Risk factors for the incidence of calcium oxalate uroliths or magnesium ammonium phosphate uroliths for dogs in Ontario, Canada, from 1998 to 2006

Lee V. Wisener, DVM, MSc; David L. Pearl, DVM, PhD; Doreen M. Houston, DVM; Richard J. Reid-Smith, DVM, DVSc; Andrew E. Moore, MSc

Objective—To investigate individual- and community-level contextual variables as risk factors for submission of calcium oxalate (CaOx) uroliths or magnesium ammonium phosphate (ie, struvite) uroliths for dogs to a national urolith center, as determined on the basis of urolith submission patterns.

Sample Population—Records of 7,297 dogs from Ontario, Canada, with CaOx or struvite uroliths submitted to the Canadian Veterinary Urolith Centre from 1998 through 2006.

Procedures—Data were analyzed via multilevel multivariable logistic regression.

Results—Individual-level main effects and interactions significantly associated with the risk of submission of CaOx uroliths rather than struvite uroliths included age, sex, breed group, neuter status, body condition, dietary moisture content, diet type, sex-neuter status interaction, sex-age interaction, body condition–age interaction, and breed group–dietary moisture content interaction. In addition, median community family income and being located within a major urban center (ie, Toronto) were significant risk factors for submission of CaOx uroliths, compared with submission of struvite uroliths.

Conclusions and Clinical Relevance—Individual-level and dietary factors for dogs affected the risk of submission of CaOx uroliths, relative to that of struvite uroliths. Interactions among these variables need to be considered when assessing the impact of these risk factors. In addition, community-level or contextual factors (such as community family income and residing in a densely populated area of Ontario) also affected submission patterns, although most of the variance in the risk for submission of CaOx uroliths, compared with the risk for submission of struvite uroliths, was explained by individual-level factors. (*Am J Vet Res* 2010;71:1045–1054)

Calcium oxalate or magnesium ammonium phosphate (ie, struvite) are the 2 most common mineral types found in uroliths of dogs in North America and Europe.[1–5] Descriptive and case-control studies of urolithiasis in dogs have revealed consistent associations between urolith type and the individual-level demographic risk factors of age, sex, and breed. Females and younger dogs are at greater risk of urinary tract infection and, consequently, of developing struvite uroliths, whereas males and older dogs are at greater risk of developing CaOx uroliths.[3–9] Descriptive studies[3,6] of dogs that developed uroliths have identified that many small breeds are overrepresented among dogs affected with both urolith types. Overrepresentation of particular breeds among dogs with urolithiasis reflects both the inherent risk of developing a particular urolith type in any given breed and the breed prevalence in the study region. In 1 case-control study[9] of dogs with CaOx urolithiasis that involved the use of time-matched control dogs without urinary tract disease, investigators identified the following breeds as having a greater risk of developing CaOx uroliths, compared with the risk for mixed-breed dogs: Miniature Schnauzer, Lhasa Apso, Yorkshire Terrier, Bichon Frise, Pomeranian, Shih Tzu, Chihuahua, Cairn Terrier, Maltese, Miniature and Toy

Abbreviations

CA	Census agglomeration
CaOx	Calcium oxalate
CMA	Census metropolitan area
CSD	Census subdivision
LR	Likelihood ratio
SAC	Statistical area classification

Received May15, 2009.
Accepted August 6, 2009.
From the Department of Population Medicine (Wisener, Pearl, Reid-Smith) and Canadian Veterinary Urolith Centre, Laboratory Services Division (Moore), Ontario Veterinary College, University of Guelph, Guelph, ON N1G 2W1, Canada; and Medi-Cal Royal Canin Veterinary Diet, 100 Beiber Rd RR No. 3, Guelph, ON N1H 6H9, Canada (Houston). Dr. Wisener's present address is Wisener Veterinary Services, 229 Barden St, Eden Mills, ON N0B 1P0, Canada.
Supported in part by Medi-Cal Royal Canin Veterinary Diet and the Canadian Veterinary Urolith Centre, Laboratory Services Division, University of Guelph.
Presented in part as an oral presentation at the Conference of Research Workers on Animal Diseases, Chicago, December 2008.
Address correspondence to Dr. Wisener (lwisener@uoguelph.ca).

Poodle, and Dachshund. In that same study,[9] investigators identified 3 breeds (Cocker Spaniel, German Shepherd Dog, and Golden Retriever) as having a reduced risk of developing CaOx uroliths.

During the past 2 decades, there has been a change in the reciprocal relationship between submissions of CaOx and struvite uroliths, with an increase in CaOx urolith submissions and a reduction in struvite urolith submissions.[2,4,5,10,11] One theory for this relationship suggests that a relative increase in the proportion of CaOx uroliths is attributable to the advent of medical treatment protocols for struvite uroliths since the introduction of dissolution diets in 1983, which has resulted in fewer struvite uroliths retrieved for submission.[2,7] However, the proportions of other (calcium phosphate, silica, and cystine) urolith submissions have not had a concomitant increase as the struvite submissions decrease.[2,10] Another theory suggests that as longevity of dogs has increased, so has CaOx urolithiasis, which is a condition of older dogs.[12] A third theory suggests that changes in regular adult maintenance diets have contributed to the reciprocal relationship in submission of struvite and CaOx uroliths for dogs over time.[7,12]

In humans, a similar pattern toward an increase in the proportional number of calcareous uroliths has been related to increased societal affluence and an associated higher consumption of meat protein.[13–15] In humans, consumption of animal protein leads to increased urinary concentrations of calcium, oxalate, and uric acid as well as decreased urinary excretion of citrate, which is an important urolith inhibitor.[16] The influence of dietary factors on the risk of developing CaOx urolithiasis in dogs has been investigated in a case-control study[17] of dogs that formed uroliths. In that study, the highest-protein diets, compared with the lowest-protein diets, had a protective effect, although the source of protein (ie, animal protein vs plant protein) was not stipulated.[17] In that same study,[17] investigators found that diets highest in calcium, phosphorus, magnesium, sodium, potassium, and chloride content all had decreased odds for development of CaOx urolithiasis. The role of calcium intake in the risk of developing CaOx urolithiasis in dogs is further complicated by evidence that some dogs that form CaOx uroliths may be hyperabsorbers of calcium.[12] The influence of dietary oxalate content may be complicated by the amount of intestinal microflora (such as bacteria that produce lactic acid, which can degrade oxalate).[18] Features of treatment diets for struvite urolithiasis include lower amounts of protein, phosphorus, and magnesium to lower substrate concentrations; elevated amounts of sodium chloride to induce diuresis; and the addition of a urinary acidifier.[8] A diet with a high moisture content is preferable.[8] In contrast to CaOx uroliths, which typically form in sterile urine, struvite uroliths largely result from urinary tract infections attributable to urease-producing bacteria, which lead to alkaline urine; thus, control of urinary tract infections is the most important factor in the prevention of struvite urolithiasis.[8] There is a dilemma with regard to dietary approaches to the prevention of struvite urolithiasis: dietary factors (such as urinary acidifiers) aimed at minimizing the risk of developing struvite uroliths may enhance the risk of developing CaOx uroliths in the many small breeds of dogs that may be at greatest risk for development of both urolith types.[8] Dietary nutrients can also affect urinary pH.[19]

Limited research has been conducted on contextual risk factors that contribute to canine urolith submission patterns. Investigators in 1 case-control study[9] detected an increase in the risk of developing CaOx urolithiasis among urban dogs, compared with the risk among rural dogs, during univariable analyses. In another study[11] conducted by our laboratory group on spatial analysis of dogs in Ontario, Canada, with uroliths from 1998 to 2006, we found more dogs with CaOx uroliths in the densely populated urban area of Toronto than was expected and more dogs with struvite uroliths in one of the most sparsely populated areas of southern Ontario than was expected. These clusters differed significantly after adjusting for spatial distribution of canine age, sex, and breed. The location of these CaOx and struvite urolith clusters could have been related to socioeconomic factors that may have influenced owner access to various types of diets for their pets. These results could also, in part, have been attributable to differences in decision making regarding treatment related to accessibility of preferred veterinary care, community income, and differences in the approach to urolith treatment between urban and rural clinics.[11]

The study reported here was conducted to investigate patient-related risk factors for development of uroliths in dogs while accounting for clustered data in the analyses and to investigate community-level risk factors that could explain these clusters in space and time. Thus, we evaluated several dog-level variables and their interactions as well as dietary-level variables and their interactions with the dog-level variables. In addition, we evaluated the year of urolith submission and community-level contextual variables for the owners; analysis of these contextual variables was intended to account for the impact of the wealth of the owner's community, degree of urban influence on a community, and accessibility to preferred veterinary care to account for nonbiological risk factors that affected submission patterns.

Materials and Methods

Sample population—Records of the Canadian Veterinary Urolith Centre were compiled for CaOx and struvite urinary calculi submitted from dogs that lived in Ontario between February 1, 1998, and December 31, 2006. Submissions that represented recurrent uroliths were excluded. A questionnaire that included demographic information, diet information, and owner and clinic addresses was submitted along with each urolith. Owner and clinic addresses were used in a spatial program[a] to code dogs and clinics with regard to location (latitude and longitude coordinates).

Dog-level variables—Individual dog–level variables included demographic variables (age, sex, breed, and neuter status), body condition (thin, normal, or obese), diet (primary diet fed and duration diet was fed), and year the urolith submission was received. Breed was grouped into 3 categories (mixed-breed dogs, small-breed dogs, and medium- or large-breed dogs).

The small-breed category included all the small or toy breeds listed by the American Kennel Club.[20] Small or toy breeds not listed by the American Kennel Club were included in the small-breed category if they were listed on a small-breed website[21] and their size could be verified from pertinent breed-specific websites. The mixed-breed category included those listed as a mixed-breed dog on the questionnaire regardless of size. The medium- or large-breed category included all remaining dogs. Their classification was verified through a listing by the American Kennel Club and information from pertinent breed-specific websites and a large-breed website.[22] Body condition of a dog was classified on the basis of the submitting veterinarian's assessment. Diet (considered the first diet listed or major diet consumed) was dichotomized into veterinary-exclusive diet fed for a minimum of 6 months or other diet, which comprised veterinary-exclusive diets fed for < 6 months or an unknown duration, commercial diets (ie, nonprescription diets), homemade diets, and unknown diets. The cutoff of 6 months was chosen to avoid any bias associated with short-term veterinary treatment diets. Veterinary-exclusive diets included any treatment, preventive, or maintenance diet that was only available by veterinarian prescription and unavailable through a retail outlet. Urinary diet was dichotomized into urolithiasis treatment diets fed for a minimum of 6 months or nonurinary diets, which comprised urinary diets fed for < 6 months or a nonurinary treatment diet. All urinary diets were veterinary-exclusive diets. One additional dietary variable was included: dietary moisture content was categorized as dry, canned, or both.

Community-level contextual variables—Canadian municipalities or communities deemed to be the equivalent of municipalities for statistical reporting purposes are classified as CSDs. Uroliths were submitted from dogs that lived in 302 CSDs. Geocoding of the owner location and linking to its Statistics Canada CSD allowed us to obtain information for the community-level socioeconomic variables median family income and SAC.[23] The CSD median family income was categorized in quartiles rounded to the nearest $1,000 (Canadian dollars). All CSDs were classified by SAC type on the basis of their degree of integration with a central urban area. The SAC is a measure of urban influence on a municipality, and SAC classification combines CSDs according to whether they are a component of a CMA (1 or more adjacent municipalities centered on an urban core with a population of ≥ 100,000), a CA (1 or more adjacent municipalities centered on an urban core with a population of 10,000 to 99,000), or a CMA- or CA-influenced zone based on the percentage of the resident employed labor force working in the urban core of these CMAs or CAs.[23] Two additional contextual variables (owner's location within a previously detected, significant spatial CaOx or struvite cluster[11] and distance between the geocoded owner and clinic location) were investigated to determine association with the outcome. The variable cluster was used to describe uroliths from dogs that were within the 122-km-diameter struvite spatial cluster centered in the municipality of Hastings Highlands, ON, Canada; the 42-km-diameter CaOx spatial cluster centered in Toronto; or neither cluster. Accessibility to a submitting veterinary clinic was determined by the distance between the owner and location of the clinic that submitted the urolith, as calculated by use of the Haversine equation.[b] Year of urolith submission was also included as a variable.

Uroliths—Uroliths had been surgically removed or passed during natural or assisted voiding procedures and submitted to the Canadian Veterinary Urolith Centre for quantitative analysis. Only uroliths comprising a minimum of 70% of CaOx or magnesium ammonium phosphate (ie, struvite) mineral were included in the study. When the nidus of a urolith differed from its overlying layers, then the urolith was classified on the basis of the mineral type in the nidus. Mineral analysis involved the use of 2 techniques (polarized light microscopy and x-ray diffraction scanning electron microscopy). These quantitative analyses were provided as a complimentary service to veterinarians and their clients. For the purposes of the study, CaOx included CaOx monohydrate and CaOx dihydrate.

Statistical analysis—Adaptive quadrature was used to build multilevel logistic regression models with a random intercept for owner CSD.[c] The outcome variable was dichotomous (ie, CaOx or struvite urolith). All tests were performed as 2-tailed tests with significance set at a value of $P \leq 0.05$. All explanatory variables were initially assessed through descriptive statistics and univariable models. The assumption of linearity for age, year of urolith submission, distance between owner and clinic location, and CSD median family income was tested by use of 3 techniques: adding a squared term, categorizing the continuous variable to determine whether the coefficients increased in a uniform manner, and plotting the logarithmic odds of the outcome against the mean of categories of the variable divided into deciles. If the independent variable's relationship with the logarithmic odds of the outcome was not linear, the variable was categorized or, if there was a quadratic relationship, the independent variable's square term was added to the model. When the correlation between 2 variables was ≥ 0.7, only 1 of the variables was chosen for subsequent analyses on the basis of completeness of the data, biological plausibility, or both. Univariable analyses by use of multilevel logistic regression with owner's CSD as the random intercept were performed. The 2-way interactions among demographic variables and diet variables were tested by use of a multilevel model that included the 2 main effects and their interaction term. The initial multivariable multilevel model was built with the significant individual dog–level main effects and interaction terms. Subsequent models were built in a forward manner with the addition of community-level contextual variables. Explanatory variables and interactions not initially included were retested in the full model and retained in the model when they were significant or acted as a confounding variable. A confounding variable was defined as a nonintervening variable that changed the coefficient of a significant variable in the logarithmic odds scale by ≥ 20%.[24,25] Odds ratios were expressed in terms of the odds for developing CaOx urolithiasis, compared with the odds for developing struvite urolithiasis.

The intraclass correlation coefficient (ie, the correlation between 2 observations within a cluster) was calculated from the variance component for the owner's CSD in the multilevel logistic model by applying the latent variable approach (ie, fixing the error variance at $\pi^2/3$) to calculate an intraclass correlation coefficient.[24,25]

Results

Descriptive statistics—Dogs in Ontario accounted for 11,414 of 26,239 (43.5%) of all uroliths submitted to the Canadian Veterinary Urolith Centre from 1998 to 2006. Calcium oxalate and struvite uroliths comprised 10,478 (91.8%) urolith submissions from dogs in Ontario during the 9-year study period. Of these, 9,764 (93.2%) were successfully geocoded. There were 7,297 uroliths (3,867 [53.0%] CaOx uroliths and 3,430 [47.0%] struvite uroliths) with full covariate information (**Table 1**). Mean age of dogs for CaOx urolith submissions was 8.2 years, whereas the mean age of dogs for struvite uroliths was 5.7 years. Of the 7,297 dogs from which uroliths were submitted, 6,932 (95.0%) were between 0.1 and 12 years of age. Small breeds were the most commonly represented breed category for both urolith types, but CaOx uroliths comprised most of the submissions for small-breed dogs. The CaOx submissions were predominantly from patients that were male, neutered, obese, or a small-breed dog. Among dogs fed a urinary diet for a minimum of 6 months, there were more CaOx urolith submissions than struvite submissions. Most dogs were fed a dry diet; the fewest dogs were fed strictly a canned diet, and only 29 medium- or large-breed dogs were fed strictly a canned diet.

Households in the lowest community median family income group (< $54,000 [Canadian dollars]) had a greater proportion of struvite submissions, whereas all higher income groups (> $54,000) had a greater proportion of CaOx urolith submissions (**Table 2**). Households within the previously identified clusters of CaOx and struvite uroliths had a higher proportion of CaOx and struvite urolith submissions, respectively. The annual number of submissions peaked at 1,122 in 2004, and the highest proportion of CaOx urolith submissions was in 2006. Median distance between an owner and the submitting clinic was 3.9 km, and for 5,473 (75%) owners, it was ≤ 10.3 km to the clinic where the urolith was removed from their dog. Households with the greatest metropolitan influence (ie, those from within a CMA) accounted for the greatest proportion of CaOx urolith submissions.

Linearity and correlations—None of the continuous explanatory variables, including age, year of submission, CSD median family income, or distance between owner and clinic location, had a linear relationship with the outcome, as determined on the basis of plots of logarithmic odds. Transformations were made to address nonlinearity of the continuous explanatory variables. A significant squared term was included to determine the curvilinear relationship between age and outcome. Year was categorized on an annual basis. The CSD median family income was categorized by quartiles (< $54,000, $54,000 to $59,000, $59,000 to $70,000, and > $70,000 [Canadian dollars]), and distance was categorized by quartiles (< 1.6, 1.6 to 3.9, 3.9 to 10.3, and > 10.3 km). None of the correlations among the explanatory variables exceeded 0.7.

Table 1—Descriptive statistics for individual dog–level categorical variables for CaOx and struvite uroliths obtained from dogs in Ontario, Canada, and submitted to the Canadian Veterinary Urolith Centre from 1998 to 2006.

	CaOx		Struvite		
Categorical variable	**No.**	**%**	**No.**	**%**	**Total**
Demographic					
Sex					
Female	1,077	25.0	3,233	75.0	4,310
Male	2,790	93.4	197	6.6	2,987
Breed					
Medium- or large-breed dog	267	35.2	491	64.8	758
Mixed-breed dog*	665	45.6	794	54.4	1,459
Small-breed dog	2,935	57.8	2,145	42.2	5,080
Neuter status					
Sexually intact	350	49.2	362	50.8	712
Neutered	3,517	53.4	3,068	46.6	6,585
Body condition					
Thin or normal	2,720	51.9	2,519	48.1	5,239
Obese	1,147	55.7	911	44.3	2,058
Diet					
Veterinary-exclusive diet fed for < 6 mo or for an unknown duration and non–veterinary-exclusive diet (commercial, homemade, or unknown diet)	2,835	50.2	2,812	49.8	5,647
Veterinary-exclusive diet fed for ≥ 6 mo	1,032	62.6	618	37.4	1,650
Urinary diet fed for ≥ 6 mo	76	58.0	55	42.0	131
Dietary moisture content					
Dry	2,831	53.2	2,492	46.8	5,323
Canned	255	53.9	218	46.1	473
Both dry and canned	781	52.0	720	48.0	1,501

*Mixed-breed dog regardless of size.

Table 2—Descriptive statistics for community-level categorical variables for CaOx and struvite uroliths obtained from dogs in Ontario and submitted to the Canadian Veterinary Urolith Centre from 1998 to 2006.

Variable	CaOx No.	CaOx %	Struvite No.	Struvite %	Total
CSD median family income (Canadian dollars)					
< 54,000	435	43.7	560	56.3	995
54,000 to 59,000	1,400	53.8	1,203	46.2	2,603
59,000 to 70,000	966	52.2	886	47.8	1,852
> 70,000	1,066	57.7	781	42.3	1,847
Spatial cluster*					
Outside either previous cluster	2,659	50.1	2,646	49.9	5,305
Within previous CaOx cluster	1,154	62.5	693	37.5	1,847
Within previous struvite cluster	54	37.2	91	62.8	145
Year of urolith submission					
1998	186	46.6	213	53.4	399
1999	269	45.2	326	54.8	595
2000	328	53.8	282	46.2	610
2001	358	52.3	326	47.7	684
2002	372	51.2	354	48.8	726
2003	525	51.2	501	48.8	1,026
2004	598	53.3	524	46.7	1,122
2005	619	55.6	494	44.4	1,113
2006	612	59.9	410	40.1	1,022
Distance between owner and clinic (km)					
< 1.6	912	53.3	800	46.7	1,712
1.6 to 3.9	1,050	53.1	927	46.9	1,977
3.9 to 10.3	978	53.9	837	46.1	1,815
> 10.3	927	51.7	866	48.3	1,793
Metropolitan influence (type of SAC)†					
1	2,690	55.8	2,134	44.2	4,824
2	468	53.3	410	46.7	878
3	288	43.2	378	56.8	666
4	237	45.4	285	54.6	522
5	114	43.2	150	56.8	264
6	70	49.0	73	51.0	143
7	0	0	0	0	0

*Owner's location was within a previously identified spatial cluster.[11] †Each SAC was as follows: 1, CSD within a CMA; 2, CSD within a CA with at least 1 census tract; 3, CSD within a CA without a census tract; 4, CSD outside a CA with CA having a strong metropolitan influence; 5, CSD outside a CA with CA having a moderate metropolitan influence; 6, CSD outside a CA with CA having a weak metropolitan influence; and 7, CSD outside a CA with CA having no metropolitan influence. A CMA is defined as 1 or more adjacent municipalities centered on an urban core with a population of ≥ 100,000. A CA is defined as 1 or more adjacent municipalities centered on an urban core with a population of 10,000 to 99,000. A census tract is an area that is small and relatively stable; a census tract usually has a population of 2,500 to 8,000 and is located in a large urban center that must have an urban core population of ≥ 50,000.

Individual dog–level risk factors and 2-way interactions—In the final multilevel model, the main effects included the following significant individual dog–level variables: age, age^2, sex, body condition, veterinary-exclusive diet, and urinary diet **(Table 3)**. Age, sex, neuter status (sexually intact or neutered), breed (mixed-breed dog, small-breed dog, or medium- or large-breed dog), body condition (thin or normal vs obese), and dietary moisture content (dry, canned, or both) were all part of significant 2-way interactions with other individual dog–level variables. These interactions comprised sex with age (LR χ^2 = 32.89 [P < 0.001]), sex with neuter status (LR χ^2 = 17.21 [P < 0.001]), body condition with age (LR χ^2 = 12.49 [P < 0.001]), and dietary moisture content with breed (LR χ^2 = 19.71 [P = 0.003]).

Individual dog–level interaction terms that were not significant were breed with age (LR χ^2 = 3.82 [P = 0.15]), breed with sex (LR χ^2 = 3.12 [P = 0.21]), sex with body condition (LR χ^2 = 0.02 [P = 0.90]), breed with age (LR χ^2 = 3.82 [P = 0.15]), breed with neuter status (LR χ^2 = 4.20 [P = 0.12]), breed with body condition (LR χ^2 = 3.58 [P < 0.17]), neuter status with body condition (LR χ^2 = 0.61 [P = 0.44]), neuter status with age (LR χ^2 = 1.47 [P = 0.23]), veterinary-exclusive diet with age (LR χ^2 = 0.29 [P = 0.59]), veterinary-exclusive diet with sex (LR χ^2 = 0.91 [P = 0.34]), veterinary-exclusive diet with breed (LR χ^2 = 3.91 [P = 0.14]), veterinary-exclusive diet with neuter status (LR χ^2 = 0.06 [P = 0.81]), veterinary-exclusive diet with body condition (LR χ^2 = 0.78 [P = 0.38]), veterinary-exclusive diet with dietary moisture content (LR χ^2 = 4.15 [P = 0.39]), veterinary-exclusive diet with urinary diet (LR χ^2 = 0.41 [P = 0.52]), urinary diet with age (LR χ^2 = 3.05 [P = 0.08]), urinary diet with sex (LR χ^2 = 0.20 [P = 0.65]), urinary diet with breed (LR χ^2 = 1.34 [P = 0.51]), urinary diet with neuter status (LR χ^2 = 0.55 [P = 0.46]), urinary diet with body condition (LR χ^2 = 0.02 [P = 0.90]), urinary diet with dietary moisture content (LR χ^2 = 1.05 [P = 0.59]), dietary moisture content with age (LR χ^2 = 4.40 [P = 0.36]), dietary moisture content with sex (LR χ^2 = 4.60 [P = 0.33]), dietary moisture content with neuter status (LR χ^2 = 1.28

[$P = 0.53$]), and dietary moisture content with body condition (LR $\chi^2 = 5.78$ [$P = 0.06$]).

The odds for a submission of a CaOx urolith, compared with the odds for submission of a struvite uro-

Table 3—Results for individual dog–level variables in a multilevel* logistic regression model for submission of CaOx uroliths, compared with submission of struvite uroliths, obtained from dogs in Ontario and submitted to the Canadian Veterinary Urolith Centre from 1998 to 2006.

Variable	OR	Confidence interval	*P* value†
Main effects			
Age (y)	2.24	2.00–2.52	< 0.001
Age^2 (y^2)	0.97	0.97–0.98	< 0.001
Sex (male vs female)	92.36	50.58–168.68	< 0.001
Breed‡			
Mixed-breed vs medium- or large-breed§	2.38	1.71–3.29	< 0.001
Small-breed vs medium- or large-breed	6.10	4.58–8.12	< 0.001
Small-breed vs mixed-breed	2.56	2.05–3.20	< 0.001
Neuter status (neutered vs sexually intact)	1.35	0.99–1.84	0.062
Body condition (obese vs thin or normal)	2.73	1.73–4.32	< 0.001
Veterinary-exclusive diet (diet fed for at least 6 mo vs other diet)	1.60	1.35–1.91	< 0.001
Urinary diet (diet fed for at least 6 mo vs nonurinary diet)	0.58	0.35–0.98	0.043
Interaction effects			
Sex × age	0.83	0.78–0.88	< 0.001
Body condition × age	0.90	0.85–0.96	< 0.001
Sex × neuter status	2.98	1.86–4.76	< 0.001
Small breed × dietary moisture content‖			
Canned vs dry	0.71	0.52–0.98	0.039
Canned vs both†	0.81	0.57–1.15	0.245
Dry vs both	0.88	0.71–1.08	0.228
Mixed-breed × dietary moisture content			
Canned vs dry	0.77	0.39–1.51	0.443
Canned vs both	0.88	0.42–1.85	0.744
Dry vs both	0.87	0.58–1.30	0.497
Medium- or large-breed × dietary moisture content			
Canned¶ vs dry	7.88	2.69–23.11	< 0.001
Canned¶ vs both	7.22	2.22–23.46	0.001
Dry vs both	1.09	0.59–1.99	0.775

*Owner CSD was the random intercept. †Values were considered significant at $P \leq 0.05$. ‡Mixed-breed dogs regardless of size. §Medium- or large-breed dogs was the referent category. ‖Reported as canned, dry, or both. ¶Based on a small sample size of only 29 observations.

Table 4—Results for year of submission and community-level variables in a multilevel* logistic regression model for submission of CaOx uroliths, compared with struvite uroliths, obtained from dogs in Ontario and submitted to the Canadian Veterinary Urolith Centre from 1998 to 2006.

Variable	OR	Confidence interval	*P* value†
Year of submission			
1999 vs 1998	0.82	0.56–1.21	0.318
2000 vs 1998	1.27	0.87–1.87	0.221
2001 vs 1998	1.24	0.85–1.80	0.269
2002 vs 1998	1.20	0.83–1.75	0.331
2003 vs 1998	1.18	0.83–1.69	0.356
2004 vs 1998	1.24	0.87–1.76	0.228
2005 vs 1998	1.11	0.78–1.59	0.546
2006 vs 1998	1.55	1.09–2.22	0.015
CSD median family income (Canadian dollars)			
$54,000–$59,000 vs < $54,000	1.16	0.90–1.49	0.247
$54,000–$70,000 vs < $54,000	1.13	0.87–1.47	0.343
> $70,000 vs < $54,000	1.38	1.05–1.81	0.021
$54,000–$59,000 vs $59,000–$70,000	1.02	0.83–1.26	0.824
$54,000–$59,000 vs > $70,000	0.84	0.68–1.04	0.110
$59,000–$70,000 vs > $70,000	0.82	0.66–1.03	0.087
Previously identified spatial cluster‡			
Struvite vs outside either cluster	0.57	0.33–1.00	0.048
CaOx vs outside either cluster	1.39	1.13–1.73	0.002
CaOx vs struvite	2.44	1.36–4.39	0.003

*Owner CSD was the random intercept. †Values were considered significant at $P \leq 0.05$. ‡Owner's location was within a previously identified CaOx or struvite spatial cluster.[11]

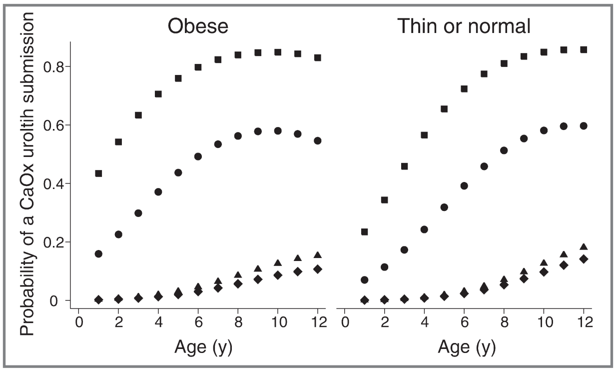

Figure 1—Predicted values for the probability of a CaOx urolith submission, compared with the probability of a struvite urolith submission, among dogs in Ontario, Canada, from 1998 to 2006 on the basis of age, sex, neuter status (neutered males [squares], sexually intact males [circles], spayed females [triangles], and sexually intact females [diamonds]), and body condition. For each variable, all other variables were held constant at their referent values.

lith, were increased by the following factors: increasing age; being a male; being a mixed-breed or small-breed dog, compared with being a medium- or large-breed dog; having an obese body condition, compared with having a thin or normal body condition; being fed a veterinary-exclusive diet for a minimum of 6 months, compared with being fed a veterinary-exclusive diet for < 6 months or for an unknown duration or being fed a commercial, homemade, or unknown diet; and dietary moisture content (canned vs dry; Table 3). The odds for submission of a CaOx urolith, compared with the odds for submission of a struvite urolith, were decreased for a urinary diet fed for a minimum of 6 months, compared with a nonurinary diet or with a urinary diet fed for < 6 months. In the multivariable model, the odds for submission of a CaOx urolith increased with age, but this effect was far greater in males than in females (**Figure 1**). In males, the odds were higher at a younger age and increased at a more rapid rate with each successive age increment up to a plateau between 9 and 10 years of age. Sex also interacted with neuter status; neutering increased the odds of developing CaOx urolithiasis, but more so in males. Obesity increased the odds of developing CaOx urolithiasis, but more so for younger dogs.

Dietary moisture content (canned vs dry) interacted with breed. In the small-breed category, eating a canned diet, compared with eating a dry diet, had a significant sparing effect on the submission of CaOx uroliths; however, this effect was not observed for the mixed-breed category. Feeding both canned and dry diets, compared with feeding only a dry diet, did not have a significant effect for either the small- or mixed-breed categories. Feeding a canned diet, compared with feeding only a dry diet or with feeding both canned and dry diets, resulted in a significant increase in the odds for submission of a CaOx urolith in medium- or large-breed dogs.

Community-level contextual risk factors—In the final multivariable model, community-level main effects that had a significant association with outcome for submission of a CaOx urolith versus submission of a struvite urolith were year of submission, cluster, and CSD median family income (**Table 4**). Compared with 1998, only 2006 had a significant increase in the odds for submission of a CaOx urolith versus submission of a struvite urolith. The odds for submission of a CaOx urolith were greater in dogs whose owners resided in the CaOx spatial cluster, compared with the odds for those whose owners resided outside a cluster or that resided in the struvite spatial cluster. The risk for submission of a CaOx urolith from dogs whose owners resided within the struvite spatial cluster was less than that for dogs whose owners resided in neither spatial cluster. In the multivariable model, median family income quartiles for the highest income group (ie, > $70,000 [Canadian dollars]), compared with the lowest CSD median family income group, was associated with a significant increase in the odds for submission of a CaOx urolith. There was no significant association between outcome and SAC type (LR $\chi^2 = 3.34$ [$P = 0.65$]) or between outcome and distance of owner from the submitting clinic (LR $\chi^2 = 0.06$ [$P = 0.99$]).

The intraclass correlation coefficient in the intercept-only model, full model excluding the cluster variable, and full model that included the cluster variable was 2.95%, 1.38%, and 0.75%, respectively. The final model was not affected by the removal of extreme Pearson residuals, and extreme residuals did not appear to be a result of errors in data entry.

Discussion

Results for the study reported here reflected findings in other studies[3–9] in that female and younger dogs were at greater risk of struvite urolith submissions, whereas male and older dogs were at greater risk of CaOx uroliths submissions. However, we found complex interactions among the demographic variables. The interaction between age and sex resulted in the effect of age differing between the sex categories. In other studies[9,10] conducted to investigate the interaction of age and sex, variables were categorized into groups. In our study, by treating age as a continuous variable, we had more power to evaluate the complex interactions between age and the other variables, including sex and body condition. Investigators in a descriptive study[1] reported an interaction between age group and sex that resulted in the median age for dogs with CaOx uroliths being older than that for dogs with struvite uroliths, but this effect was more marked in males. We found that the effect of age began earlier and peaked when dogs were 9 to 10 years old in males.

Although obesity has been recognized as a factor contributing to CaOx urolithiasis,[9] the nature of interactions between obesity and other factors has not been clear. In our study, the interaction between age and body condition resulted in the effect of age differing between body conditions (obesity increased the odds of developing CaOx urolithiasis in younger males, compared with the odds in older males).

The study reported here also revealed an interaction between sex and neuter status, similar to that observed in another study[26] of dogs that formed uroliths. However, males in our study were more affected by neutering than were females, whereas investigators in that other study[26] found that females, rather than males, appeared to be more affected by neutering with regard to the risk of developing struvite urolithiasis and CaOx urolithiasis, as determined on the basis of univariable analyses to compare dogs with a particular urolith type with those that had any other urolith type.

In another study[27] in which investigators evaluated urine variables in healthy Miniature Schnauzers (n = 8 dogs) and healthy Labrador Retrievers (8), the urine frequency and urine volume per kilogram of body weight of the Miniature Schnauzers were both reduced, compared with results for the Labrador Retrievers. The findings in that study[27] may reflect general differences in urine variables between small- and large-breed dogs and could partly explain the overrepresentation of small-breed dogs among those that form struvite and CaOx uroliths. We detected significantly increased odds for submission of CaOx uroliths, compared with the odds for submission of struvite uroliths, in small-breed dogs, compared with the odds for mixed-breed and medium- or large-breed dogs; however, this may not necessarily reflect the risk in all small and toy breeds. The breed categories in the present study can only crudely represent risk differences between the 2 urolith types. Some medium and large purebred dogs, such as Standard Schnauzers, may have an inherent risk for developing CaOx urolithiasis, as determined in 1 study[26] in which investigators evaluated urolith risk within breed while adjusting for breed popularity.

Analysis of results of our study suggested that feeding only canned diets to small-breed dogs decreased the risk for submission of CaOx uroliths, compared with the risk for submission of struvite uroliths. This protective effect of canned food did not extend to feeding regimens that included both canned and dry diets. In contrast to small-breed dogs, high dietary moisture content (canned vs dry or canned vs both canned and dry) was a significant risk factor for development of CaOx uroliths in medium- and large-breed dogs. This effect of dietary moisture content in medium- and large-breed dogs fed exclusively a diet of canned food was based on a small sample size (n = 29 dogs); consequently, the impact of dietary moisture content in these breeds requires further investigation. Our results for small-breed dogs are consistent with results from the challenge trial conducted by other investigators who reported[28] that Miniature Schnauzers, a small-breed dog, had a reduction in CaOx relative supersaturation (ie, a measure of the potential for forming CaOx uroliths) when fed a diet with a high moisture content, whereas this effect was absent in Labrador Retrievers, a large-breed dog.[28]

In the study reported here, we found that dogs fed a veterinary-exclusive diet for > 6 months had increased odds for submission of a CaOx urolith, compared with the odds for submission of a struvite urolith. Other investigators[8] have alluded to the dilemma in formulating diets that control risk factors for development of both CaOx and struvite uroliths. However, it is important to mention that because we compared the relative odds for the submission of 1 urolith type with that of another, our study cannot estimate the absolute risk of developing either urolith type. It is possible that by comparing cases of both CaOx and struvite urolithiasis to a true control group we might find different patterns concerning the risk of urolith formation associated with different diet types. In addition, we have no information as to why these dogs were fed these veterinary-exclusive diets, so we cannot control for predisposing conditions in our analyses. However, it is worth considering further epidemiological investigations into the components of these diets because formulation of diets that result in a reduction of urine pH, phosphorus concentrations, and magnesium concentrations to control the risk of developing struvite uroliths may predispose dogs to formation of CaOx uroliths.[7,8] In addition, 2 challenge studies[28,29] have revealed that increased dietary sodium content can reduce the CaOx relative supersaturation. Veterinary-exclusive diets and nonveterinary diets may differ in their sodium, magnesium, and phosphorus content and hence their effect on urinary pH. In addition, if veterinary-exclusive diets contain more meat protein, compared with that in nonveterinary diets, they may differ with regard to the risk for development of CaOx urolithiasis.

The first or major diet listed for each dog was considered to be the main diet and was used for analysis in the present study. However, the diet variable lacked specificity for dogs that were fed > 1 diet, and there was inadequate information from the current registry to assess the composition of these diets. Increased efforts to record specific dietary information and the components of these diets should be considered to improve the epidemiological quality of these data for future studies. We found that dogs fed urinary diets for a minimum of 6 months had lower odds for submission of a CaOx urolith, compared with the odds for submission of a struvite urolith. However, our data lacked information concerning the reasons these dogs were being fed urinary diets, which makes it difficult to interpret this finding. It is possible that some dogs may have been incorrectly classified as incident cases rather than recurrent cases, and overinterpretation of these results should be avoided.

Dogs of owners residing in CSDs with the highest community income, as measured by CSD median family income, had an increased risk for submission of a CaOx urolith, compared with the risk for submission of a struvite urolith, even after controlling for a previously identified spatial cluster. Community income level can reflect the influence of personal income or the access of a community member to treatment options or diet types. Dogs of owners residing in the high-density–population area of Toronto had an increased risk for the submission of CaOx uroliths, compared with the risk for dogs whose owners resided in the struvite cluster or outside either cluster, even after controlling for community income. These owners may have preferentially chosen to treat their dogs medically rather than surgically for suspected struvite uroliths. Similarly, owner location and community income levels may influence the medical management given to dogs with urinary tract infections, thereby reducing their risk for developing struvite uroliths. To further investigate the effect of these contextual variables, we examined 2 variables: distance between owner and submitting clinic location (as a surrogate for convenient access to preferred medical care) and owners' CSD-SAC type (as a measure of the degree of urban influence on the owner's location); however, neither variable had significant effects in our model. Additional case-control studies that also include data from patients medically treated at community clinics would be needed to fully evaluate the impact of contextual factors on submission patterns.

We detected a significant difference in outcome in 2006, compared with outcome in 1998, but there was no evidence of a linear or consistent increase in the odds for submission of a CaOx urolith in the intervening years. In contrast, other investigators have reported[2,10] a linear pattern toward an increase in the incidence of CaOx uroliths and a decrease in the incidence of struvite uroliths. However, our model included covariates whose distribution could change over time, and this may have accounted for the fact that the findings of our study differed from the results of the 2 aforementioned studies.[2,10] Reporting of dogs with presumptive struvite uroliths that receive medical treatment may provide additional insight regarding the incidence of struvite urolithiasis and submission patterns.

Use of multilevel data allow for an estimation of the relative importance of variations in risk at the various levels of organization.[30] In our intercept-only model, with owner CSD as the random intercept, the proportion of the total variation that could be attributed to variation among the owner CSD groups was small. This decreased even further with the inclusion of the individual-dog– and community-level fixed effects. In our model, the community-level variables CSD median family income and cluster had significant effects and indicated areas of interest for future studies; however, the greatest amount of variation and thus the greatest potential for intervention was detected at the individual-dog level.

Although registry data are commonly used to understand the epidemiological aspects of urolithiasis and have been useful in identifying important risk factors for urolith formation,[5,6,10,26] it is important to mention some inherent limitations of these data. Comparisons between 2 urolith types do not provide a true control group, so the distribution of exposure among actual control dogs in the population is unlikely to be represented by those associated with another urolith type.[24,25] In addition, admission bias is an inherent part of working with any secondary database, and this is especially true when struvite uroliths are being examined. The decision to treat dogs with struvite uroliths medically or surgically, which determines whether these animals will enter the registry, can be related to a number of potential factors, including choice of diet, income-related issues, and the nature of veterinary practice in various regions. Consequently, the findings in any registry-based study of uroliths should be used as a foundation for designing primary-based studies that evaluate the nature of urolith formation.

a. GeoPinpoint Suite 5.4, version 2, DMTI Spatial Inc, Markham, ON, Canada.
b. Veness C, Movable Type Ltd, Cambridge, England. Available at: www.movable-type.co.uk/scripts/latlong.html. Accessed Dec 20, 2007.
c. Xtmelogit, Stata/IC 10.0 for Windows, Stata Corp, College Station, Tex.

References

1. Ling GV, Franti CE, Ruby AL, et al. Urolithiasis in dogs. I: mineral prevalence and interrelations of mineral composition, age, and sex. *Am J Vet Res* 1998;59:624–629.
2. Osborne CA, Lulich JP, Polzin DJ, et al. Analysis of 77,000 canine uroliths: perspectives from the Minnesota urolith center. *Vet Clin North Am Small Anim Pract* 1999;29:17–38.
3. Houston DM, Moore AEP, Favrin MG, et al. Canine urolithiasis: a look at over 16,000 urolith submissions to the Canadian Veterinary Urolith Centre from February 1998 to April 2003. *Can Vet J* 2004;45:225–230.
4. Sosnar M, Bulkova T, Ruzicka M. Epidemiology of canine urolithiasis in the Czech Republic from 1997 to 2002. *J Small Anim Pract* 2005;46:177–184.
5. Picavet P, Detilleux J, Verschuren S, et al. Analysis of 4,495 canine and feline uroliths in the Benelux. A retrospective study: 1994–2004. *J Anim Physiol Anim Nutr (Berl)* 2007;91:247–251.
6. Ling GV, Franti CE, Ruby AL, et al. Urolithiasis in dogs. II: breed prevalence, and interrelations of breed, sex, age, and mineral composition. *Am J Vet Res* 1998;59:630–642.
7. Lulich JP, Osborne CA, Thumchai R, et al. Epidemiology of canine calcium oxalate uroliths: identifying risk factors. *Vet Clin North Am Small Anim Pract* 1999;29:113–122.
8. Osborne CA, Lulich JP, Polzin DJ, et al. Medical dissolution and prevention of canine struvite urolithiasis: twenty years of experience. *Vet Clin North Am Small Anim Pract* 1999;29:73–111.
9. Lekcharoensuk C, Lulich JP, Osborne CA, et al. Patient and environmental factors associated with calcium oxalate urolithiasis in dogs. *J Am Vet Med Assoc* 2000;217:515–519.
10. Ling GV, Thurmond MC, Choi YK, et al. Changes in proportion of canine urinary calculi composed of calcium oxalate or struvite in specimens analyzed from 1981 through 2001. *J Vet Intern Med* 2003;17:817–823.
11. Wisener LV, Pearl DL, Houston DM, et al. Spatial and temporal clustering of calcium oxalate and magnesium ammonium phosphate uroliths in dogs living in Ontario, Canada from 1998 to 2006. *Prev Vet Med* 2010;95:144–151.
12. Stevenson AE, Blackburn JM, Markwell PJ, et al. Nutrient intake and urine composition in calcium oxalate stone-forming dogs: comparison with healthy dogs and impact of dietary modification. *Vet Ther* 2004;5:218–231.
13. Ramello A, Vitale C, Marangella M. Epidemiology of nephrolithiasis. *J Nephrol* 2000;13(suppl 3):S45–S50.
14. Menon M, Resnick MI. Urinary lithiasis: etiology, diagnosis, and medical management. In: Campbell MF, Walsh PC, Retik AB, eds. *Campbell's urology*. 8th ed. Philadelphia: WB Saunders Co, 2002;3229–3267.
15. Trinchieri A. Epidemiological trends in urolithiasis: impact on our health care systems. *Urol Res* 2006;34:151–156.
16. Curhan GC. Epidemiology of stone disease. *Urol Clin North Am* 2007;34:287–293.
17. Lekcharoensuk C, Osborne CA, Lulich JP, et al. Associations between dry dietary factors and canine calcium oxalate uroliths. *Am J Vet Res* 2002;63:330–337.
18. Weese JS. Oxalate degradation by intestinal lactic acid bacteria in dogs and cats. *Vet Microbiol* 2004;101:161–166.
19. Yamka RM, Mickelsen SL. The prediction of urine pH using dietary cations and anions in dogs fed dry and wet foods. *Int J Appl Res Vet Med* 2006;4:355–361.
20. American Kennel Club. Breed list. Available at: www.akc.org/breeds/index.cfm. Accessed May 1, 2007.
21. AllSmallDogBreeds. All small dog breeds. Available at: www.allsmalldogbreeds.com. Accessed May 1, 2007.
22. BigPawsOnly. Community and information for large breed dogs and their people. Available at: www.bigpawsonly.com. Accessed May 1, 2007.
23. Statistics Canada. *Stats Canada—boundary files, reference guide census year 2006. Table 5.6.1:21–22*. Catalogue No. 92–160-GIE. Ottawa: Statistics Canada, 2006.
24. Dohoo IR, Martin SW, Stryhn H. Chapter 20. In: *Veterinary epidemiologic research*. Charlottetown, PE, Canada: AVC Inc, 2003;459–471.
25. Dohoo IR, Martin SW, Stryhn H. Chapter 22. In: *Veterinary*

epidemiologic research. Charlottetown, PE, Canada: AVC Inc, 2003;499–520.
26. Weichselbaum RC, Feeney DA, Jessen CR, et al. Evaluation of the morphologic characteristics and prevalence of canine urocystoliths from a regional urolith center. *Am J Vet Res* 1998;59:379–387.
27. Stevenson AE, Markwell PJ. Comparison of urine composition of healthy Labrador Retrievers and Miniature Schnauzers. *Am J Vet Res* 2001;62:1782–1786.
28. Stevenson AE, Hynds WK, Markwell PJ. Effect of dietary moisture and sodium content on urine composition and calcium oxalate relative supersaturation in healthy Miniature Schnauzers and Labrador Retrievers. *Res Vet Sci* 2003;74:145–151.
29. Lulich JP, Osborne CA, Sanderson SL. Effects of dietary supplementation with sodium chloride on urinary relative supersaturation with calcium oxalate in healthy dogs. *Am J Vet Res* 2005;66:319–324.
30. Schukken YH, Grohn YT, McDermott B, et al. Analysis of correlated discrete observations: background, examples and solutions. *Prev Vet Med* 2003;59:223–240.