Association between breed and renal biomarkers of glomerular filtration rate in dogs

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Abstract

Background Kidney disease, especially chronic kidney disease (CKD), is common in older dogs. The biomarkers symmetric dimethylarginine (SDMA) and creatinine (Cr) are indicators of glomerular filtration rate (GFR). This retrospective study used these biomarkers to identify groups at risk of decreased GFR at the breed level.

Methods Data from dogs with a single serum chemistry result that included Cr and SDMA submitted between July 2015 through December 2017 were included. Dogs were identified by breed and age group. Decreased GFR was defined as Cr above 1.9 mg/dl or SDMA above 18 µg/dl.

Results Fourteen breeds had a significantly higher percentage of dogs with increased SDMA or Cr for one or more age groups. Geriatric and senior Shetland sheepdogs, Yorkshire terriers and Pomeranians were significantly more likely to have increased renal biomarkers. Boxers were identified with significantly increased renal biomarkers in the age groups spanning two months to 10 years of age.

Conclusion Evidence of decreased GFR occurred commonly in older dogs of most breeds, especially geriatric dogs greater than 10 years of age, but there were some exceptions, with more significant changes affecting younger animals of several breeds. The combination of SDMA and Cr identified more cases of decreased GFR than either SDMA or Cr alone.

Introduction

Kidney disease, especially chronic kidney disease (CKD), is common in older dogs. The prevalence of kidney disease has been estimated to range between 0.5 per cent and 7 per cent in dogs.[1] It has been suggested that a reasonable estimate of the overall prevalence of CKD in general small animal practice in the USA would be 0.5–1.5 per cent of dogs.[2] However, kidney disease (acute kidney injury or CKD) associated with kidney dysfunction can occur at any age, caused by diverse aetiologies such as familial nephropathies,[1] urinary tract infection,[3] leptospirosis,[4 5] vectorborne disease,[6] or toxic insults from medications or environmental hazards.[4 5] Veterinarians rely heavily on routine laboratory testing to recognise alterations in kidney function associated with both acute and chronic kidney disease. Extrarenal conditions such as dehydration, hypovolaemia and hypotension may reduce glomerular filtration rate (GFR); impairment of kidney function by these conditions increases the risk of kidney injury.[7] An increased symmetric dimethylarginine (SDMA) concentration has been shown to correlate with decreased GFR.[8 9] Investigation of an increased SDMA or creatinine (Cr) to identify the underlying cause or associated disease is recommended to support a diagnosis.

The purpose of this study was to explore canine kidney health using established renal biomarkers to identify dogs potentially at risk for decreased GFR, at the breed and life stage levels. Results obtained from this analysis can be used to provide evidence to support the regular monitoring of some popular breeds, especially as ageing occurs, thereby reinforcing best practices for preventive care medicine.

Materials and methods

A commercial US laboratory database (IDEXX Laboratories) was used in this cross-sectional retrospective study. Results of chemistry testing on canine blood samples submitted to the laboratory from July 2015 through December 2017 were identified. To

be eligible for inclusion into this study, each dog was required to have a Cr and SDMA measured on a single serum or plasma sample and has a birth date recorded. SDMA was determined using a commercially available high-throughput immunoassay (IDEXX SDMA Test). Serum Cr was determined by a colorimetric method, Jaffe's reaction using picrate at alkaline pH (Beckman Coulter, Brea, California). When available, breed designation was collected. For dogs with multiple serum chemistry profile submissions, one submission was randomly selected without consideration of order of sampling, as representative for that dog. Random selection was done using a random number generator (RAND Function, SAS V.9.4). Each sample was obtained and submitted to the reference laboratory by a practising veterinarian during the normal diagnostic work-up and monitoring of clinically well and ill dogs in his or her care. All samples were obtained with the consent of the pet owner. To ensure privacy, additional demographic information on the pet, pet owner or veterinarian who submitted the sample was not collected.

Dogs in each breed were stratified by age into five groups: puppy (aged two to less than 12 months); young (aged one to less than three years); adult (aged three to less than seven years); senior (aged seven to 10 years); and geriatric (aged more than 10 years). Kidney health, as defined by decreased GFR, at the time of sampling was estimated using Cr and SDMA concentrations. In the initial analysis, dogs with decreased GFR were defined as having SDMA above 18 µg/dl or Cr above 1.9 mg/dl. These concentrations were selected because patient data were extremely limited (eg, no urine specific gravities, no longitudinal laboratory information, no clinical diagnosis) and to increase confidence that the measured increase in renal biomarkers was indicative of decreased GFR. The method for determination and selection of the critical concentrations for SDMA and Cr is found in online supplementary appendix I. To evaluate the contribution of the individual markers in evaluating GFR, two additional analyses were conducted: dogs having SDMA above 18 µg/dl with Cr up to 1.9 mg/dl; and dogs having Cr above 1.9 mg/dl with SDMA up to 18 µg/dl.

To establish the baseline concentration for renal biomarkers in the sample population, the percentage of dogs with increased renal biomarkers was determined by age group for *all breeds* in the sample. The *all breeds* category included all results from dogs identified by a single breed and included mixed breed dogs. The percentage of dogs with increased renal biomarkers

markers was then determined by age group for *each* breed. Ninety-five per cent confidence intervals (CI) were calculated for each percentage using the binomial exact method. The percentages and 95 per cent CI for each age group of the top 25 breeds (ie, the 25 breeds with the most submission numbers) were compared with the percentage and 95 per cent CI of the baseline all-breed age groups. Age groups for each breed with patient percentages and 95 per cent CI above those of the baseline all-breed age group were considered significant.

Results

SDMA and Cr concentrations were available for 847,886 dogs identified as a single breed and 499,684 mixed breed dogs. The distribution of dogs by age group is shown in table 1.

The top 25 breeds, based on numbers in the sample database, are found in table 2.

The percentages of dogs with SDMA above 18 µg/dl or Cr above 1.9 mg/dl by age group for the top 25 breeds are found in table 3 and figures 1–5. Of the top 25 breeds, 14 breeds had a statistically significantly higher percentage of dogs with SDMA above 18 µg/dl or Cr above 1.9 mg/dl as compared with the baseline for one or more age groups. Greater than 10 per cent of geriatric shih tzus, miniature pinschers, toy poodles, Jack Russell terriers, chihuahuas and Border collies had either SDMA above 18 µg/dl or Cr above 1.9 mg/dl; and greater than 14 per cent of geriatric Shetland sheepdogs, Yorkshire terriers and Pomeranians had increased concentrations of SDMA or Cr. Some breeds had significantly increased percentage of dogs with

Table 2	Top 25 dog breeds		
Breed	n (%*)	Breed	n (%*)
1 Labrador retriever	799,647 (7.4)	14 Toy poodle	15,294 (1.1)
2 Golden retriever	47,613 (3.5)	15 American pit bull terrier	14,467 (1.1)
3 Chihuahua	39,309 (2.9)	16 American cocker spaniel	14,351 (1.1)
4 Yorkshire terrier	38,953 (2.9	17 Boston terrier	14,321 (1.1)
5 Shih tzu	37,137 (2.8)	18 Bichon frise	14,274 (1.1)
6 Dachshund	37,093 (2.8)	19 Australian shepherd	12,771 (0.9)
7 German shepherd dog	26,648 (2.0)	20 Cavalier King Charles spaniel	11,001 (0.8)
8 Boxer	23,824 (1.8)	21 West Highland white terrier	10,508 (0.8)
9 Beagle	17,525 (1.3)	22 Siberian husky	10,204 (0.8)
10 Jack Russell terrier	17,110 (1.3)	23 Shetland sheepdog	9859 (0.7)
11 Pug	17,002 (1.3)	24 Miniature pinscher	9658 (0.7)
12 Miniature schnauzer	16,739 (1.2)	25 Border collie	9271 (0.7)
13 Pomeranian	15,809 (1.2)		
*Percentages based off of all breeds (n=1,348,316).			

Table 1	Distribution of dogs by age group					
	Puppy (2 to ‹12 months)	Young (1 to ‹3 years)	Adult (3 to ‹7 years)	Senior (7–10 years)	Geriatric (>10 years)	Total
Purebred	32,089	29,594	146,912	297,988	342,049	847,886
Mixed breed	19,527	73,178	54,782	170,718	181,479	499,684
All breeds	51,616	102,772	201,694	468,706	523,528	1,348,316

Table 3 Per cent of dogs with SDMA above 18 µg/dl or Cr above 1.9 mg/dl by age group and breed, calculated as the number of abnormal dogs over the total number of dogs of that age and breed

Breed (n)	Puppy (2 to <12 months)	Young (1 to <3 years)	Adult (3 to <7 years)	Senior (7–10 years)	Geriatric (>10 years)
All breeds (1,348,316)	2.0 (1044/51,616)	1.7 (1777/102,772)	2.1 (4274/201,694)	2.8 (12,948/468,706)	9.2 (47,964/523,528)
Shetland sheepdog (9859)	4.3 (10/234)	2.6 (10/388)	2.1 (22/1054)	5.9 (201/3376)	18.7 (901/4807)
Yorkshire terrier (38,953)	2.0 (23/1166)	1.6 (37/2381)	1.9 (112/5921)	3.7 (534/14,421)	17.4 (2626/15,064)
Pomeranian (15,809)	3.8 (15/392)	1.0 (8/772)	2.1 (42/1982)	3.6 (204/5607)	14.1 (994/7056)
Shih tzu (37,137)	1.8 (19/1026)	1.6 (28/1794)	2.1 (96/4464)	3.0 (373/12,221)	12.1 (2129/17,632)
Miniature pinscher (9658)	0.0 (0/0)	1.4 (5/354)	2.2 (22/1004)	2.8 (90/3213)	11.4 (567/4965)
Toy poodle (15,294)	1.8 (10/545)	1.1 (10/893)	1.4 (25/1842)	1.7 (79/4743)	11.0 (803/7271)
Jack Russell terrier (17,110)	0.0 (0/0)	0.6 (3/499)	1.0 (13/1336)	2.1 (93/4333)	11.0 (1179/10,698)
Border collie (9271)	2.4 (7/297)	1.9 (11/580)	2.1 (22/1070)	2.3 (64/2750)	10.1 (464/4574)
Chihuahua (39,309)	1.1 (8/744)	1.3 (25/1943)	1.2 (65/5329)	1.9 (259/13,738)	10.1 (1772/17,555)
Beagle (17,525)	0.8 (3/360)	0.7 (5/716)	1.1 (22/1930)	3.0 (181/5999)	10.0 (851/8520)
American cocker spaniel (14,351)	0.7 (2/280)	0.4 (2/484)	1.5 (22/1442)	2.6 (127/4802)	9.5 (700/7343)
West Highland white terrier (10,508)	1.3 (3/225)	0.5 (2/390)	1.5 (13/861)	2.1 (64/3098)	9.4 (561/5934)
Bichon frise (14,274)	0.8 (2/263)	0.5 (2/380)	1.1 (11/1044)	1.4 (56/4080)	9.3 (790/8507)
Mixed breed dog (499,684)	1.8 (341/19,527)	1.5 (668/43,755)	1.8 (1520/84,205)	2.5 (4179/170,718)	9.0 (16,327/181,479)
Australian shepherd (12,771)	1.7 (13/767)	1.3 (15/1171)	2.0 (37/1830)	3.1 (126/4051)	8.1 (399/4952)
American pit bull terrier (14,467)	3.0 (22/726)	2.3 (44/1895)	3.4 (110/3194)	4.1 (209/5139)	7.9 (276/3513)
Cavalier King Charles spaniel (11,001)	1.8 (11/612)	0.6 (5/840)	0.8 (14/1849)	1.7 (80/4681)	7.8 (237/3019)
Dachshund (37,093)	0.3 (2/784)	0.7 (10/1457)	1.0 (41/4080)	1.1 (138/12,493)	7.2 (1308/18,279)
Miniature schnauzer (16,739)	2.8 (13/468)	1.4 (12/861)	1.4 (29/2041)	2.3 (136/5922)	7.1 (526/7447)
Boxer (23,824)	4.6 (46/995)	3.3 (66/1984)	4.6 (209/4522)	4.7 (525/11,219)	6.6 (336/5104)
Siberian husky (10,204)	2.0 (14/697)	3.1 (35/1145)	2.7 (46/1679)	3.0 (97/3282)	6.5 (221/3401)
Golden retriever (47,613)	2.6 (61/2377)	2.2 (77/3567)	1.9 (123/6389)	2.9 (521/17,903)	6.2 (1082/17,377)
Labrador retriever (99,647)	2.3 (87/3780)	2.0 (136/6836)	2.3 (285/12,341)	2.8 (982/35,715)	6.0 (2461/40,975)
Pug (17,002)	0.8 (4/468)	1.1 (7/664)	1.5 (26/1705)	1.6 (94/5871)	5.5 (453/8294)
Boston terrier (14,321)	0.7 (4/580)	0.5 (4/848)	1.6 (28/1750)	1.4 (72/5256)	5.4 (316/5887)
German shepherd dog (26,648)	3.2 (62/1908)	2.8 (107/3789)	2.7 (141/5221)	2.8 (284/9998)	4.4 (253/5732)

Breeds are listed in decreasing order based on the percentage in the geriatric age group. Breed age groups highlighted in blue are significantly higher than the all breeds baseline for the same age group.
Cr, creatinine; SDMA, symmetric dimethylarginine.

SDMA above 18 µg/dl or Cr above 1.9 mg/dl in the senior age groups, including Shetland sheepdogs, Yorkshire terriers and Pomeranians, with 3.6 per cent or greater in that age group. On average, 4 per cent of boxers, two months to 10 years of age, and 2.8 per cent of German shepherd dogs, one to six years of age, had significantly increased SDMA above 18 µg/dl and Cr above 1.9 mg/dl, approximately twice the average baseline values.

The percentages of dogs with SDMA above 18 µg/dl and Cr up to 1.9 mg/dl by age group for the top 25 breeds are found in online supplementary appendix II, table 1. Using this definition to identify decreased GFR in this study, 13 breeds had a statistically increased SDMA as compared with the baseline for one or more age groups. Results were very similar to those seen above. Geriatric Shetland sheepdogs, Yorkshire terriers, Pomeranians, shih tzus, miniature pinschers, toy poodles, Jack Russell terriers and chihuahuas had increased SDMA. Greater than 10 per cent of geriatric Shetland sheepdogs and Yorkshire terriers had concentrations of SDMA above 18 µg/dl and Cr up to 1.9 mg/dl.

The percentages of dogs with SDMA up to 18 µg/dl and Cr above 1.9 mg/dl by age group for the top 25 breeds are found in online supplementary appendix II, table 2. Unlike the two previous scenarios, only two breeds were found to have a statistically significantly higher percentage of dogs with increased Cr above 1.9 mg/dl, as compared with baseline. Two breeds, the Pomeranian and bichon frise, were only found to be significant in the geriatric age group.

Discussion

Decreased GFR was identified by SDMA above 18 µg/dl or Cr above 1.9 mg/dl, in most age groups of the top 25 common breeds. Decreased GFR was most common in the large population of geriatric dogs (n=523,528), with a per cent frequency of 9.2 per cent of dogs of all breeds greater than 10 years of age (table 3).

In this retrospective study, where available patient data were extremely limited, cut-offs higher than the canine laboratory reference intervals for both SDMA above 18 µg/dl (0–14 µg/dl) and Cr above 1.9 mg/dl (0.5–1.5 mg/dl) were selected to increase confidence that measured increases in the renal biomarkers were indicative of decreased GFR and potential kidney disease. Results of an unpublished longitudinal canine study demonstrated that SDMA remained persistently increased above the reference interval (14 µg/dl) on the next visit approximately 70 per cent of the time when SDMA was initially above 18 µg/dl, indicating decreased GFR (online supplementary appendix I). Previous studies have shown that in dogs with CKD, SDMA increases up to 27 months earlier than Cr.[10] Persistent
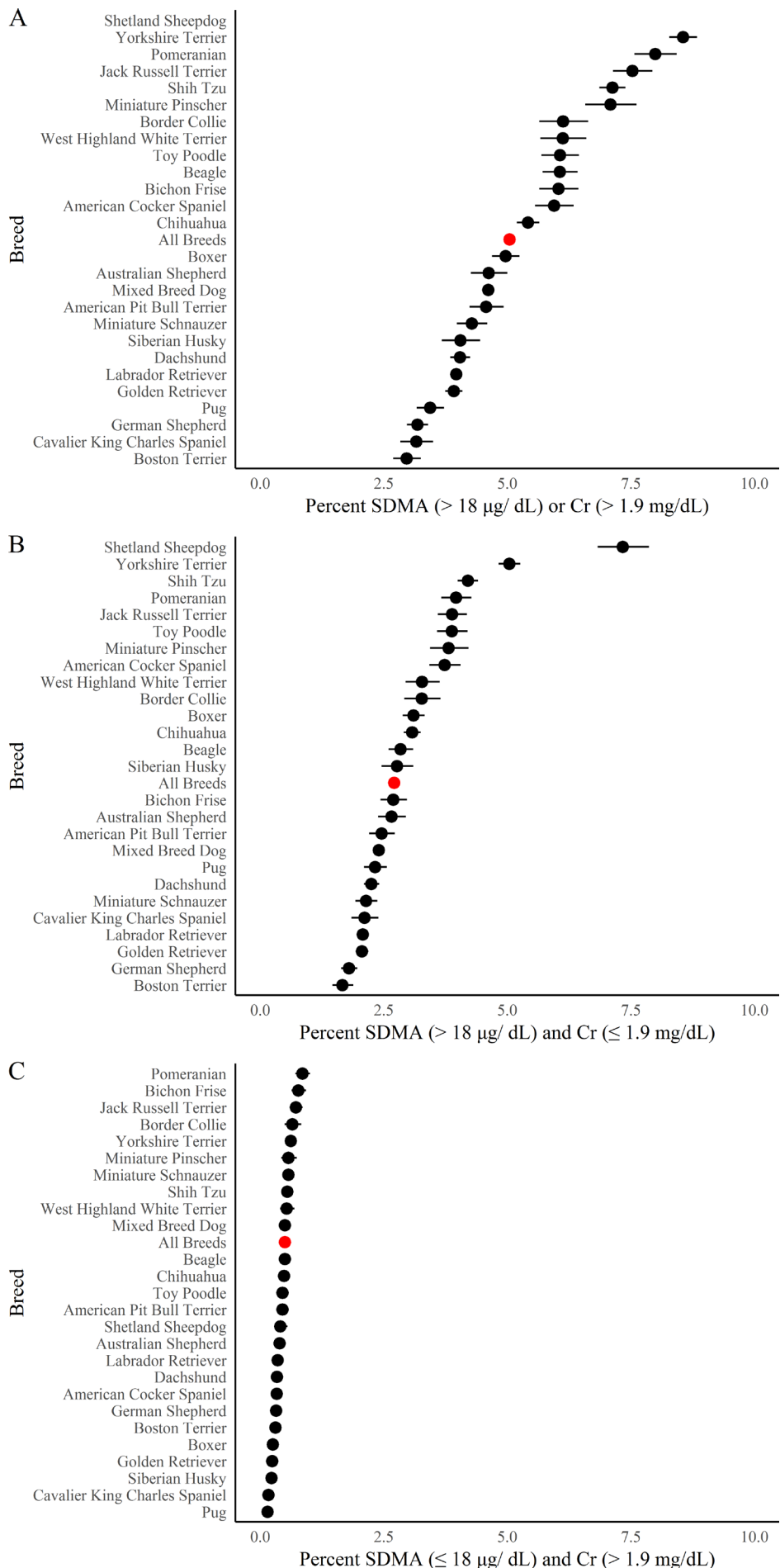
Figure 1 Per cent of puppies (two to less than 12 months of age) with decreased GFR by breed: top 25 dog breeds. Baseline result for all breeds is shown in red. (A) Per cent of puppies with either SDMA above 18 μg/dl or Cr above 1.9 mg/dl. (B) Per cent of puppies with increased SDMA above 18 μg/dl and Cr up to 1.9 mg/dl. (C) Per cent of puppies with SDMA up to 18 μg/dl and increased Cr above 1.9 mg/dl. Cr, creatinine; GFR, glomerular filtration rate; SDMA, symmetric dimethylarginine.
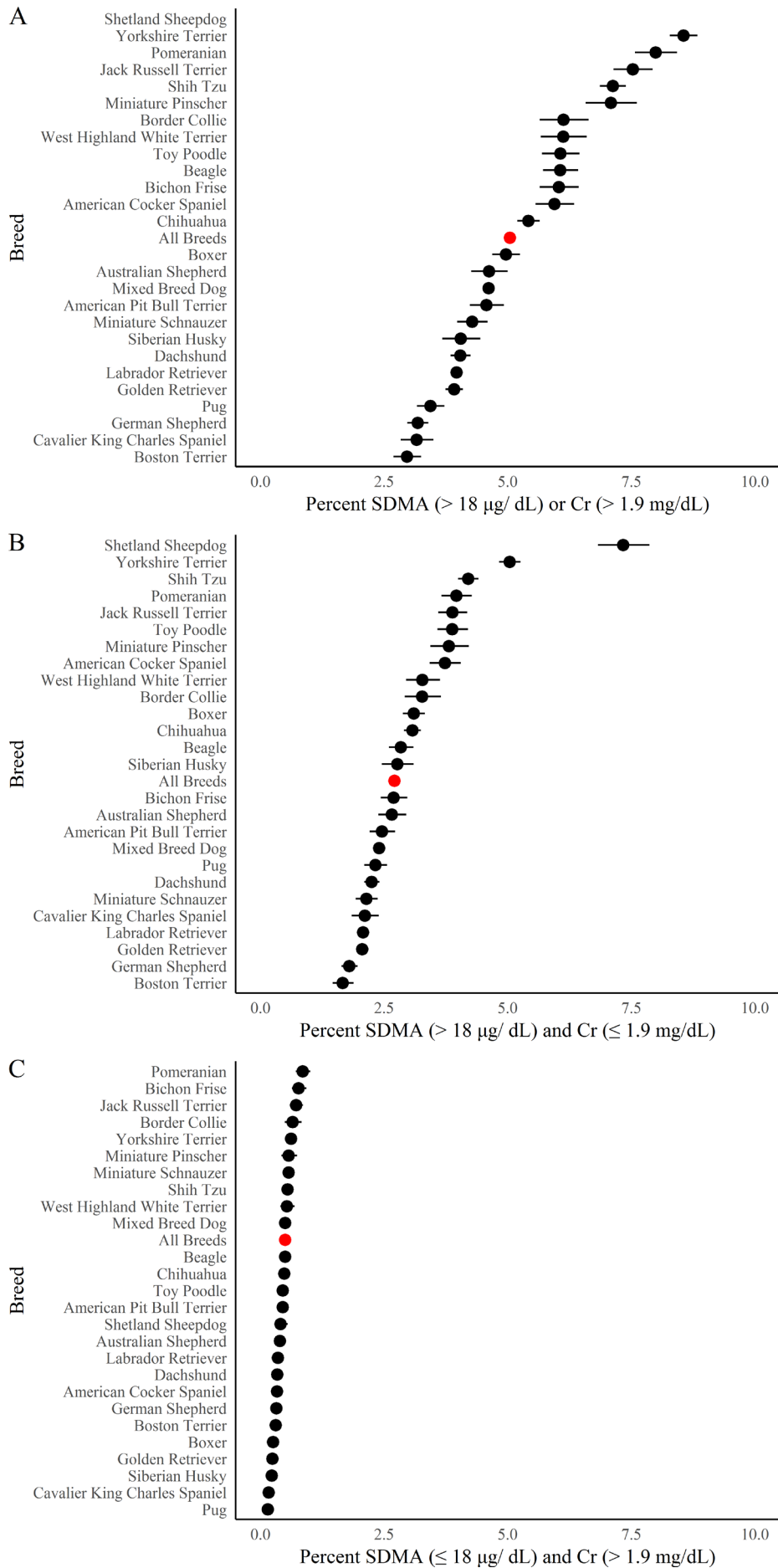
Figure 2 Per cent of young dogs (one to less than three years of age) with decreased GFR by breed: top 25 dog breeds. Baseline result for all breeds is shown in red. (A) Per cent of young dogs with either SDMA above 18 µg/dl or Cr above 1.9 mg/dl. (B) Per cent of young dogs with increased SDMA above 18 µg/dl and Cr up to 1.9 mg/dl. (C) Per cent of young dogs with SDMA up to 18 µg/dl and increased Cr above 1.9 mg/dl. Cr, creatinine; GFR, glomerular filtration rate; SDMA, symmetric dimethylarginine.
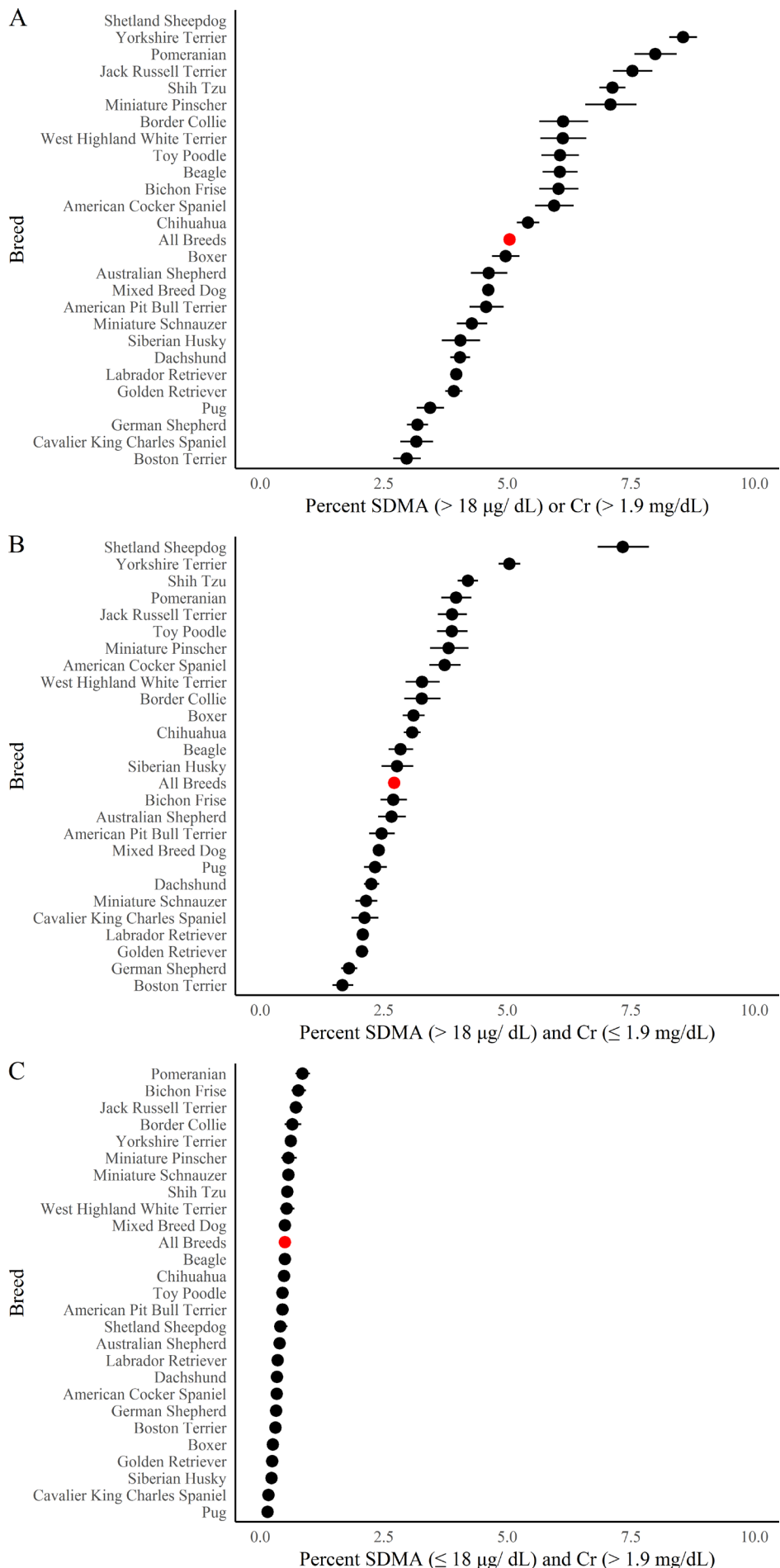
Figure 3 Per cent of adult dogs (three to less than seven years of age) with decreased GFR by breed: top 25 dog breeds. Baseline result for all breeds is shown in red. (A) Per cent of adult dogs with either SDMA above 18 µg/dl or Cr above 1.9 mg/dl. (B) Per cent of adult dogs with increased SDMA above 18 µg/dl and Cr up to 1.9 mg/dl. (C) Per cent of adult dogs with SDMA up to 18 µg/dl and increased Cr above1.9 mg/dl. Cr, creatinine; GFR, glomerular filtration rate; SDMA, symmetric dimethylarginine.
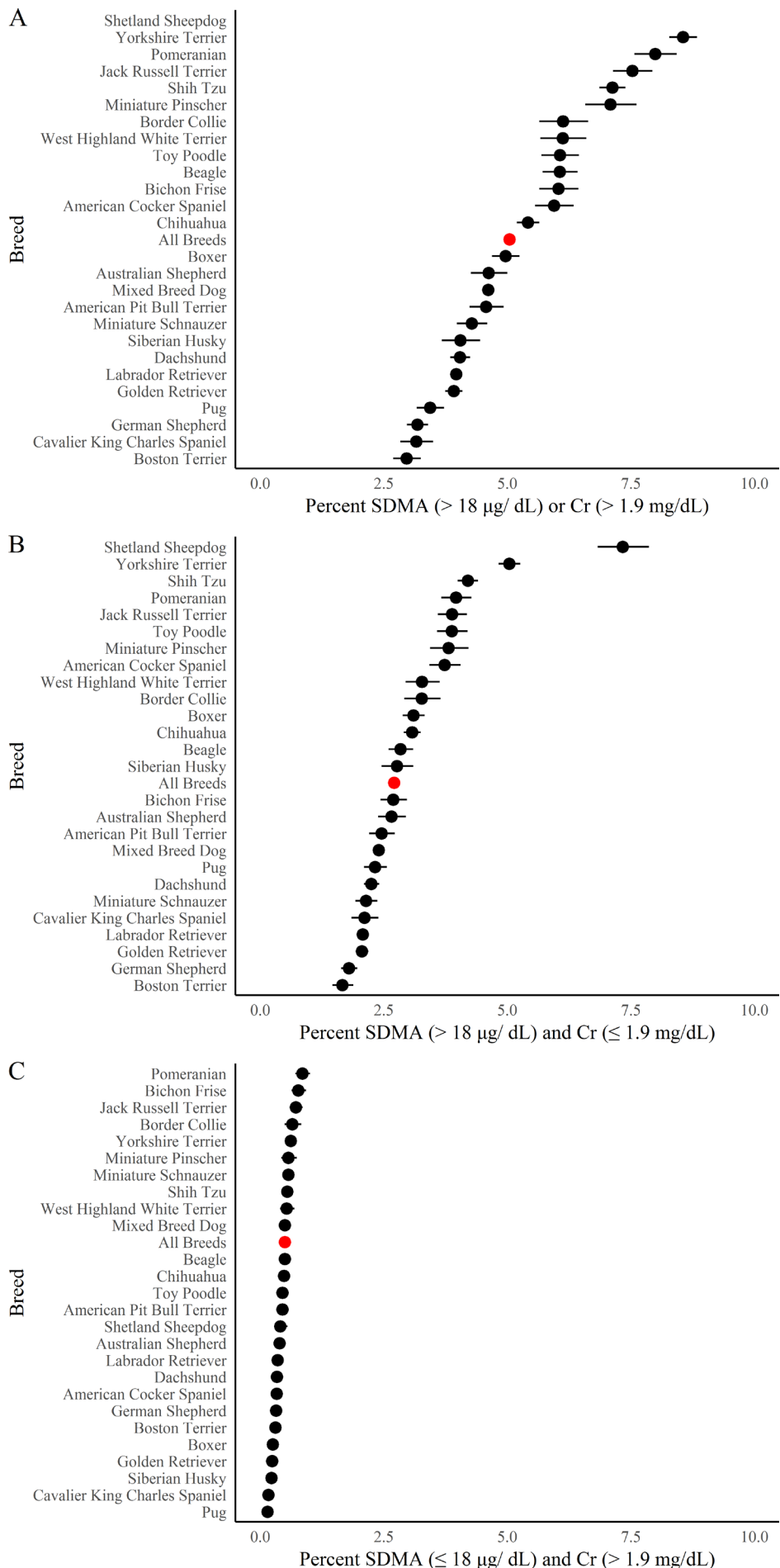
Figure 4 Per cent of senior dogs (seven to 10 years of age) with decreased GFR by breed: top 25 dog breeds. Baseline result for all breeds is shown in red. (A) Per cent of senior dogs with either SDMA above 18 μg/dL or Cr above 1.9 mg/dl. (B) Per cent of senior dogs with increased SDMA above 18 μg/dl and Cr up to 1.9 mg/dl. (C) Per cent of senior dogs with SDMA up to 18 μg/dl and increased Cr above 1.9 mg/dl. Cr, creatinine; GFR, glomerular filtration rate; SDMA, symmetric dimethylarginine.
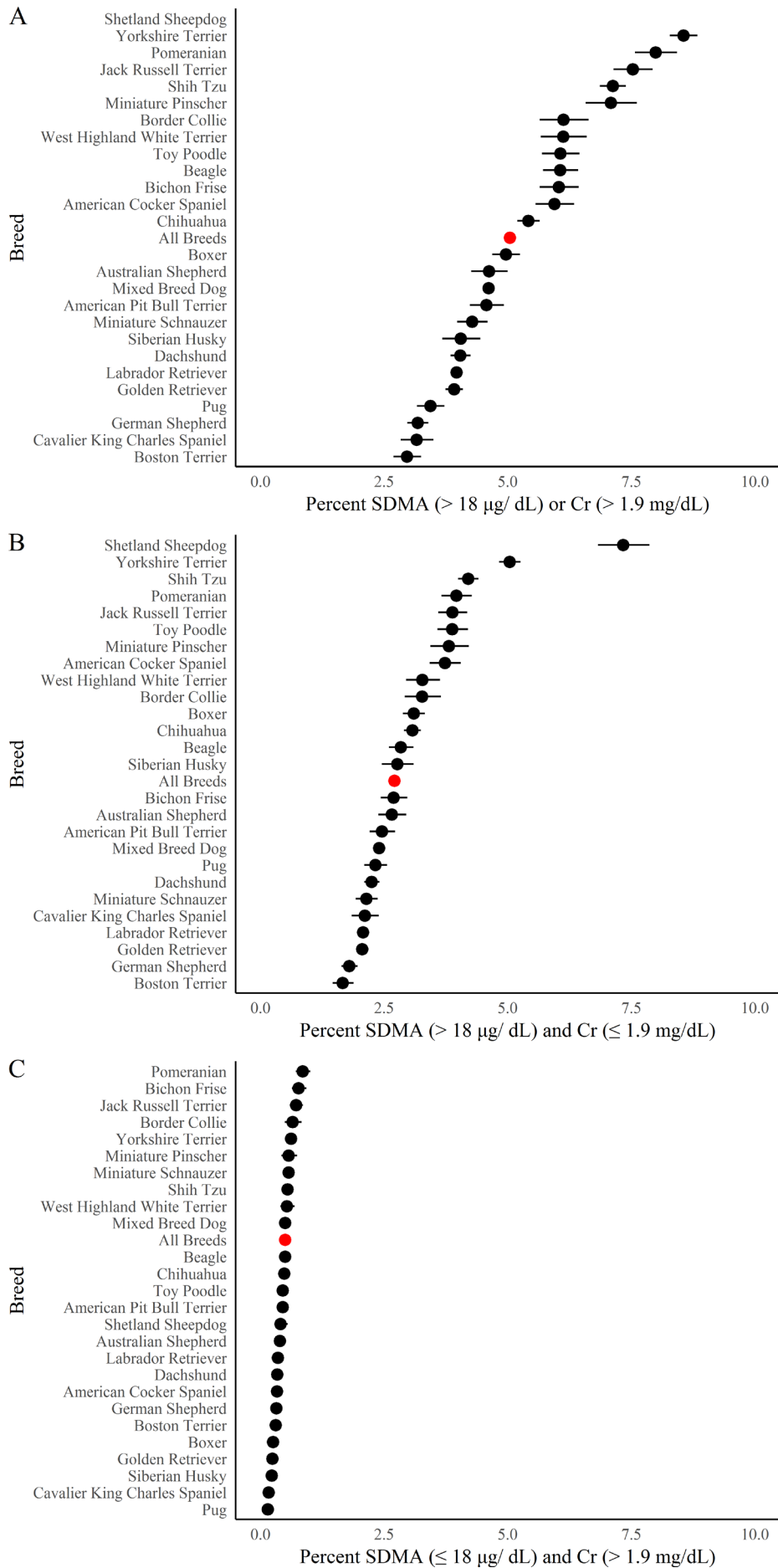
Figure 5 Per cent of geriatric dogs (greater than 10 years of age) with decreased GFR by breed: top 25 dog breeds. Baseline result for all breeds is shown in red. (A) Per cent of geriatric dogs with either SDMA above 18 µg/dl or Cr above 1.9 mg/dl. (B) Per cent of geriatric dogs with increased SDMA above 18 µg/dl and Cr up to 1.9 mg/dl. (C) Per cent of geriatric dogs with SDMA up to 18 µg/dl and increased Cr above 1.9 mg/dl. Cr, creatinine; GFR, glomerular filtration rate; SDMA, symmetric dimethylarginine.

increases in SDMA or Cr are considered more suggestive of meaningful kidney dysfunction and challenges to kidney health than are transient changes, such as might occur with acute kidney injury, dehydration or various types of shock (hypovolaemic, septic, cardiogenic) that resolve with treatment. In this retrospective study, use of SDMA and Cr was unable to discriminate between pre-renal, intrarenal or postrenal causes of reduced GFR and could not differentiate between acute kidney injury or CKD by dog breed or age group.

In comparison with the geriatric age group, dogs with SDMA above 18 μg/dl or Cr above 1.9 mg/dl were much less common in other age groups of all breeds or mixed breeds. The baseline per cent frequency of reduced GFR that was established as the control level was in the range of 1.7–2.8 per cent of dogs of all breeds aged two months to 10 years. These findings are consistent with expectations, since older patients are more likely than younger patients to have CKD or concurrent diseases that negatively impact kidney health secondarily, including cardiac disease, endocrine diseases such as hyperadrenocorticism or diabetes mellitus, chronic inflammatory conditions including periodontal disease or pancreatitis, or neoplasia.[11] Confounding conditions such as systemic hypertension and/or proteinuria may also be more common in older patients. In puppies, young dogs and adult dogs, infectious aetiologies, exposures to toxins and familial nephropathies may be more common causes of decreased kidney function than CKD. Investigation for potentially treatable or reversible causes of acute kidney injury and confounding factors that contribute to loss of kidney function is indicated for affected dogs of all ages and breeds.

When analysing the data from the top 25 dog breeds (table 3), 14 breeds had a significantly higher percentage with increased SDMA above 18 μg/dl or increased Cr above 1.9 mg/dl as compared with the baseline for one or more age groups. Geriatric and senior Shetland sheepdogs, Yorkshire terriers and Pomeranians were significantly more likely to have increased renal biomarkers than the baseline population of all breeds. These dog breeds are not consistently listed as breeds at risk for CKD[11] or familial nephropathies.[11 12] A familial predisposition to renal agenesis/hypoplasia has been described for Shetland sheepdogs, with variable signs and prognosis depending on the degree of hypoplasia and effect on kidney function.[13] Among insured Swedish dogs Shetland sheepdogs had significant mortality associated with kidney disease, with 80 per cent of cases due to undetermined aetiology.[14] In the same study Yorkshire terriers were reported as one of the 15 breeds with the highest incidence of kidney disease; most cases (58 per cent) had undetermined aetiology.[14] Nephropathy with features of renal dysplasia has been reported in a Yorkshire terrier.[15] It is also possible that Shetland sheepdogs, Yorkshire terriers or Pomeranians studied were affected with concurrent diseases that secondarily affected kidney function. Some sources suggest that other dog breeds are predisposed to CKD, including Chinese shar pei,[16] bull terriers,[17] English cocker spaniels,[18 19] Cavalier King Charles spaniels,[18] West Highland white terriers[20] and boxers,[21] and a number of familial nephropathies have been described that reduce kidney function in some puppies and younger dogs, leading to juvenile onset CKD, typically before dogs are five years of age.[11] Amyloidosis was observed to be over-represented in kidney biopsies of Chinese shar peis and English bulldogs suspected of having glomerular disease.[22] A recent study on greyhounds, not one of the breeds enrolled in this analysis, suggests breed-specific reference intervals for SDMA might be appropriate.[23] Although Cavalier King Charles spaniels and West Highland white terriers were counted among the top 25 breeds, this study did not identify a significant increase in renal biomarkers above the baseline for either breed.

Boxers in this study were identified with significant reductions in GFR, on average 4 per cent, in four of five age groups, spanning two months to 10 years of age (table 3). In fact, boxers were the only puppy group by breed to show increases in SDMA above 18 μg/dl or Cr above 1.9 mg/dl compared with baseline, with 46 of 995 puppies, or 4.6 per cent, affected. In this study, slightly increased numbers of geriatric boxers, 336 of 5104 dogs, or 6.6 per cent, were found to have increased SDMA above 18 μg/dl or increased Cr above 1.9 mg/dl, but this is well below the baseline of 9.2 per cent for geriatric dogs of all breeds. The authors' overall findings are consistent with a recent Swedish study that reported boxers in the top 3 dog breeds with the highest incidence of kidney disease and kidney-related mortality, noting a median age of diagnosis of 5.9 years of age.[14] A possible explanation for the smaller number of geriatric boxers with potential kidney dysfunction than other age groups could be earlier mortality in boxers.[14] In a recent North American mortality study including 1093 boxers, dogs of this breed were more likely to die of neoplasia than urogenital disease, at rates higher than most other breeds; the relative frequency of neoplasia peaked in the group that included 10-year-old dogs.[24] Kidney-related mortality was shown to be high in Swedish boxer dogs,[13] and an ongoing study into the possible aetiology of kidney disease in US boxer dogs has been described.[25]

There are several limitations associated with this retrospective study. Breed designation was provided by the veterinarian or pet owner, not based on breed registration or verification. It should not be assumed that all dogs in each breed were purebreds. Mixed breed dogs that shared physical characteristics with the more popular breeds (eg, Labrador or golden retrievers, German shepherd dogs) may have been misclassified. However, since these breeds are among the most popular with pet owners in the USA and are among the most

numerous in the database, the effect of misclassification should be insignificant. Misclassification should have a lesser impact on more unusual breeds (eg, whippets, chow chows) because they are less well known to the public and have more distinguishing physical features specific to the breed.

Although the biomarkers SDMA and Cr were evaluated in this retrospective study to give an indication of kidney health, a definitive diagnosis of kidney disease could not be made. SDMA and Cr concentrations were evaluated for each dog in the study at a single time point only. It was not possible to determine if the samples from this study came from healthy or ill dogs. The breeds identified with decreased GFR are also among the most common dog breeds within the USA, so it was not possible to differentiate between popularity and increased likelihood of monitoring. No follow-up testing, urinalysis, urine specific gravity nor medical records were evaluated for dogs with either increased SDMA above 18 μg/dl or increased Cr above 1.9 mg/dl. Pre-renal and postrenal factors can increase concentrations of these analytes, along with acute and chronic kidney disease.

Puppies in general have more body water and are less muscled compared with adult dogs, decreasing the utility of Cr in assessing kidney function in these patients. Young animals, because of their smaller size and decreased muscle mass, have lower Cr than mature or well-muscled individuals.[4 26] SDMA concentrations are also higher in puppies than in adult dogs, with the upper limit of the reference interval for puppies being 16 μg/dl. This upper limit represents 3 sd above the mean of 11 μg/dl seen in puppies. For this analysis, the authors did not adjust the SDMA concentration higher nor the Cr concentration lower for the definition of reduced GFR for this age group, believing that these concentrations of SDMA above 18 μg/dl *or* Cr above 1.9 mg/dl would adequately identify puppies with decreased GFR.

In this analysis, SDMA and Cr were evaluated as complementary kidney biomarkers, which allowed dogs with either increased SDMA above 18 μg/dl *or* Cr above 1.9 mg/dl to be characterised as having reduced GFR. Cr has been the most widely used veterinary kidney function biomarker, but it has several limitations, including the fact that it is relatively insensitive, increasing with up to 75 per cent loss of renal mass in an early study.[27] SDMA is a sensitive indicator of kidney function that detects as little as 25 per cent reduction in GFR in both acute and chronic kidney disease.[9 10 28] SDMA can, therefore, detect mild to moderate decreases in GFR that Cr misses. Also, Cr can be falsely lowered in patients with poor muscle mass.[29] Reductions in lean body mass are common with ageing and chronic disease, when accurate detection of alterations in kidney function may become increasingly important.[30] It is interesting that, in this analysis, many of the breeds with increased SDMA concentrations but

not increased Cr concentrations were small breeds. Smaller dogs have been shown to have higher GFRs and potentially lower Cr concentrations due to smaller muscle mass.[31 32] One recent study found significant renal abnormalities on biopsy in Yorkshire terriers with otherwise normal serum Cr concentrations.[33] Unlike Cr, SDMA concentrations are not impacted by muscle mass or advanced age or disease state.[10 34–37]

Using SDMA and Cr concentrations combined identified more cases of reduced GFR than using either SDMA or Cr concentrations alone. Results of this analysis support the regular monitoring of some popular dog breeds at risk of decreased GFR with renal biomarkers, especially as ageing occurs, thereby reinforcing best practices for preventive care medicine. Routine patient management should include provisions to support kidney health at all life stages, especially for geriatric dogs.

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