group had 1.49 the odds (95% CI 1.29 - 1.73, P < 0.001) and the "Pastoral" group had 1.42 the odds (95% CI 1.26 - 1.61, P < 0.001). Dogs with an adult (> 18months) bodyweight ≥ 40.00 kg had 1.24 times the odds (95% CI 1.08 - 1.41, P = 0.002) compared with dogs < 10.00 kg (Table 4).

4 | DISCUSSION

This study explored the occurrence of seizures in a UK dog population under primary veterinary care. It benefitted from a large sample size of over 450,000 dogs. The study reports an overall 1-year period prevalence of 0.82% and identified the Pug, Boxer, Basset Hound, Border Terrier and Border Collie as the breeds with the highest seizure prevalence. Increasing age, being male, being purebred and weighing over 40kg were highlighted as significant risk factors. These results can assist veterinary clinicians, researchers, breeders and pharmacovigilance agencies by providing a reliable evidence resource. This study also highlights the value of developing similar large-scale systems for collection and analysis of veterinary clinical data outside of the UK in order to generate evidence that will be more generalizable to their national animal populations.

TABLE 1 Prevalence of seizures in commonly affected dog breeds

Breed	No. Cases	No. Dogs in study	Median age in years of cases(IQR)	Prevalence %	95% CI[a]
Pug	101	5376	4.95 (2.76-6.99)	1.88	1.52-2.24
Boxer	111	6288	9.52 (6.95-11.04)	1.77	1.44-2.09
Basset Hound	22	1263	6.22 (3.19-9.36)	1.74	1.02-2.46
Border Terrier	91	5449	7.06 (4.85-11.35)	1.67	1.33-2.01
Border Collie	178	12268	6.43 (4.18-12.18)	1.45	1.24-1.66
Beagle	48	3508	5.71 (5.46-7.35)	1.37	0.98-1.75
King Charles Spaniel	21	1666	5.18 (3.03-11.33)	1.26	0.72-1.80
Dogue de Bordeaux	23	1858	3.76 (2.05-5.91)	1.24	0.73-1.74
British Bulldog	39	3374	2.54 (1.58-4.46)	1.16	0.80-1.52
Weimaraner	18	1568	8.30 (6.90-10.73)	1.15	0.62-1.68
Yorkshire Terrier	178	15426	8.23 (5.33-12.44)	1.15	0.99-1.32
Cavalier King Charles Spaniel	112	10143	6.95 (4.91-9.20)	1.10	0.90-1.31
Patterdale Terrier	26	2433	5.58 (3.35-8.31)	1.07	0.66-1.48
Pomeranian	22	2147	4.95 (1.81-6.97)	1.02	0.60-1.45
Labrador Retriever	323	33321	7.21 (4.48-9.91)	0.97	0.87-1.06
Toy Poodle	18	1881	7.60 (4.06-12.83)	0.69	0.52-1.40
Golden Retriever	54	5670	8.33 (5.02-12.40)	0.95	0.70-1.21
German Shepherd Dog	116	12520	8.59 (5.35-10.98)	0.93	0.76-1.09
Chihuahua	101	11782	4.04 (1.85-6.67)	0.86	0.69-1.02
Akita	17	2105	7.36 (3.45-13.32)	0.81	0.42-1.19
Miniature Schnauzer	31	3857	6.30 (3.04-10.66)	0.80	0.52-1.09
French Bulldog	19	2397	2.18 (1.56-6.00)	0.79	0.44-1.15
Jack Russell Terrier	218	27691	8.59 (5.39-12.83)	0.79	0.68-0.89
Labradoodle	23	3132	4.47 (3.73-6.80)	0.73	0.44-1.03
Miniature Dachshhund	20	2792	5.64 (4.07-8.14)	0.72	0.40-1.03
Staffordshire Bull Terrier	228	32635	7.97 (4.40-10.97)	0.70	0.61-0.79
Crossbred	681	98931	8.23 (4.57-12.71)	0.96	0.64-0.74
Lurcher	22	3222	5.78 (3.17-11.32)	0.68	0.40-0.97
Husky	28	4162	4.55 (1.66-5.91)	0.67	0.42-0.92
West Highland White Terrier	73	12017	10.94 (5.78-13.83)	0.61	0.47-0.75
Springer Spaniel	35	5800	10.04 (5.71-12.78)	0.60	0.40-0.80
Lhasa Apso	38	6840	8.80 (4.75-12.91)	0.56	0.38-0.73
Bichon	36	6607	8.67 (3.84-12.63)	0.54	0.37-0.72
English Springer Spaniel	29	5384	7.86 (3.92-11.71)	0.54	0.34-0.73
Unrecorded	10	2009	9.18 (4.58-14.76)	0.50	0.19-0.81
Rottweiler	24	5321	6.34 (4.91-10.69)	0.45	0.27-0.63
Designer	33	7492	3.11 (1.89-4.98)	0.44	0.29-0.59
Cocker Spaniel	62	15827	8.08 (4.72-11.15)	0.39	0.29-0.49
Shih-tzu	57	15038	8.24 (4.75-13.56)	0.38	0.28-0.48
Other purebreds and designers breed types	445	54353	7.32 (4.19-10.90)	0.82	0.74-0.89
Overall total	3731	455553	7.27 (4.23-11.07)	0.82	0.79-0.84

One-year period prevalence of seizures in commonly affected dog breeds under primary veterinary care in the UK; aCI confidence interval.

The VetCompass™ database was selected as a useful data source for the current study that aimed to provide a prevalence estimate for dogs with seizures with high levels of validity, generalizability and precision for the general population of dogs in the UK. Primary-care veterinary clinical data might lack diagnostic precision for complicated disorders due to financial constraints on clinical work-up, but are much less affected by the selection biases and therefore the results are thought to have greater validity than referral studies that preferentially select for dogs that are by definition sick and generally affected with more complicated disease and more severe presentations and owned by more motivated owners.[23] Primary-care data collected and merged from many hundreds of clinics now offers study sample sizes of sufficiently large size to allow much greater numerical precision in results than has previously been possible.[23] It is estimated that 70% of UK dogs are registered with a veterinary practice and therefore results of studies using primary-care data offer good prospects of generalization to the wider dog population and clinical relevance of the emergent results to veterinarians.[19,24]

TABLE 2 Descriptive and univariable regression results

Variable	Category	Case No. (%)	Non-case No. (%)	Odds ratio	95% CI[a]	Category P-value	Variable P-value
Purebred	Crossbred	681 (18.3)	98250 (21.7)	Base			< 0.001
	Designer	78 (2.1)	13768 (3.0)	0.82	0.65-1.03	0.092	
	Purebred	2962 (79.4)	337805 (74.8)	1.27	1.16-1.38	< 0.001	
	Unrecorded	10 (0.3)	1999 (0.4)	0.72	0.39-1.35	0.31	
Breeds	Labrador Retriever	323 (8.7)	32998 (7.3)	Base		< 0.001	< 0.001
	Pug	101 (2.7)	5275 (1.2)	1.96	1.56-2.45	< 0.001	
	Boxer	111 (3.0)	6177 (1.4)	1.84	1.48-2.28	< 0.001	
	Basset Hound	22 (0.6)	1241 (0.3)	1.81	1.17-2.80	0.008	
	Border Terrier	91 (2.4)	5358 (1.2)	1.74	1.37-2.19	< 0.001	
	Border Collie	178 (4.8)	12090 (2.7)	1.50	1.25-1.81	< 0.001	
	Beagle	48 (1.3)	3460 (0.8)	1.42	1.04-1.92	0.025	
	King Charles Spaniel	21 (0.6)	1645 (0.4)	1.30	0.84-2.03	0.24	
	Dogue de Bordeaux	23 (0.6)	1835 (0.4)	1.28	0.84-1.96	0.26	
	British Bulldog	39 (1.0)	3335 (0.7)	1.19	0.86-1.67	0.30	
	Yorkshire Terrier	178 (4.8)	15248 (3.4)	1.19	0.99-1.43	0.061	
	Weimaraner	18 (0.5)	1550 (0.3)	1.19	0.74-1.91	0.48	
	Cavalier King Charles Spaniel	112 (3.0)	10031 (2.2)	1.14	0.92-1.42	0.23	
	Patterdale Terrier	26 (0.7)	2407 (0.5)	1.10	0.74-1.65	0.63	
	Pomeranian	22 (0.6)	2125 (0.5)	1.06	0.69-1.63	0.80	
	Toy Poodle	18 (0.5)	1863 (0.4)	0.99	0.61-1.59	0.96	
	Golden Retriever	54 (1.4)	5616 (1.2)	0.98	0.74-1.31	0.90	
	German Shepherd Dog	116 (3.1)	12404 (2.7)	0.96	0.77-1.18	0.68	
	Chihuahua	101 (2.7)	11681 (2.6)	0.88	0.71-1.11	0.28	
	Akita	17 (0.5)	2088 (0.5)	0.83	0.51-1.36	0.46	
	Miniature Schnauzer	31 (0.8)	3826 (0.8)	0.83	0.57-1.20	0.32	
	French Bulldog	19 (0.5)	2378 (0.5)	0.82	0.51-1.30	0.39	
	Jack Russell Terrier	218 (5.8)	27473 (6.1)	0.81	0.68-0.96	0.017	
	Labradoodle (Designer)	23 (0.6)	3109 (0.7)	0.76	0.49-1.16	0.20	
	Miniature Dachshund	20 (0.5)	2772 (0.6)	0.74	0.47-1.16	0.19	
	Staffordshire Bull Terrier	228 (6.1)	32407 (7.2)	0.72	0.61-0.85	< 0.001	
	Crossbred	681 (18.3)	98250 (21.7)	0.71	0.62-0.81	< 0.001	
	Lurcher (Designer)	22 (0.6)	3200 (0.7)	0.70	0.46-1.08	0.11	
	Husky	28 (0.8)	4134 (0.9)	0.69	0.47-1.02	0.063	
	West Highland White Terrier	73 (2.0)	11944 (2.6)	0.62	0.48-0.81	< 0.001	
	Springer Spaniel	35 (0.9)	5765 (1.3)	0.62	0.44-0.88	0.007	
	Lhasa Apso	38 (1.0)	6802 (1.5)	0.57	0.41-0.80	0.001	
	Bichon	36 (1.0)	6571 (1.5)	0.56	0.40-0.79	0.001	
	English Springer Spaniel	29 (0.8)	5355 (1.2)	0.55	0.38-0.81	0.002	
	Rottweiler	24 (0.6)	5297 (1.2)	0.46	0.31-0.70	< 0.001	
	Designer	33 (0.9)	7459 (1.6)	0.45	0.32-0.65	< 0.001	
	Cocker Spaniel	62 (1.7)	15765 (3.5)	0.40	0.31-0.53	< 0.001	
	Shih-tzu	57 (1.5)	14981 (3.3)	0.39	0.29-0.52	< 0.001	
	Unrecorded	10 (0.3)	1999 (0.4)	0.51	0.27-0.96	0.037	
	Other purebreds and designers breed types	445 (11.9)	53908 (11.9)	0.84	0.73-0.97	0.02	
Kennel Club Breed Groups	Breed not Kennel Club recognized	1074 (28.8)	151937 (33.6)	Base			< 0.001
	Gundog	589 (15.8)	72359 (16.0)	1.15	1.04-1.27	0.006	
	Hound	139 (3.7)	15832 (3.5)	1.23	1.03-1.47	0.021	
	Pastoral	331 (8.9)	29374 (6.5)	1.59	1.41-1.80	< 0.001	
	Terrier	462 (12.4)	58643 (13.0)	1.12	0.99-1.24	0.052	

TABLE 2 (Continued)

Variable	Category	Case No. (%)	Non-case No. (%)	Odds ratio	95% CI[a]	Category P-value	Variable P-value
	Toy	617 (16.5)	56704 (12.6)	1.54	1.39-1.70	< 0.001	
	Utility	307 (8.2)	44855 (9.9)	0.97	0.85-1.10	0.62	
	Working	212 (5.7)	22118 (4.9)	1.36	1.17-1.57	< 0.001	
Adult (>18months) bodyweight (kg)	< 10.00	878 (23.5)	98359 (21.8)	Base		< 0.001	< 0.001
	10.00 - ≤ 20.00	830 (22.3)	91219 (20.2)	1.02	0.93-1.12	0.69	
	20.00 - ≤ 30.00	641 (17.2)	67845 (15.0)	1.06	0.95-1.17	0.29	
	30.00 - ≤ 40.00	526 (14.1)	46004 (10.2)	1.28	1.15-1.43	< 0.001	
	≥ 40.00	313 (8.4)	24860 (5.5)	1.41	1.24-1.61	< 0.001	
	Unrecorded	543 (14.6)	123535 (27.2)	0.49	0.44-0.55	< 0.001	
Bodyweight relative to breed and sex mean	Lower	1636 (43.9)	182105 (40.3)	Base			< 0.001
	Equal/Higher	1550 (41.5)	145848 (32.4)	1.18	1.10-1.27	< 0.001	
	Unrecorded	545 (14.6)	123869 (27.3)	0.49	0.44-0.54	< 0.001	
Age (years)	0.00 - ≤ 0.50	25 (0.7)	25508 (5.6)	0.28	0.19-0.42	< 0.001	< 0.001
	0.50 - ≤ 3.00	522 (14.0)	148813 (32.9)	Base			
	3.00 - ≤ 6.00	923 (24.7)	114584 (25.4)	2.30	2.06-2.56	< 0.001	
	6.00 - ≤ 9.00	832 (22.3)	76360 (16.9)	3.10	2.78-3.46	< 0.001	
	9.00 - ≤ 12.00	636 (17.1)	47228 (10.5)	3.84	3.42-4.31	< 0.001	
	≥ 12.00	767 (20.6)	33180 (7.3)	6.59	5.89-7.37	< 0.001	
	Unrecorded	26 (0.7)	6149 (1.4)	1.21	0.81-1.79	0.35	
Sex	Female	1592 (42.7)	217440 (48.1)	Base			< 0.001
	Male	2131 (57.1)	232080 (51.4)	1.25	1.17-1.34	< 0.001	
	Not recorded	8 (0.2)	2302 (0.5)	0.48	0.24-0.95	0.036	
Neuter status	Entire	1150 (30.8)	177066 (39.1)	Base			< 0.001
	Neutered	1767 (47.3)	203252 (45.0)	1.34	1.24-1.44	< 0.001	
	Unrecorded	814 (21.8)	71504 (15.9)	1.75	1.60-1.92	< 0.001	
Sex-neuter	Female/Entire	412 (11.0)	83498 (18.5)	Base			< 0.001
	Female/Neutered	832 (22.3)	100164 (22.2)	1.68	1.50-1.90	< 0.001	
	Female/Unrecorded	348 (9.3)	33778 (7.5)	2.09	1.81-2.41	< 0.001	
	Male/Entire	731 (19.6)	91692 (20.3)	1.62	1.43-1.82	< 0.001	
	Male/Neutered	934 (25.0)	102968 (22.8)	1.84	1.64-2.06	< 0.001	
	Male/Unrecorded	466 (12.5)	37420 (8.3)	2.52	2.21-2.88	< 0.001	
	Unrecorded/Unrecorded	8 (0.2)	2302(0.5)	0.70	0.35-1.42	0.33	

Descriptive and univariable regression results for risk factors associated with seizure events in dogs under veterinary primary-care in the UK. Percentages shown in brackets aCI confidence interval.

The current study reported a 1-year prevalence of 0.82% for dogs affected by at least one seizure. To our knowledge, no previous studies have reported on the prevalence of seizures in the general dog population that can be used for direct comparison to this result. An earlier VetCompass™ study using primary-care data reported a prevalence of 0.62% for epilepsy of unknown origin in the UK.[9] This earlier study covered a longer period from January 2010 to April 2011 and focused specifically on the subset of dogs with "epilepsy of unknown origin", excluding any dogs which had a clinically identified underlying disease causing epilepsy, whereas the current study included all dogs with seizures from any etiology during a 1-year period. Thus, the previous reported prevalence is lower than the value reported in the current study as would be expected. Analysis of claim data from a large insurance database in Sweden reported a 0.75% prevalence of insured dogs with a recorded claim for epilepsy.[8] However, this prevalence among

insured dogs might be higher than in the wider dog population under veterinary care because certain breed types perceived to have higher health risks may be preferentially insured.[25] Furthermore, the study dogs contributed an average of 4.2 years to the insurance study compared with the 1-year period included in the current study. Further studies have also reported on referral populations.[13,26,27] One of these studies reported a total seizure prevalence of 2.6% in a hospital population in Germany comprising 394 seizure case dogs admitted between January 2002 and March 2008.[13] This prevalence may exceed the 0.82% reported in the current UK primary-care study because primary-care caseloads include 24.2% of dogs that have no diseases recorded and many of the remaining have minor ailments.[23,28] However, further factors that could partially account for the differences need to be considered and may include geographic and temporal differences between the studies as well as differing sample size and breed compositions.
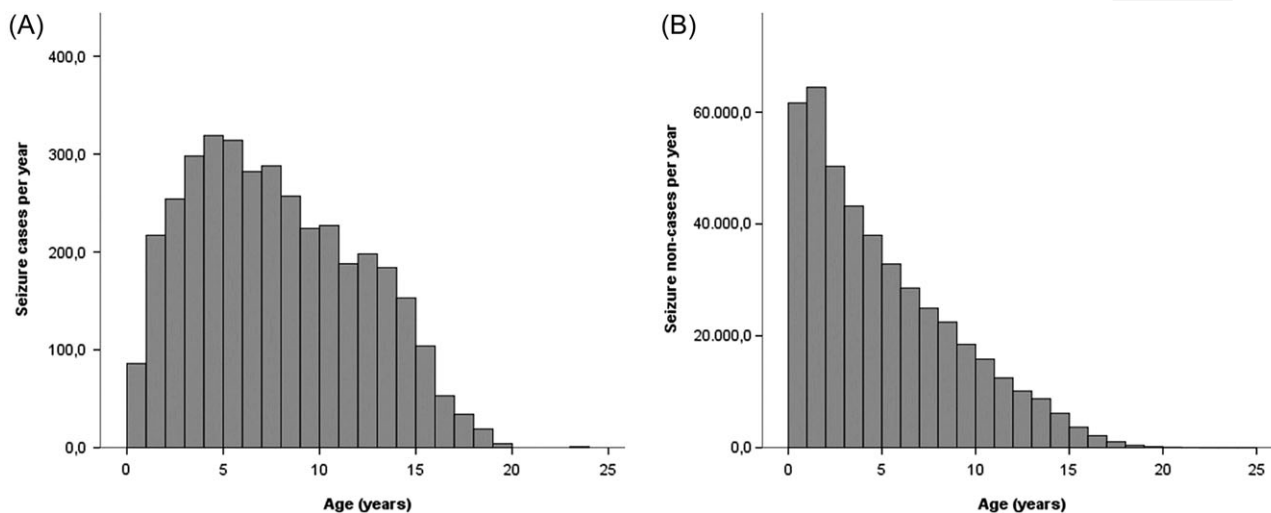
FIGURE 1 A: Seizure cases per year (n = 3,704) in the UK dog population under primary veterinary care B: Seizure non-cases per year (n = 445,674) in the UK dog population under primary veterinary care

The 1-year period prevalence of 0.82% identifies seizures as a relatively frequent clinical presentation in the UK dog population under primary veterinary care. Seizures are a clinical manifestation that can result from a wide variety of causes, but are not limited to, genetic predisposition, primary brain disease, intoxication, cardiovascular disease, electrolyte disturbance and endocrine and metabolic disorders.[23] The proportional contribution of reactive seizures to the total seizure case burden has been variously estimated at between 13.6% and 32% respectively.[13,26,27] The differences between the study outcome might result from variation between study design (e.g. prospective versus retrospective analyses), countries, diagnostic procedures and animal population selection (e.g. primary-care versus referral caseloads). The results of the current study underline the relevance of undergraduate training and continuing education about the multiple causes of seizure events, the optimal diagnostic procedures, and the management options for seizure events in dogs. These period prevalence data should also be considered as a useful background presence of seizures when considering suspected adverse events reported to pharmacovigilance monitoring systems.[29,30]

Risk factors results can provide valuable information to improve veterinary diagnosis of disease and hence to improve animal welfare monitoring.[31] The current study placed special focus on exploring breed as a risk factor for seizure occurrence because of prior evidence of genetic associations with epilepsy in dogs.[26] As might have been expected, seizures proved to be more frequent in purebreds compared to crossbred and designer dogs although the purebred predisposition could be heavily influenced by the subgroup of dogs with idiopathic epilepsy. In a recent longitudinal study at Copenhagen University Hospital, dogs with idiopathic epilepsy exhibited a breed distribution of 83.6% purebred and 16.4% crossbred.[26] However, hereditary factors might also contribute to structural epilepsy as well as non-epileptic seizures cases as the genetic background might, for instance, predispose to epilepsy development after a brain injury or might predispose to a peripheral disease associated with non-epileptic seizures.

Hybrid vigor (also known as heterosis or crossbred vigor) describes a phenomenon whereby the average performance of first-generation crosses for specified traits outperforms the average performance of their parental breeds [32] and has been proposed to enhance the health of crossbred compared with purebred animals for over 150 years.[33] Substantial evidence exists for these effects in production species of plants [34] and animals.[35–37] However, pet dogs are generally not kept for production traits and the strength of evidence to support the true impact of hybrid vigor in dogs has recently been questioned.[38] The findings in the current study that purebred dogs had 1.28 times higher odds of being seizure cases compared with crossbreds might add further weight to the existence of hybrid vigor in domestic dogs. Although the difference in effect shown might not appear to be substantial, it is likely that many of the crossbreds in our study were not first-generation crosses and therefore would have lost much of the additional health gains shown by first-generation crosses.[32] It is possible that any true reduction in seizure prevalence in crossbreds may have been much higher specifically in the first-generation subset of crosses but it was not possible to identify these dogs in the current study. The heterogeneity in genetics and health among the many individual breeds that exist among the purebred grouping should act as a further caveat to facile acceptance of the hybrid vigor concept.[28] Relative changes in the proportions of some common breeds that are either predisposed or protected to certain diseases could dramatically affect the overall probability of disease in purebred dogs overall. From this it is clear that resolving the hybrid vigor question in dogs has quite some way to go.

Exploration of associations, in both predisposition and protective directions, between individual breeds and the occurrence of seizures was of particular interest in this study. After accounting for other relevant factors, the final multivariable identified predisposition to seizures in 11 breeds with odds ratios ranging up to 3.41 times higher than that of Labrador Retrievers. Although the Labrador Retriever itself has previously been reported as a predisposed breed for epilepsy with a reported lifetime prevalence of 3.1%,[39] the current study elected to use the Labrador Retriever instead of crossbreds as the comparator breed in contrast to other previous studies[9]. Crossbred dogs, by definition, provide highly uncertain genetic structure, body

TABLE 3 Final breed multivariable logistic regression results

Variable		Odds ratio	95%Cla	p-value	Variable P-value
Breeds	Labrador Retriever	Base			< 0.001
	Pug	3.41	2.71-4.28	< 0.001	
	Basset Hound	2.13	1.38-3.30	0.001	
	Dogue de Bordeaux	2.10	1.37-3.22	0.001	
	Boxer	1.95	1.57-2.42	< 0.001	
	Beagle	1.91	1.40-2.59	< 0.001	
	French Bulldog	1.87	1.17-2.98	0.009	
	British Bulldog	1.84	1.31-2.58	< 0.001	
	Border Terrier	1.79	1.42-2.27	< 0.001	
	Pomeranian	1.57	1.01-2.43	0.043	
	Chihuahua	1.50	1.20-1.89	< 0.001	
	Border Collie	1.41	1.17-1.69	< 0.001	
	King Charles Spaniel	1.39	0.89-2.17	0.15	
	Patterdale Terrier	1.26	0.84-1.88	0.27	
	Cavalier King Charles Spaniel	1.22	0.98-1.52	0.070	
	Yorkshire Terrier	1.14	0.95-1.37	0.16	
	Labradoodle	1.13	0.74-1.74	0.56	
	Weimaraner	1.13	0.70-1.82	0.62	
	Akita	1.11	0.68-1.81	0.68	
	Toy Poodle	1.06	0.66-1.72	0.80	
	Husky	1.05	0.71-1.55	0.81	
	German Shepherd Dog	1.02	0.82-1.26	0.88	
	Designer	1.00	0.70-1.44	0.99	
	Miniature Schnauzer	0.97	0.67-1.40	0.854	
	Miniature Dachshund	0.83	0.53-1.31	0.435	
	Golden Retriever	0.83	0.62-1.11	0.215	
	Staffordshire Bull Terrier	0.81	0.68-0.96	0.016	
	Jack Russell Terrier	0.79	0.66-0.94	0.007	
	Crossbred	0.75	0.66-0.86	< 0.001	
	Bichon	0.69	0.49-0.97	0.034	
	Lurcher	0.68	0.44-1.05	0.083	
	Springer Spaniel	0.66	0.47-0.94	0.022	
	Lhasa Apso	0.65	0.46-0.91	0.011	
	Rottweiler	0.54	0.36-0.82	0.004	
	Shih-tzu	0.53	0.40-0.70	< 0.001	
	West Highland White Terrier	0.52	0.40-0.67	< 0.001	
	English Springer Spaniel	0.50	0.34-0.74	< 0.001	
	Cocker Spaniel	0.44	0.34-0.58	< 0.001	
	Unrecorded	0.72	0.38-1.37	0.31	
	Other purebreds and designers breed types	0.89	0.77-1.03	0.11	
Age (years)	0.00 - ≤ 0.50	0.30	0.20-0.45	< 0.001	< 0.001
	0.50 - ≤ 3.00	Base		< 0.001	
	3.00 - ≤ 6.00	2.13	1.90-2.39	< 0.001	
	6.00 - ≤ 9.00	2.89	2.57-3.25	< 0.001	
	9.00 - ≤ 12.00	3.63	3.21-4.11	< 0.001	
	≥ 12.00	6.63	5.88-7.47	< 0.001	
	Unrecorded	1.46	0.98-2.18	0.065	

TABLE 3 (Continued)

Variable		Odds ratio	95%CIa	p-value	Variable P-value
Bodyweight relative to breed and sex mean	Lower	Base		< 0.001	< 0.001
	Equal/Higher	1.06	0.99-1.14	0.082	
	Unrecorded	0.76	0.69-0.84	< 0.001	
Sex-neuter	Female/Entire	Base		< 0.001	< 0.001
	Female/Neutered	1.14	1.01-1.28	0.039	
	Female/ Unrecorded	1.43	1.24-1.65	< 0.001	
	Male/Entire	1.47	1.30-1.66	< 0.001	
	Male/Neutered	1.34	1.19-1.51	< 0.001	
	Male/ Unrecorded	1.73	1.51-1.99	< 0.001	
	Not recorded/ Unrecorded	1.00	0.49-2.05	0.99	

Multivariable logistic regression model for risk factors associated with seizures in dogs under primary-care in the UK; aCI confidence interval.

conformation and parental-breed contribution compared with their purebred counterparts that are more standardized with higher genetic homozygosity, breed standards for conformation and defined parentage [40] The high count of Labrador Retrievers in the study also enabled high statistical power to explore breed risks.[41] However, interested readers who still wish to evaluate breed predisposition using crossbreds as the comparator category can still check for overlap of the 95% CI for each category; categories that do not overlap can be interpreted as showing statistically significant differences in their odds of diagnosis as seizure cases. The 11 breeds with significantly higher odds ratios compared to the Labrador Retriever were the Pug, Basset Hound, Dogue de Bordeaux, Boxer, Beagle, French Bulldog, British Bulldog, Border Terrier, Pomeranian, Chihuahua and Border Collie.

The majority of previous studies in this area have focused on epilepsy in dog breeds and often went even further by specifically targeting the epilepsy subset with a suspected inheritance of idiopathic epilepsy.[10] Many of these earlier studies relied on relatively small groups of dogs or families that made it problematic to generalize the findings to the overall breed although recently some larger studies have reported breed-specific epilepsy prevalence estimates.[10]

There are differing etiologies for epileptic seizures for Pugs (necrotizing encephalopathy) [42] and the Basset Hounds (Lafora disease).[43] Seizure activity in the Dogue de Bordeaux is associated with a genetic predisposition but based on a small sample size of 5 dogs.[44] Seizures and their etiology have also been investigated for 3 of the other predisposed breeds found in the current study: the Border Collie,[45]

TABLE 4 Multivariable logistic regression results for variables that replaced breed

Variable	Category	Odds ratio	95%CIa	p-value	Variable P-value
Purebred	Crossbred	Base			< 0.001
	Purebred	1.28	1.18-1.39	< 0.001	
	Designer	1.18	0.93-1.50	0.16	
	Unrecorded	0.94	0.50-1.78	0.86	
Kennel Club Breed Groups	Breed not Kennel Club recognized	Base			< 0.001
	Gundog	1.05	0.95-1.16	0.34	
	Hound	1.20	1.01-1.44	0.042	
	Pastoral	1.42	1.25-1.60	< 0.001	
	Terrier	1.03	0.92-1.15	0.59	
	Toy	1.68	1.52-1.86	< 0.001	
	Utility	1.09	0.96-1.24	0.16	
	Working	1.49	1.28-1.72	< 0.001	
Adult (>18months) bodyweight (kg)	< 10.00	Base			< 0.001
	10.00 - ≤ 20.00	0.92	0.84-1.01	0.092	
	20.00 - ≤ 30.00	0.92	0.83-1.02	0.110	
	30.00 - ≤ 40.00	1.11	1.00-1.24	0.061	
	≥ 40.00	1.24	1.08-1.41	0.002	
	Unrecorded	0.74	0.66-0.83	< 0.001	

Results for variables that replaced the breed variable in the final breed multivariable logistic regression model (with age category, bodyweight relative to breed mean sex and neuter status) to evaluate risk factors associated with seizures in dogs under primary veterinary care in the UK. Bodyweight relative to breed mean was also removed for adult bodyweight, aCI confidence interval.

Border Terrier,[9,46] Labrador Retriever,[39] and the Chihuahua.[47] However, there are no reliable reports on seizure activity in the French Bulldog, British Bulldog and Pomeranian. The findings of the current study go further than many of these previous studies and additionally include dogs with seizures that are both reactive as well as epileptic in order to give a more holistic view of the seizure predispositions that includes both genetic and environmental proclivities.

A protective effect for seizures was identified in Shih-tzu, West Highland White Terrier, English Springer Spaniel and Cocker Spaniel. A previous primary-care veterinary study similarly showed reduced risk to epilepsy of unknown origin in English Springer Spaniels and West Highland White Terrier in the UK.[9] Breed health studies to date have heavily focused on predisposition to disease.[28,48] However, evidence to support protective disease effects, both between and within breeds, is increasing needed to support planned breed health reforms such as outcrossing to other breeds or to breed strains from other countries.[49]

Increased risk for epileptic seizures in male dogs is recognized across all dogs types [8,9,50–53] as well as within specific breeds.[10] Our analysis of UK primary-care veterinary data that included both epileptic and reactive seizures also revealed a higher risk for male dogs. An interaction effect was noted between neutering and sex whereby the effect the neutering was not equal between the sexes. For this reason, the final multivariable model reported the values for each combination of sex and neuter status separately. Although neutering is a time dependent event whereby animals have an increased opportunity to become neutered as they age, the final multivariable model did take age into account and still showed an increased odds of seizures in neutered compared with entire bitches. This effect appears to be quite sex-specific however and no significant effect of neutering on seizure risk in males was noted. However, a word of caution in relation to the potential benefits of neutering in bitches: studies such as the current cross-sectional analysis can only show statistical association and must not be taken on their own as evidence of causality.[31,54] It is also possible that these associations stem from reverse causality effects whereby bitches that show seizures might be more likely to be removed from the breeding pool and then neutered rather than the other way around.[52,55] Future cohort analyses that follow animals over time to collect date information on the seizure onset and neutering as well as the rationale for the neutering decision are required to clarify the true role of neutering and seizure occurrence.

In agreement with previous studies, the current study identified increasing seizure risk with aging.[39,52] It is also worth noting that our study design reported the age of all cases during 2013 rather than reporting the age that these animal *first* became a case. This means that the inference from the results describes the probability for seizure cases *existing* within these age groups (prevalence) rather than the probability of new cases *developing* during these ages (incidence). However, a detailed investigation of seizure etiologies within the age groups was beyond the scope the study and would be required to further explore differing seizure etiologies across the age groups. A study of dogs referred for examination in Austria showed that idiopathic epilepsy was 3.25 times more likely to be the cause for seizure onset in dogs aged one to five years compared to structural epilepsy [56]

whereas a US study of referred dogs identified that 65% of seizure cases older than five years were associated with structural epilepsy.[57]

Dogs weighing over 40.00 kg in absolute bodyweight had significantly higher odds and dogs weighing between 30.00 - ≤ 40.00 kg had a tendency to higher odds for seizures compared with dogs weighing under 10.00 kg. Although these findings might suggest increased seizure risk in larger dogs, it is also possible that these associations with bodyweight might result from seizure disease management using anti-convulsive treatment. Bodyweight gain due to polyphagia has been described as a common adverse effect of many antiepileptic drugs.[58] It is also worth noting that no effect was identified within breeds between dogs that weighed over or under their breed and sex average bodyweight.

In common with other epidemiological studies using primary-care veterinary clinical data, this study had some limitations.[16,59] Retrospective identification of cases with seizures relied on the diagnostic acumen and reporting of the veterinarians contributing data to the VetCompass™ Program. Information about seizure occurrence is often based on description by owners and the veterinarian might not often witness the actual seizure event directly, and therefore some seizures that occur when dogs are not under observation by the owner might be missed or conversely falsely classified as seizure. In addition, less severe, non-generalized seizures might not even be recognized as seizures by the owner and therefore might not be reported to the veterinarian. Even in human patients with epilepsy, up to 38% of focal seizures go unrecognized [60–62] and similar under-reporting of seizures has been considered in dogs.[63] Thus, the results of the present study might underestimate the true absolute period prevalence of seizures in the UK canine population but these effects are unlikely to affect the results of the risk factor analyses where similar under-reporting is expected across all categories within each variable.[64]

In conclusion, this analysis of over 450,000 dogs under primary veterinary care shows that the combined effects of epileptic and reactive seizures are a relatively common clinical finding with 0.82% of UK dogs affected in a 1-year period. As seizure diagnosis and management therefore constitute an important role in clinical practice, these results highlighting particular breeds, sex and aging as significant risk factors should assist veterinarian practitioners to identify and alert owners to dogs at higher risk. Enhanced owner awareness could promote earlier, faster and more reliable diagnosis and treatment to support improved animal welfare. These results can also assist pharmacovigilance efforts by providing baseline data from the overall population to optimize interpretability of seizures when reported as suspected adverse reaction to medication use.

Pharmacy, Ludwig-Maximilians-University, Königinstr. 16, 80539 Munich, Germany, Bayer Animal Health GmbH, 51373 Leverkusen.

The study was supported by Bayer Animal Health GmbH, Kaiser-Wilhelm - Allee 10 51373 Leverkusen, Germany.

CONFLICT OF INTEREST DECLARATION

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

ORCID

Alexander Erlen http://orcid.org/0000-0002-2193-4684

REFERENCES

1. Berendt M, Farquhar RG, Mandigers PJ, et al. International veterinary epilepsy task force consensus report on epilepsy definition, classification and terminology in companion animals. *BMC Vet Res*. 2015; 11:182.
2. De Risio L, Newton R, Freeman J, et al. Idiopathic epilepsy in the Italian Spinone in the United Kingdom: Prevalence, clinical characteristics, and predictors of survival and seizure remission. *J Vet Intern Med*. 2015;29:917-924.
3. Brauer C, Jambroszyk M, Tipold A. Metabolic and toxic causes of canine seizure disorders: A retrospective study of 96 cases. *The Veterinary Journal*. 2011;187:272-275.
4. Platt SR, McDonnell JJ. Status epilepticus: Clinical features and pathophysiology. *Compendium on Continuing Education for the Practicing Veterinarian*. 2000;22:660-669.
5. Packer RMA, Volk HA. Epilepsy beyond seizures: a review of the impact of epilepsy and its comorbidities on health-related quality of life in dogs. *Vet Rec*. 2015;177:306-315.
6. Packer RMA, Lucas R, Volk HA. Owner perception of focal seizures in canine epilepsy. *Veterinary Record*. 2017;180:150.
7. Wessmann A, Volk H, Packer R, et al. Quality-of-life aspects in idiopathic epilepsy in dogs. *Veterinary Record*. 2016;179:229.
8. Heske L, Nødtvedt A, Jäderlund KH, et al. A cohort study of epilepsy among 665,000 insured dogs: Incidence, mortality and survival after diagnosis. *The Veterinary Journal*. 2014;202:471-476.
9. Kearsley-Fleet L, O'Neill DG, Volk HA, et al. Prevalence and risk factors for canine epilepsy of unknown origin in the UK. *Vet Rec*. 2013; 172:338.
10. Hülsmeyer V-I, Fischer A, Mandigers PJJ, et al. International Veterinary Epilepsy Task Force's current understanding of idiopathic epilepsy of genetic or suspected genetic origin in purebred dogs. *BMC Vet Res*. 2015;11:1–28.
11. Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE Official Report: A practical clinical definition of epilepsy. *Epilepsia*. 2014;55:475-482.
12. Tauber C-A. Epidemiologische Untersuchungen zum Vorkommen von Epilepsie bei Hund und Katze in der Kleintierpraxis. *lmu*. 2017.
13. Zimmermann R, Hülsmeyer V-I, Sauter-Louis C, Fischer A. Status Epilepticus and Epileptic Seizures in Dogs. *J Vet Intern Med*. 2009;23: 970-976.
14. VetCompass. VetCompass: Health surveillance for UK companion animals. In. London: RVC Electronic Media Unit; 2017.
15. The VeNom Coding Group. VeNom Veterinary Nomenclature [http://www.venomcoding.org]. Accessed 15 March 2017.
16. O'Neill DG, Lee MM, Brodbelt DC, et al. Corneal ulcerative disease in dogs under primary veterinary care in England: epidemiology and clinical management. *Canine Genet Epidemiol*. 2017;4:5.
17. Pearce N. Classification of epidemiological study designs. *International Journal of Epidemiology*. 2012;41:393-397.
18. Epi Info 7 CDC. Centers for Disease Control and Prevention (US): Introducing Epi Info 7 [http://wwwn.cdc.gov/epiinfo/7]. Accessed 20 January 2017.
19. Asher L, Buckland E, Phylactopoulos CL, et al. Estimation of the number and demographics of companion dogs in the UK. *BMC Vet Res*. 2011;7:74.
20. Oliver JAC, Gould DJ. Survey of ophthalmic abnormalities in the labradoodle in the UK. *Vet Rec*. 2012;170:390.
21. De Risio L, Bhatti S, Muñana K, et al. International veterinary epilepsy task force consensus proposal: diagnostic approach to epilepsy in dogs. *BMC Vet Res*. 2015;11:148.
22. Kirkwood BR, Sterne JAC. *Essential Medical Statistics*. 2nd ed. Oxford: Blackwell Science; 2003.
23. Bartlett PC, Van Buren JW, Neterer M, et al. Disease surveillance and referral bias in the veterinary medical database. *Prev Vet Med*. 2010; 94:264-271.
24. Nattinger AB, McAuliffe TL, Schapira MM. Generalizability of the surveillance, epidemiology, and end results registry population: Factors relevant to epidemiologic and health care research. *Journal of Clinical Epidemiology*. 1997;50:939-945.
25. Egenvall A, Bonnett BN, Olson P, et al. Validation of computerized Swedish dog and cat insurance data against veterinary practice records. *Preventive Veterinary Medicine*. 1998;36:51-65.
26. Fredsø N, Toft N, Sabers A, et al. A prospective observational longitudinal study of new-onset seizures and newly diagnosed epilepsy in dogs. *BMC Vet Res*. 2016;13:54.
27. Steinmetz S, Tipold A, Löscher W. Epilepsy after head injury in dogs: A natural model of posttraumatic epilepsy. *Epilepsia*. 2013;54:580-588.
28. O'Neill DG, Church DB, McGreevy PD, et al. Prevalence of disorders recorded in dogs attending primary-care veterinary practices in England. *PLoS ONE*. 2014;9:e90501-e90516.
29. Woodward KN. Veterinary pharmacovigilance. Part 3. Adverse effects of veterinary medicinal products in animals and on the environment. *J Vet Pharmacol Ther*. 2005;28:171-184.
30. Keck G, Ibrahim C. Veterinary pharmacovigilance: between regulation and science. *Journal of Veterinary Pharmacology and Therapeutics*. 2002;24:369-373.

31. Dohoo I, Martin W, Stryhn H. *Veterinary Epidemiologic Research*. 2nd ed. Charlottetown, Canada: VER Inc; 2009.

32. Nicholas FW. *Introduction to Veterinary Genetics*. 3rd ed. Oxford: Wiley-Blackwell; 2010.

33. Darwin C. *On the Origin of Species by means of Natural Selection, or the preservation of favoured races in the struggle for life*. London: John Murray; 1859.

34. Troyer AF. Adaptedness and heterosis in corn and mule hybrids. *Crop Science*. 2006;46:528-543.

35. Lalev M, Mincheva N, Oblakova M, et al. Estimation of heterosis, direct and maternal additive effects from crossbreeding experiment involving two White Plymouth Rock lines of chickens. *Bio Anim Husb*. 2014;30:103-114.

36. Ferreira VC, Rosa GJM, Berger YM, et al. Survival in crossbred lambs: Breed and heterosis effects. *J Anim Sci*. 2015;93:912-919.

37. Buckley F, Lopez-Villalobos N, Heins BJ. Crossbreeding: implications for dairy cow fertility and survival. *Animal*. 2014;8:122-133.

38. Nicholas FW, Arnott ER, McGreevy PD. Hybrid vigour in dogs? *The Veterinary Journal*. 2016;214:77-83.

39. Berendt M, Gredal H, Pedersen LG, et al. A Cross-Sectional Study of Epilepsy in Danish Labrador Retrievers: Prevalence and Selected Risk Factors. *Journal of Veterinary Internal Medicine*. 2002;16:262-268.

40. Mellanby RJ, Ogden R, Clements DN, et al. Population structure and genetic heterogeneity in popular dog breeds in the UK. *Vet J*. 2013;196:92-97.

41. Dohoo IR, Martin SW, Stryhn H. *Methods in Epidemiologic Research*. 2012. VER Inc.: Charlottetown, Prince Edward Island.

42. Levine JM, Fosgate GT, Porter B, et al. Epidemiology of Necrotizing Meningoencephalitis in Pug Dogs. *Journal of Veterinary Internal Medicine*. 2008;22:961-968.

43. Kaiser E, Krauser K, Schwartz-Porsche D. Lafora disease (progressive myoclonic epilepsy) in the Bassett hound–possibility of early diagnosis using muscle biopsy? *Tierarztl Prax*. 1991;19:290-295.

44. Escriou C, Quignon P, Menzer E, et al. Genetic Epilepsy In Cane Corso And Dogue De Bordeaux. *Journal of Veterinary Internal Medicine*. 2016;30:464.

45. Hülsmeyer V, Zimmermann R, Brauer C et al. Epilepsy in Border Collies: clinical manifestation, outcome, and mode of inheritance. *Journal of Veterinary Internal Medicine*. 2010;24:171-178.

46. Kloene J, Sewell AC, Hamann H, et al. Clinical investiagtion of seizures in Border Terriers. *Kleintierpraxis*. 2008;8:5-12.

47. Higgins RJ, Dickinson PJ, Kube SA, et al. Necrotizing Meningoencephalitis in Five Chihuahua Dogs. *Vet Pathol*. 2008;45:336-346.

48. Bateson P. *Independent inquiry into dog breeding. In*. Cambridge: University of Cambridge; 2010.

49. Farrell L, Schoenebeck J, Wiener P, et al. The challenges of pedigree dog health: approaches to combating inherited disease. *Canine Genet Epidemiol*. 2015;2:3.

50. Casal ML, Munuve RM, Janis MA, et al. Epilepsy in Irish Wolfhounds. *J Vet Intern Med*. 2006;20:131-135.

51. Kathmann I, Jaggy A, Busato A, et al. Clinical and genetic investigations of idiopathic epilepsy in the Bernese mountain dog. *J Small Anim Pract*. 1999;40:319-325.

52. Short A, Dunne A, Lohi H, et al. Characteristics of epileptic episodes in UK dog breeds: an epidemiological approach. *Veterinary Record-English Edition*. 2011;169:48.

53. Van Meervenne SAE, Volk HA, Matiasek K, et al. The influence of sex hormones on seizures in dogs and humans. *Vet J*. 2014;201:15-20.

54. Woodward KN. Veterinary pharmacovigilance. Part 5. Causality and expectedness. *J Vet Pharmacol Ther*. 2005;28:203-211.

55. Flanders W, Augestad L. Adjusting for reverse causality in the relationship between obesity and mortality. *Int J Obes*. 2008;32:S42-S46.

56. Pákozdy A, Leschnik M, Tichy AG, et al. Retrospective clinical comparison of idiopathic versus symptomatic epilepsy in 240 dogs with seizures. *Acta Vet Hung*. 2008;56:471.

57. Ghormley TM, Feldman DG, Cook JR Jr. Epilepsy in dogs five years of age and older: 99 cases (2006–2011). *J Am Vet Med Assoc*. 2015;246:447-450.

58. Bhatti SFM, De Risio L, Muñana K, et al. International Veterinary Epilepsy Task Force consensus proposal: medical treatment of canine epilepsy in Europe. *BMC Vet Res*. 2015;11:176.

59. O'Neill DG, Riddell A, Church DB, et al. Urinary incontinence in bitches under primary veterinary care in England: prevalence and risk factors. *J Small Anim Pract*. 2017;58:685-693.

60. Kerling F, Mueller S, Pauli E, et al. When do patients forget their seizures? An electroclinical study. *Epilepsy & Behavior*. 2006;9:281-285.

61. Hoppe C, Poepel A, Elger CE. Epilepsy: accuracy of patient seizure counts. *Arch Neurol*. 2007;64:1595-1599.

62. Tatum WO, Winters L, Gieron M, et al. Outpatient Seizure Identification: Results of 502 Patients Using Computer-Assisted Ambulatory EEG. *journal of Clinical Neurophysiology*. 2001;18:14-19.

63. Packer RM, Berendt M, Bhatti S, et al. Inter-observer agreement of canine and feline paroxysmal event semiology and classification by veterinary neurology specialists and non-specialists. *BMC Vet Res*. 2015;11:39.

64. Elwood M. *Critical appraisal of epidemiological studies and clinical trials*. 3rd ed. Oxford, UK: Oxford University Press; 2007.