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# The association between taurine concentrations and dog characteristics, clinical variables, and diet in English cocker spaniels: The Canine taURinE (CURE) project

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## Abstract

**Background:** Occurrence of low blood taurine concentrations (B-TauC) and predisposing factors to taurine deficiency in English Cocker Spaniels (ECS) are incompletely understood.

**Objectives:** Investigate the occurrence of low B-TauC in a Swedish population of ECS and evaluate the association between B-TauC and dog characteristics, clinical variables, and diet composition.

**Animals:** One-hundred eighty privately owned ECS.

**Methods:** Dogs were prospectively recruited and underwent physical examination, blood analyses, and echocardiographic and ophthalmic examinations. Dogs with clinical signs of congestive heart failure (CHF) also underwent thoracic radiography. Taurine concentrations were analyzed in plasma (EDTA and heparin) and whole blood. Diets consumed by the dogs at the time of the examination were analyzed for dietary taurine- (D-TauC), cysteine- (D-CysC), and methionine concentrations (D-MetC).

**Results:** Fifty-three of 180 dogs (29%) had low B-TauC, of which 13 (25%) dogs had clinical and radiographic signs of CHF, increased echocardiographic left ventricular (LV) dimensions and volumes, and impaired LV systolic function. Five (9%) dogs with low B-TauC had retinal abnormalities. Dietary MetC, dietary animal protein source (red/white meat), and age were associated with B-TauC in the final multivariable regression model ($P < .001$, $R^2_{adj} = .39$).

**Abbreviations:** <B-TauC:CHF+, low taurine concentrations in one or more blood tube additive and clinical and radiographic signs of congestive heart failure; <B-TauC:CHF−, low taurine concentrations one or more blood tube additive and normal cardiac morphology; ACS, American Cocker Spaniel; ACVIM, American College of Veterinary Internal Medicine; AO, aorta; B-TauC, blood (plasma and/or whole blood) taurine concentrations; BW, body weight; CHF, congestive heart failure; CM, cardiomyopathy; CS, Cocker Spaniel; D-CysC, dietary cysteine concentrations; D-MetC, dietary methionine concentrations; D-TauC, dietary taurine concentrations; DCM, dilated cardiomyopathy; ECS, English Cocker Spaniel; EDTA-TauC, EDTA taurine concentrations; EDV, end diastolic volume; EF, ejection fraction; EPSS, E point to septal separation; ESV, end-systolic volume; FS, fractional shortening; Hep-TauC, heparinized plasma taurine concentrations; IQR, interquartile range; LA, left atrium; LA/AO, left atrium to aortic ratio; LV, left ventricle; LVIDd, left ventricular internal diameter in diastole; LVIDdn, left ventricular internal diameter in diastole normalized to body weight; LVIDs, left ventricular internal diameter in systole; LVIDsn, left ventricular internal diameter in systole normalized to body weight; nB-TauC, normal blood taurine concentrations; SLU, Swedish University of Agricultural Sciences; TauC, taurine concentrations; UC Davis AAL, University of California Amino Acid Laboratory; WB, whole blood; WB-TauC, whole blood taurine concentrations.

**Conclusions and Clinical Importance:** Low B-TauC suggests that taurine deficiency may play a role in the development of myocardial failure and CHF in ECS. Low D-MetC and diets with red meat as the animal protein source were associated with low B-TauC. Dogs with B-TauC below the normal reference range were older than dogs with normal concentrations.

**KEYWORDS**

amino acids, diet-associated DCM, dogs, heart disease, retinal degeneration, taurine deficiency

## 1 | INTRODUCTION

The amino acid taurine plays an essential role in various physiological processes.[1-3] Taurine synthesis depends on sufficient enzymatic activity and the availability of precursors methionine and cysteine, with synthesis capacity varying among species.[1,2]

Taurine is considered a dietary, nonessential amino acid in dogs receiving a balanced and bioavailable diet.[4-7] Nevertheless, taurine-responsive cardiomyopathy (CM) has been reported in certain breeds and individuals.[8-12] Insufficient dietary intake of methionine and cysteine has been associated with low blood taurine concentrations (<B-TauC) in dogs.[13] Potential associations between dietary factors and taurine deficiency have been investigated by several research groups, and although various dietary compositions have been proposed to cause taurine deficiency in dogs, no definitive conclusions have been reached.[7,14-18]

The first reports of taurine-responsive CM in dogs were published in the 1990s.[8,12] A prospective placebo-controlled study involving 11 American Cocker Spaniels with a dilated CM (DCM) phenotype and <B-TauC identified improved echocardiographic variables after taurine normalization.[8] Although these early reports led to a recommendation to supplement dogs with DCM phenotype and <B-TauC, they did not result in any general recommendations for taurine content in commercial dog foods.

The English Cocker Spaniel (ECS) traditionally has been considered predisposed to primary DCM rather than taurine-responsive CM.[19,20] However, a retrospective study reported that 13 of 16 ECS with a DCM phenotype and congestive heart failure (CHF) had <B-TauC.[11] Taurine deficiency also has been associated with retinal degeneration in dogs, although only a few reports have been published in the area.[15,21]

The Canine taURinE (CURE) project is a research project with an overall aim to investigate the occurrence of <B-TauC in selected dog populations and identify potential underlying causative factors and clinical consequences of taurine deficiency in dogs. The ultimate goal of the project is to increase knowledge about taurine deficiency in dogs and thereby decrease morbidity and mortality in the dog population. Our aims were to investigate the occurrence of <B-TauC in a Swedish population of ECS and evaluate a possible association between B-TauC and dog characteristics, clinical variables, and diet composition.

## 2 | MATERIALS AND METHODS

The study was approved by the Ethical Committee for Animal Welfare in Stockholm, Sweden (5.8.18-01548/2017, 5.8.18-21508/2021, and 5.8.18-04682/2020).

Client-owned dogs were prospectively recruited to the cardiology units at the University Animal Hospital of the Swedish University of Agricultural Sciences (SLU), Uppsala, Sweden, and at Anicura Albano Animal Hospital in Danderyd, Sweden, between September 2018 and April 2022. All owners received verbal and written information about the study and gave their consent before inclusion.

### 2.1 | Inclusion and exclusion criteria

English Cocker Spaniels were eligible for inclusion from 6 months of age, with no specified upper age limit. At the time of enrollment, dogs could either be clinically healthy, as assessed by their owners, or exhibit clinical signs indicative of cardiac disease, such as increased respiratory rate, increased respiratory effort, syncopal events, and exercise intolerance. Presumed healthy dogs were recruited via breeders, advertisements in breed magazines, and social media. Dogs with clinical signs of cardiac disease were recruited from the emergency clinics at the respective hospital and underwent study examinations after clinical signs related to cardiac disease had resolved. Exclusion criteria were clinically relevant noncardiac, systemic, or organ-related disease based on history, physical examinations, and results from blood analyses (CBC and serum biochemistry), or echocardiographic findings indicating congenital or acquired non-DCM phenotype-related cardiac disease. Congestive heart failure treatment and taurine supplementation were initiated in dogs diagnosed with CHF at enrollment. Dogs receiving cardiac medical treatment or taurine supplementation before enrollment were excluded.

### 2.2 | Procedures

All dogs underwent systemic blood pressure measurement, complete physical examination including assessment of body condition score on a 9-point scale, ECG registrations, echocardiographic and ophthalmologic examinations, and blood sample collection

(CBC, serum biochemistry, and B-TauC). Fasting was not required before blood sampling because fasting status does not appear to impact taurine concentration in dogs.[22,23]

Dogs with CHF initially were managed by the emergency clinic at either hospital, and received standard CHF treatment at the discretion of the attending veterinarian. The diagnosis of CHF was based on case history, physical examination findings, and results from radiographic and echocardiographic examinations. All dogs with CHF received taurine supplementation (250 mg PO q12h) after blood samples for taurine analyses had been collected, without waiting for the results of the blood taurine analyses. Dogs presenting to the emergency clinic with clinical signs of CHF were included even if only EDTA samples had been collected before initiation of taurine supplementation.

## 2.3 | Questionnaire

Owners completed a questionnaire regarding the dog's health status (previous diseases, medications, and surgical interventions), reproductive history (neutered yes/no, number of litters, potential reproductive problems, congenital diseases in litters), and diet (current diet, amount and type of treats, access to other animals' food or leftovers).

## 2.4 | Blood pressure measurements

Measurements were made using high-definition oscillometry (Vet HDO Monitor S+B medVET GmbH, Babenhausen, Germany) after a standardized protocol according to published guidelines.[24]

## 2.5 | Echocardiography

All echocardiographic examinations were performed and assessed by a board-certified specialist in cardiology (ILJ, JH, AT, and MD) or a resident in veterinary cardiology under supervision (KK). Dogs were unsedated and gently restrained in right and left lateral recumbency. Transthoracic echocardiographic examinations were performed during simultaneous ECG monitoring with an ultrasound unit using 5.0 to 9.2 MHz phased-array transducers (EPIQ 7G; Philips Ultrasound, Bothell, WA, USA). The echocardiographic examinations included the use of color flow Doppler, M-mode, and 2-dimensional echocardiographic modalities and were performed as previously described.[23] Left ventricular internal dimensions at end-diastole (LVIDd) and end-systole (LVIDs) were normalized for body weight (LVIDDn and LVIDSn) using the formulas by Cornell et al.[25] Measurements of LV fractional shortening (LV FS%) were made on right parasternal short axis view. E-point to septal separation (EPSS) measurements were made on right parasternal long-axis views. Left ventricular end-diastolic volume (LVEDV), end-systolic volume (LVESV), and ejection fraction (EF) were calculated using Simpson's modified method of disks. All echocardiographic measurements were made on 3 consecutive cardiac cycles, and the mean value was used for statistical analyses.

## 2.6 | ECG

A 3-minute standard 6-lead ECG was registered with the dog gently restrained in right lateral recumbency. Registrations were evaluated by a board-certified cardiology specialist (ILJ, JH, AT, and MD) or a cardiology resident under supervision (KK).

## 2.7 | Ophthalmic examinations

Each dog underwent a complete ophthalmic examination including neuro-ophthalmic testing (menace response, dazzle reflex, pupillary light reflexes, and palpebral reflexes), slit-lamp biomicroscopy of the adnexa and anterior segment, rebound tonometry and, after pharmacologic mydriasis (Tropikamid, eye drops, 0.5%, Bausch&Lomb, Stockholm, Sweden), indirect ophthalmoscopy. Fundus photography was performed in dogs with fundic lesions (Optibrand ClearView 2 Retinal Camera, Eickemeyer, Germany) and all images were reviewed by a board-certified ophthalmology specialist.

## 2.8 | Blood sampling

Blood samples were collected by jugular venipuncture using a butterfly needle with a Luer adapter (21G; BD Vacutainer, Eysins, Switzerland) collecting blood directly into serum, heparin, and EDTA vacutainer tubes (Greiner Bio-One GmbH, Kremsmünster, Austria).

## 2.9 | Hematology and biochemistry analyses

One milliliter of blood was collected in EDTA tubes for CBC and hematology. Three milliliters of blood was collected in serum tubes for routine biochemistry analyses (creatinine, blood urea nitrogen, phosphate, alanine aminotransferase, alkaline phosphatase, bile acids, potassium, sodium, calcium, albumin, total protein, c-reactive protein, thyroid stimulating hormone, and thyroxine). All samples were analyzed at the accredited commercial veterinary laboratory at the SLU or the in-house laboratory at Albano animal hospital on the same day as the samples were collected.

## 2.10 | Blood taurine analyses

Six milliliters of blood was collected in 2 separate heparinized tubes for whole blood (WB) samples (2 mL) and heparinized (Hep) plasma samples (4 mL), and 4 mL of blood was collected in EDTA tubes for EDTA plasma samples. Plasma samples (Hep and EDTA) were centrifuged at 3000 rpm for 5 minutes within 30 minutes of collection. EDTA plasma stored at −20°C at the in-house laboratory samples (0.5 mL) were transferred into microcentrifuge tubes (VWR International AB) until being transported frozen to IDEXX Laboratories in Germany within 5 days after collection of blood samples. Analyses of

EDTA plasma were made using liquid chromatography with mass spectrometry.[26]

Heparinized plasma samples (0.2 mL) were transferred into Eppendorf tubes and mixed with sulfosalicylic acid (0.2 mL) for deproteinization according to published recommendations.[27,28] Heparinized WB samples (2 mL) were transferred into Eppendorf tubes (1 mL). Heparinized plasma and WB samples were stored at −80°C at SLU, and at −70°C at Albano and transported frozen as a batch to the University of California Davis Amino Acid Laboratory (UC Davis AAL) within 9 months of collection. Heparinized plasma samples and WB samples were analyzed using ion exchange chromatography.[28] All blood samples were treated according to recommendations established by the respective laboratory.[26,28] The majority (94%) of samples were handled by 1 person (KK) to minimize differences in handling procedures. Plasma samples were centrifuged and separated within 30 minutes after collection and only the top layer of the plasma was transferred from each sample to avoid contamination of taurine-rich cells from the buffy coat. Hemolyzed plasma samples were not analyzed. Results are reported in nmol/mL.

Reference ranges for WB taurine concentrations (WB-TauC), EDTA plasma taurine concentrations (EDTA-TauC), and heparinized plasma taurine concentrations (Hep-TauC) in dogs were provided by the analyzing laboratory.[26,28] Thresholds established by UC Davis AAL for low blood taurine concentrations are <60 nmol/mL for heparinized plasma and <200 nmol/mL for WB. Heparinized plasma-TauC <40 nmol/mL and WB-TauC <150 nmol/mL are considered critically low, indicating a risk for taurine deficiency and potential secondary disorders.[28] Detailed thresholds have, to our knowledge, not been established for EDTA-TauC, and the single cutoff provided by IDEXX laboratories (<44 nmol/mL) was used in our study.[26] Lowest limits of quantification for B-TauC, communicated from respective laboratories, were 0.4 nmol/mL for WB-TauC and Hep-TauC, and 7.99 nmol/mL for EDTA-TauC.

## 2.11 | Diets

Information regarding the diet each dog consumed at the time of the examination and 3 months preceding was recorded upon enrollment. Samples consisting of 100 g each were collected from identical formulas of the various dry diets that the dogs included in the study had been consuming to analyze dietary concentrations of taurine (D-TauC), cysteine (D-CysC), and methionine (D-MetC). Samples from raw food diets were not collected for analysis because of the inconsistent content between batches in such diets. All collected samples were securely stored in sealed plastic bags at room temperature and protected from direct sunlight until shipped to an accredited external laboratory (Food&Feed Testing Sweden AB, Lidköping, Sweden) for analyses. The maximum storage time before shipping was 4 months.

Protein and carbohydrate sources were extracted from the diet ingredient list provided by the manufacturer. Dietary protein sources were categorized into 4 groups: red meat (lamb, beef, pork, reindeer, and venison), white meat (poultry and fish), mixed red/white meat, and other protein sources (soy, vegetables, and insects). A diet was classified as based on red or white meat only if all protein sources could be categorized as either red or white meat. Fish oil or animal fat were not taken into consideration in the categorization. Diets were categorized as grain-inclusive or grain-free based on whether they contained grains or grain-derived ingredients. Diets were categorized as potatoes or pulses inclusive, or both, if they contained potato, sweet potato or pulses (legumes, soybeans, peas, and lentils) or some combination of these as 1 of the first 10 ingredients on the ingredient list. Dogs that were subjected to diet changes <3 months before enrollment were excluded from analyses regarding B-TauC relation to diets.

## 2.12 | Grouping

Dogs were categorized based on B-TauC as normal B-TauC (nB-TauC) or B-TauC below the normal reference range (<B-TauC; EDTA-TauC <44 nmol/mL; Hep-TauC <60 nmol/mL; WB-TauC <200 nmol/mL). All dogs with clinical and radiographic signs of CHF had low B-TauC and dogs were accordingly further subdivided into <B-TauC:CHF+ or <B-TauC:CHF−.

## 2.13 | Statistics

Statistical analyses were performed using a commercially available software program (JMP Pro v. 16.0.0, Cary, NC, USA). Data were analyzed using descriptive as well as inferential statistics. The level of statistical significance was set at $P < .05$, if not otherwise indicated. Continuous variables were presented as medians and interquartile range (IQR).

Nonparametric Wilcoxon signed-rank test was used to analyze continuous data: age, weight, systolic blood pressure, and echocardiographic variables (LV dimension, volume, and functional variables) among groups (nB-TauC, <B-TauC:CHF−, and <B-TauC:CHF+). Chi-square and Fisher's exact tests were used to test for differences in proportions comparing categorical data (sex and neuter status).

Uni- and multivariable analyses were used to investigate the effect of dog characteristics (age, weight, sex, and neuter status), dietary factors (D-TauC, D-CysC, and D-MetC; protein source: red/white meat, grain-free y/n, and potatoes or pulses or both y/n) on B-TauC. Variables that reached a significance of $P < .2$ in the univariable regression analyses subsequently were included in the multivariable analyses. Furthermore, D-TauC, D-CysC, and D-MetC were compared between diets with red and white protein sources, and diets categorized as grain-free or grain-inclusive.

# 3 | RESULTS

A total of 180 ECS, 109 (60.5%) females (101 intact and 8 neutered) and 71 (39.5%) males (58 intact and 13 neutered) were included. A

total of 167 dogs were assessed as healthy, and 13 dogs presented with clinical and radiographic signs of CHF. Dog characteristics and clinical variables are presented in Table 1.

### 3.1 | Questionnaire

All owners filled out the questionnaire. Twenty-seven female dogs had ≥1 litter, of which 5 had ≥1 stillborn puppies in ≥1 litters. Three dogs had given birth to puppies with congenital diseases (patent ductus arteriosus n = 1 and cleft palate n = 2). All dogs experiencing reproductive problems had nB-TauC. Twenty-six dogs had a history of recurrent periods of mild self-limiting diarrhea or vomiting. Twenty of these had nB-TauC and 6 had <B-TauC.

### 3.2 | Blood taurine concentrations

Taurine concentrations were analyzed in EDTA plasma (n = 180), heparinized WB (n = 175), and heparinized plasma (n = 172) and results are presented in Table 1.

Fifty-three dogs (29%) had B-TauC below the normal reference range, of which 38 (21%) had B-TauC considered critically low. All 13 dogs presenting with clinical and radiographic signs of CHF had critically low B-TauC (Figure 1). A total of 42/172 (24%) dogs had <Hep-TauC, of which 26 (62%) had critically low Hep-TauC, 35/180 (19%) dogs had <EDTA-TauC, all with critically low EDTA-TauC, and 27/175 (15%) dogs had <WB-TauC, of which 15 (56%) had critically low WB-TauC. Analyses for WB-TauC and Hep-TauC were not performed in 5 and 8 dogs, respectively, because some of the dogs presenting with signs of CHF initially were managed out of hours at the emergency clinic where blood sampling for EDTA-TauC analyses was prioritized (as European commercial veterinary laboratories at that time only offered EDTA plasma-based TauC analyses) before taurine supplementation. EDTA-TauC was analyzed in all 180 dogs and used for subsequent comparisons and statistical analyses.

### 3.3 | Echocardiography

All 13 dogs presenting with CHF had increased LV dimensions (LVIDDn, LVIDSn) and volume variables (LVEDV and LVESV), as well as increased EPSS. The measured values of FS were within or slightly below the reported normal reference range[29-31] in 11 of the 13 < B-TauC:CHF+ dogs.

A total of 167 dogs had echocardiographic dimensional, volume, and functional variables within normal reference ranges. Forty of these dogs had <B-TauC and 127 had nB-TauC. Summary

**TABLE 1** Summary of dog characteristics, taurine concentrations in EDTA-plasma, heparin plasma, and whole blood, and echocardiographic data in 180 English Cocker Spaniels.

| | All dogs n = 180 | nB-TauC n = 127 | <B-TauC:CHF− n = 40 | <B-TauC:CHF+ n = 13 |
|---|---|---|---|---|
| Age (years) | 3.6 (1.7-6.3) | 3.5 (1.6-5.9)[a] | 3.6 (1.4-7.0)[ab] | 8.2 (3.8-10.0)[b] |
| BW (kg) | 12.8 (11.3-14.5) | 12.9 (11.4-14.5)[a] | 12.3 (10.9-14.5)[a] | 12.8 (11.7-15.6)[a] |
| BCS (U/N/O) | (0/141/39) | (0/102/25)[a] | (0/33/7)[a] | (0/6/7)[a] |
| Sex (f/m) | 109/70 | 79/48[a] | 23/16[a] | 7/5[a] |
| Neutered (y/n) | 21/158 | 15/112[a] | 4/35[a] | 1/11[a] |
| Taurine EDTA nmol/mL | 71.91 (47.94-103.87) | 87.89 (71.91-111.86)[a] | 39.95 (31.96-55.93)[b] | 7.99 (7.99-7.99)[c] |
| Taurine Heparin nmol/mL | 92 (59-111) | 103 (86-119)[a] | 40 (23-54)[b] | 5.5 (3.25-82.25)[b] |
| Taurine WB nmol/mL | 261 (231.5-294) | 279.5 (252.3-303.5)[a] | 204 (173-245)[b] | 35 (27.3-49.8)[c] |
| LVIDDn | 1.59 (1.51-1.7) | 1.57 (1.5-1.68)[a] | 1.57 (1.53-1.65)[a] | 2.36 (2.19-2.49)[b] |
| LVIDSn | 1.08 (.98-1.2) | 1.07 (.97-1.19)[a] | 1.08 (0.96-1.13)[a] | 1.84 (1.66-1.93)[b] |
| LVEDV (mL) | 30.3 (26.3-36) | 29.8 (26-34.1)[a] | 30.1 (4.9-35.1)[a] | 66.2 (52.6-73.05)[b] |
| LVESV (mL) | 12.7 (10.2-15.6) | 12.3 (9.7-14.3)[a] | 12.7 (.5-16.3)[a] | 43.6 (33.2-47.75)[b] |
| EPSS (cm) | .4 (.33-.5) | .4 (.3-.49)[a] | .37 (.33-.43)[a] | 1.05 (.98-1.13)[b] |
| FS (%) | 28 (24.42-32.2) | 28.79 (24.73-32.71)[a] | 27.81 (25.07-32.54)[a] | 18.89 (16.3-20.78)[b] |
| EF (%) | 58.50 (52.51-63.91) | 60 (53.58-64.6)[a] | 56.52 (53.31-62.68)[a] | 32.91 (31.54-38.86)[b] |

*Note*: Values are reported as median and interquartile ranges (IQR). Body condition score was based on a 9-point scale and divided into underweight (BCS 1-3), normal weight (BCS 4-5), and overweight (BCS 6-9). Within each row, values with the same superscript letter did not differ significantly ($P > .017$).
Abbreviations: <B-TauC:CHF−, dogs with low taurine concentrations one or more blood tube additive and normal cardiac morphology; <B-TauC:CHF+, dogs with low taurine concentrations in one or more blood tube additive and clinical and radiographic signs of CHF; BCS, body condition score; BW, body weight; CHF, congestive heart failure; DCM, dilated cardiomyopathy; LVEDV, left ventricular end-diastolic volume; EF, ejection fraction; EPSS, E point to septal separation; LVESV, left ventricular end-systolic volume; FS, fractional shortening; LVIDDn, left ventricular inner diameter in diastole normalized to body weight; LVIDSn, left ventricular inner diameter in systole normalized to body weight; nB-TauC, dogs with normal taurine concentrations and normal cardiac morphology; U/N/O, underweight/normal weight/overweight; WB, whole blood.

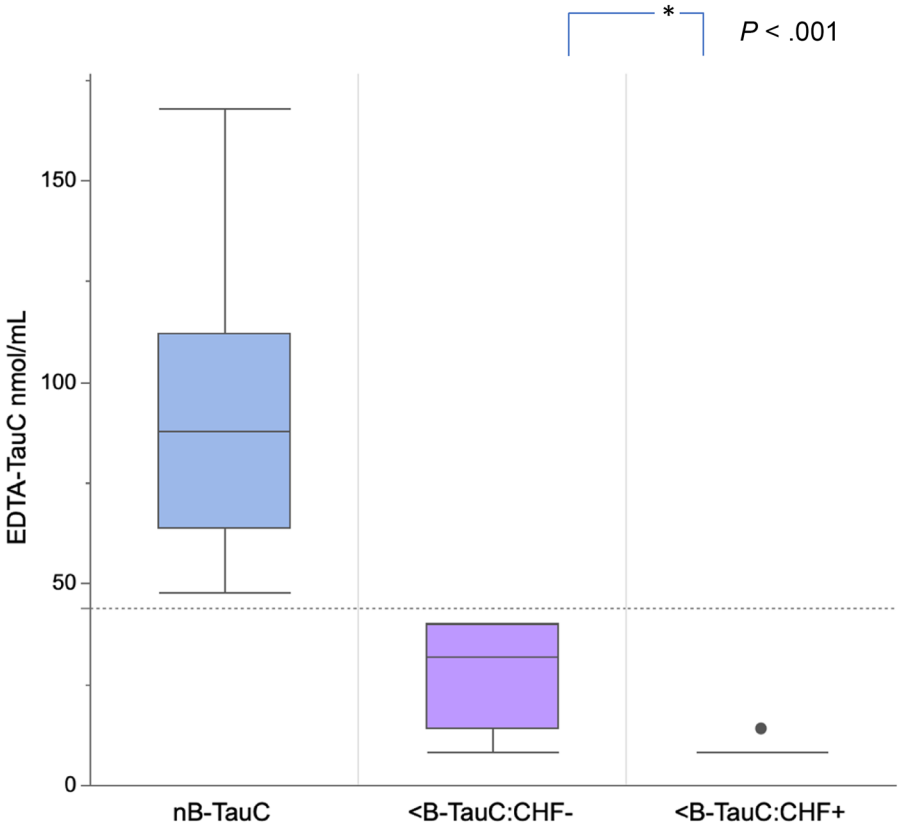


**FIGURE 1** Box and whiskers plots demonstrating EDTA-plasma taurine concentrations (EDTA-TauC) in dogs with normal taurine concentrations (nB-TauC) n = 127, dogs with low taurine concentrations and normal echocardiograms (<B-Tau:CHF−) n = 40, and dogs low taurine concentrations and CHF (<B-Tau:CHF+) n = 13. The horizontal line corresponds to the normal lower reference value for EDTA plasma provided by the analyzing laboratory. Asterisk (*) indicates significant differences. Solid circle corresponds to outliers. The boxes (top, bottom, and central line) correspond to the 75th percentile, the 25th percentile, and 50th percentile (median), respectively. Whiskers corresponds to 10th and 90th quantiles, respectively. CHF, congestive heart failure.

statistics of echocardiographic variables in the different groups (nB-TauC, <B-TauC:CHF−, and <B-TauC:CHF+) are presented in Table 1.

All <B-TauC:CHF+ dogs had mild to moderate mitral regurgitation assessed as secondary to ventricular dilatation in the absence of mitral valve pathology. Trivial mitral regurgitation also was found in dogs with normal cardiac morphology and was assessed as nonpathologic in all cases.

### 3.4 | Electrocardiography

One dog with CHF and <B-TauC presented with atrial fibrillation at enrollment. All other dogs presented with sinus rhythm.

### 3.5 | Ophthalmic examinations

Five dogs with <B-TauC had bilateral and symmetrical elliptical hyperreflective lesions in the area centralis, dorso-temporal to the optic disk (Figure 2A-C). Similar changes were seen in 1 dog with nB-TauC. Also, in 2 <B-TauC dogs, bilateral symmetric tapetal hyperreflectivity and mild to moderate vessel attenuation were observed. Additional abnormal ophthalmic findings observed in a population of dogs that all had nB-TauC included multifocal retinal dysplasia (3 dogs), focal, inactive postinflammatory chorioretinal scars (7 dogs), and an optic nerve coloboma (1 dog).

### 3.6 | Diets

Each dog's main diet was registered. The distribution of dietary protein sources is presented in Figure 3. A total of 173 dogs (96%) were fed a commercial complete dry food, and 7 dogs (4%) were fed commercially prepared raw food. All but 5 (97%) of the included dogs had access to treats, leftovers, or other animals' food in addition to their regular diet.

Sixty-eight different diets (60 dry foods and 8 raw foods) from 29 different food manufacturers were identified. Thirty diets contained red meat (lamb, beef, pork, reindeer, and venison) as protein source, 23 diets contained white meat (poultry and fish) as protein source, 3 diets contained a mix of red and white protein sources, and 4 diets contained other protein sources (soy, vegetables, and insects). Twenty-eight (41%) diets were categorized as grain-free, and 23 (34%) diets were categorized as "potatoes with or without pulses inclusive". Fifteen (54%) grain-free diets were categorized as potatoes with or without pulses inclusive.

Sixty dry food samples were analyzed for D-TauC, D-CysC, and D-MetC (g/100 g), and results are presented in Tables S1 and S2. The diet analyses were performed "as fed" and the results were converted into dry matter basis by using a presumed moisture content of 10%.[32] Forty-two dogs (79%) with <B-TauC consumed diets with D-TauC below median concentrations of the 60 analyzed diets, 9 <B-TauC dogs (17%) consumed diets above median concentrations of the 60 analyzed diets and 2 <B-TauC dogs (4%) consumed raw food. All <B-TauC:CHF+ dogs consumed diets with D-TauC below the median concentration of the

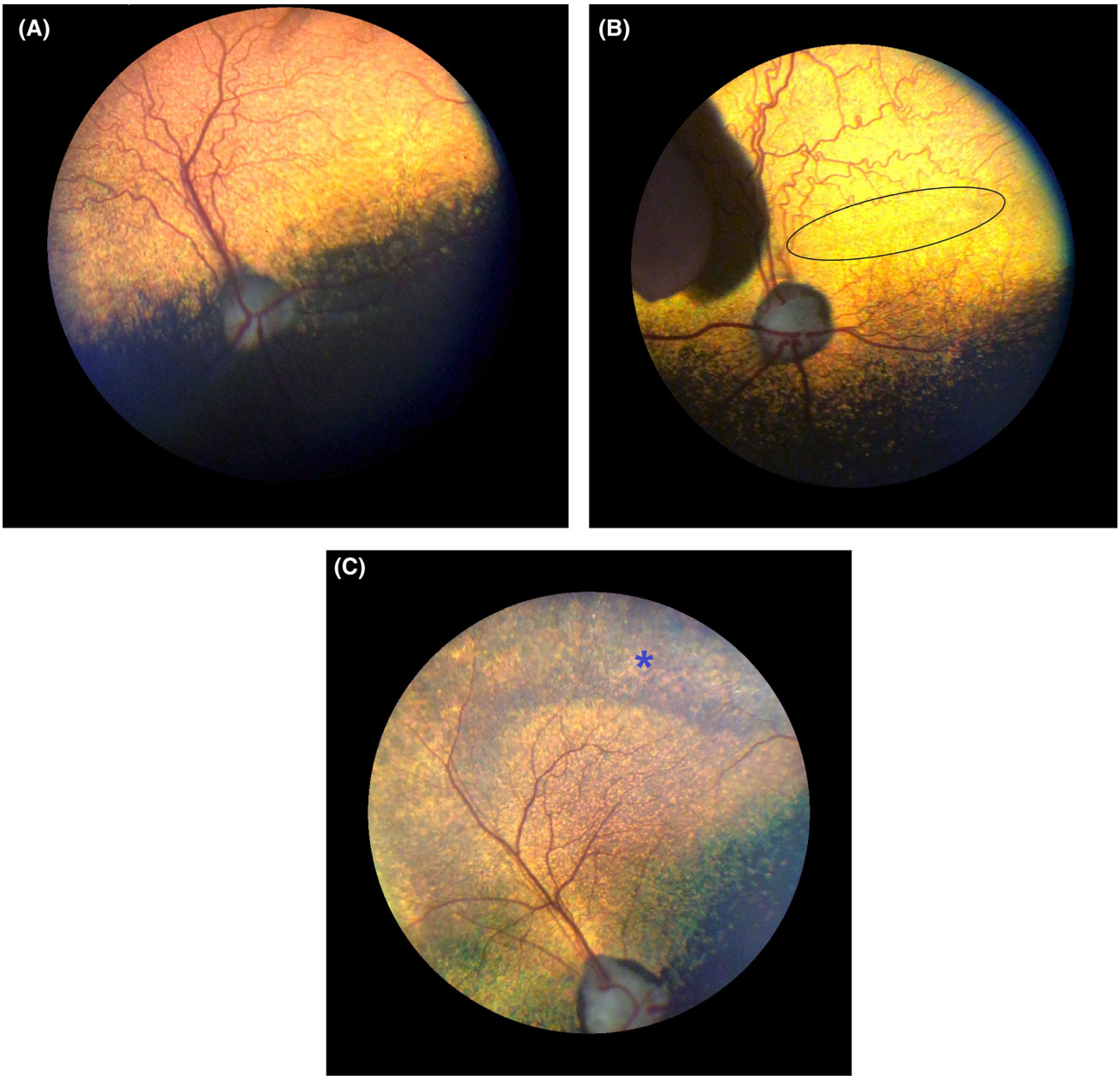


**FIGURE 2** (A) Fundoscopy of a dog with normal fundus. (B) Fundoscopy in a 5-year-old female English Cocker Spaniel with abnormal EDTA-plasma taurine concentration (<7.99 nmol/mL) showing retinal lesions similar to those reported in taurine-depleted cats, including an elliptical hyperreflective lesion in the area centralis and visual streak (encircled area). Lesions were bilaterally symmetrical. (C) Fundoscopy in an 8-year-old female English Cocker Spaniel with abnormal EDTA-plasma taurine concentration (<7.99 nmol/mL) showing retinal lesions including tapetal hyperreflectivity and vessel attenuation in the periphery (*). Lesions were bilaterally symmetrical. The dog was severely visually impaired.

60 analyzed diets. Five (8%) and 3 (5%) diets had D-MetC and D-MetC +D-CysC below or just meeting the recommended daily requirements stated by The American National Research Council.[33] Four diets with <D-MetC contained red meat as protein source, and 1 diet contained mixed protein (red and white meat) as protein source. All 3 diets with <D-MetC +D-CysC contained red meat as protein source. All diets with D-MetC and D-MetC+D-CysC below recommended daily requirements were associated with <BTauC and <D-TauC. The concentrations of the 3 amino acids in the food were covariate; D-MetC and D-TauC ($P < .001$), and D-MetC and D-CysC ($P = .02$).

### 3.7 | Univariable analyses

Diets with red meat as the animal protein source contained lower D-TauC ($P < .001$, $R^2_{adj} = .18$), D-CysC ($P < .001$, $R^2_{adj} = .07$), and D-MetC ($P < .001$, $R^2_{adj} = .1$) compared with diets with white meat as the animal protein source. EDTA-TauC were associated with D-TauC ($P < .001$, $R^2_{adj} = .2$), and D-MetC ($P < .001$, $R^2_{adj} = .23$). Diets with red meat as the animal protein source were associated with lower EDTA-TauC when compared with diets with white meat as the animal protein source ($P < .001$, $R^2_{adj} = .21$). Diets categorized as grain-free, and diets containing potatoes

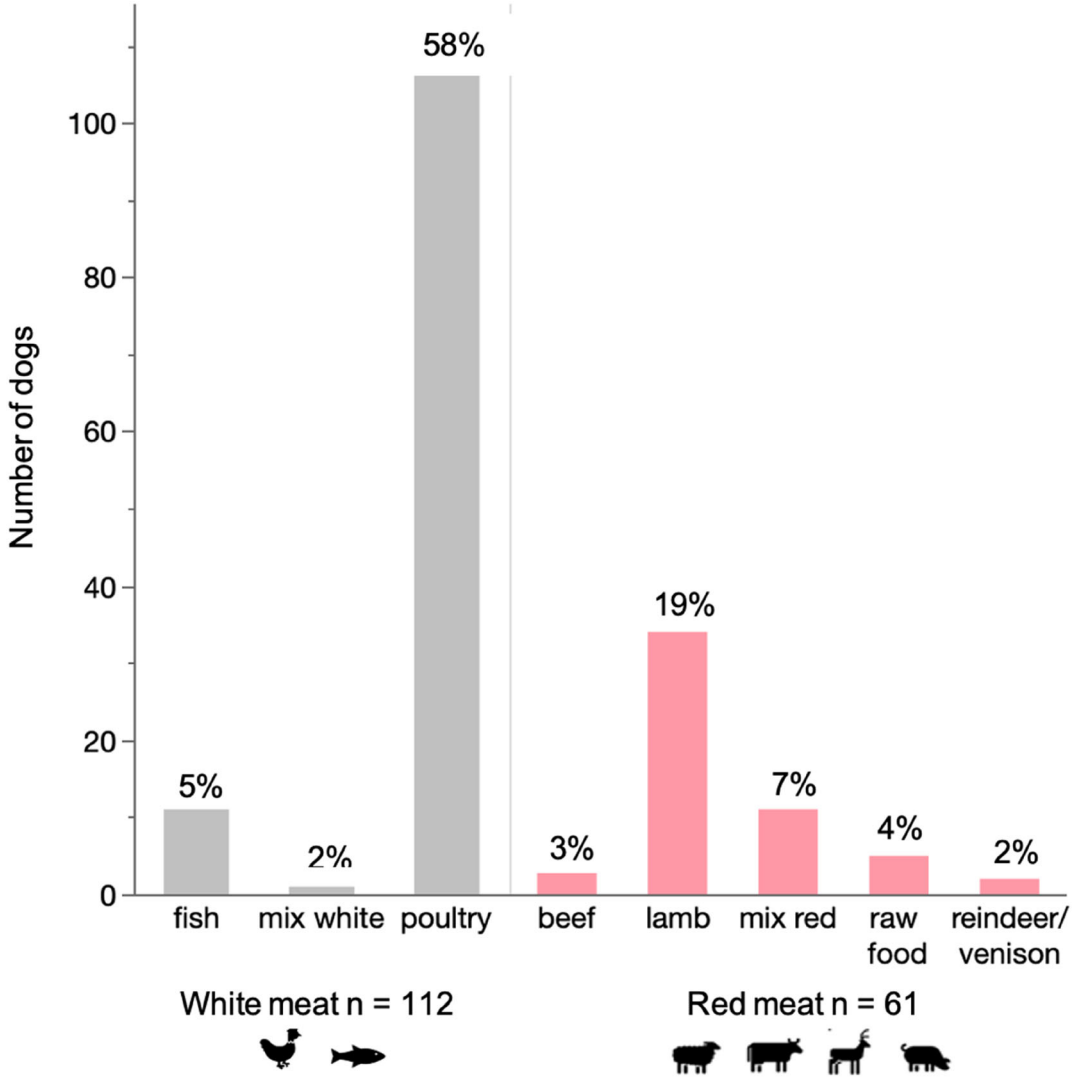


**FIGURE 3** Staple diagram demonstrating the distribution of protein sources in the various diets consumed by the included dogs. Diets with several different red or white meat components in the same diet were categorized as "mix red" and "mix white". Diets based on a mixture of red and white meat in the same diet, and diets based on soy, vegetables, and insects and were excluded in this analysis. Percentages indicate the proportion of the 173 dogs that consumed the different diets containing either red or white meat as protein source.

or pulses, or both, as 1 of the top 10 ingredients were associated with lower EDTA-TauC compared with grain-inclusive diets ($P = .05$, $R^2_{adj} = .02$). Diets containing potatoes or pulses, or both, as one of the top 10 ingredients were associated with lower EDTA-TauC compared with diets that did not contain potatoes or pulses, or both ($P = .01$, $R^2_{adj} = .03$). The association between EDTA-TauC and diets with red meat as the animal protein source remained, regardless of whether or not the diets were grain-free or included potatoes or pulses, or both. Additionally, B-TauC decreased with increasing age in the dogs included in the study ($P = .02$, $R^2_{adj} = .02$).

### 3.8 | Multivariable analyses

Dietary MetC, protein source: red or white meat, and age remained associated with EDTA-TauC in the final multivariable regression model ($P < .001$, $R^2_{adj} = .39$; Figure 4A-C).

## 4 | DISCUSSION

In our study, 29% of the included dogs had B-TauC below the normal reference range, and 21% had critically low concentrations. Of dogs with low B-TauC, 25% presented with signs of CHF and 9% with retinal abnormalities. Low D-MetC, and red meat-based diets were associated with <B-TauC, and dogs with <B-TauC were older than dogs with normal concentrations.

To the best of our knowledge, ours is the first prospective exploratory study investigating the occurrence of low B-TauC in a relatively large group of ECS, including both healthy dogs and dogs presenting with CHF. One-hundred eighty ECS were examined prospectively, and 25% of the 53 dogs presenting with B-TauC below the normal reference range had signs of increased LV dimensions, systolic dysfunction, and CHF. A similar occurrence was found in a previous study including 115 Irish wolfhounds, where 53% of the included dogs had

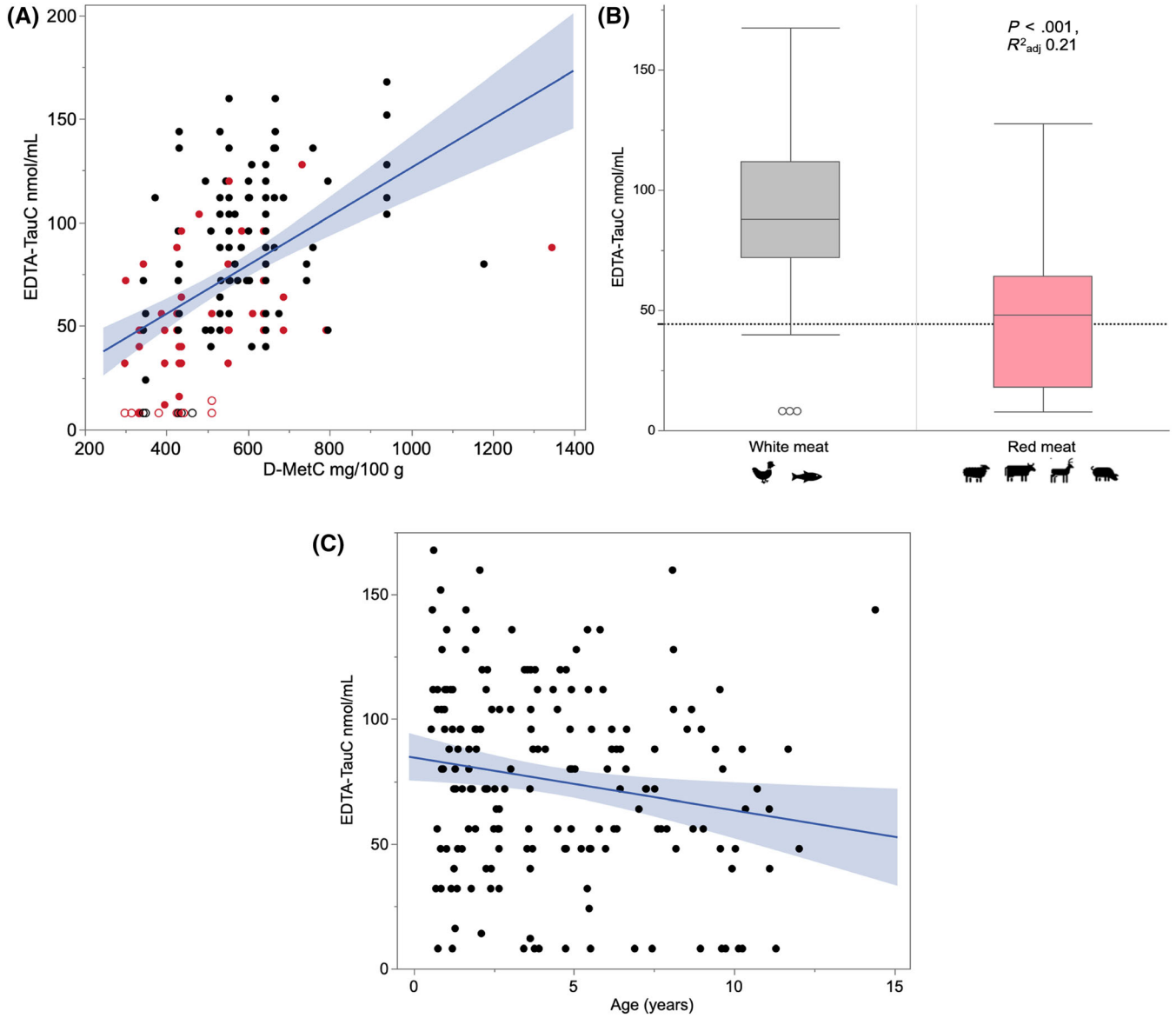


**FIGURE 4** (A) Scatterplots demonstrating EDTA-taurine concentrations by dietary methionine concentrations and regression line with shaded 95% confidence interval (CI) in 167 English Cocker Spaniels consuming dry diets. Red-filled small dots represent dogs consuming diets based on red meat and black-filled small dots represent dogs consuming diets based on white meat. Red and black circles represent dogs diagnosed with congestive heart failure and low taurine concentrations that had consumed diets based on red (red circles) and white (black circles) meat, respectively. Low dietary methionine concentrations were associated with low EDTA-taurine concentrations ($P < .001$, $R^2_{adj} = .23$). D-MetC: Dietary methionine concentrations, EDTA-TauC: EDTA-taurine concentrations. (B) Box and whiskers-plot demonstrating B-TauC in 173 dogs consuming diets based on protein sources categorized as red meat (lamb, beef, venison, and pork; n = 61) and protein sources categorized as white meat (fish, poultry; N = 112). Seven dogs consumed diets based on a mixture of red and white meat or diets based on soy, vegetables, and insects, and these dogs were excluded in this analysis. Taurine concentrations were significantly lower in dogs fed a diet based on red meat then dogs fed a diet based on white meat ($P < .001$, $R^2_{adj} = .21$). The horizontal line corresponds to the normal lower reference value for EDTA-plasma communicated by IDEXX laboratories, Germany. TauC: Taurine concentrations. (C) EDTA-taurine concentrations by age and regression line with shaded 95% confidence interval (CI) in 180 ECS. Taurine concentrations decreased with increasing age ($P < .02$, $R^2_{adj} = .02$).

WB-TauC below the normal reference range, and 41% of dogs with <WB-TauC were diagnosed with a DCM phenotype.[34] A comparable number of dogs with nB-TauC also were identified with a DCM phenotype in that study, resulting in no discernible differences between the 2 groups. Taurine concentrations, however, were only analyzed in WB in that study, which leaves the possibility that dogs with low plasma-TauC might have been missed. Possibly 2 different forms of CM may coexist in the same breed.

All <B-TauC:CHF+ dogs had EDTA-TauC <15 nmol/mL, whereas many of the <B-TauC:CHF− dogs, all with normal cardiac morphology on echocardiography, had mildly decreased EDTA-TauC. This finding may suggest that severe myocardial changes primarily appear in dogs

with depleted taurine reserves. However, EDTA-TauC <15 nmol/mL also were identified in 5 dogs with echocardiographically normal hearts, indicating that the response to low B-TauC varies among individual dogs. A similar pattern has been found in studies conducted on cats fed a taurine-depleted diet over an extended time period, where only 25% to 30% of the cats developed myocardial failure although both plasma and myocardial taurine concentrations were low in all cats.[4,35] The progression from having subthreshold B-TauC to developing deficiency and secondary disorders has yet to be investigated in dogs. Also, the time required to develop clinical signs in taurine-deficient dogs remains unknown. In our study population, <B-TauC:CHF+ dogs were older than nB-TauC dogs and <B-TauC:CHF− dogs, which might indicate that disease progression is age-dependent. However, a large age range (7 months–12 years) in dogs with CHF suggests that the impact of taurine deficiency varies considerably among individuals.

The association of low B-TauC with echocardiographic signs of LV systolic dysfunction and CHF in ECS in our study corresponds with the findings in a previous retrospective study where 81% of the 16 included ECS with a DCM phenotype and CHF had low B-TauC.[11] All 13 <B-TauC:CHF+ dogs in our study population had LV dimensions, volumes, EF, and EPSS compatible with a DCM phenotype. Fractional shortening, considered indicative of LV systolic function, however, was within or just below the reported normal reference ranges in 11 of the 13 dogs.[29,30] These findings suggest that increased LV inner diameters and volumes, decreased EF, and increased EPSS may be more prominent features of taurine-responsive CM in ECS.

Six dogs had ocular changes similar to those previously reported in cats with taurine deficiency and 5 of these dogs had B-TauC below the normal reference range.[36] Retinal degeneration and subsequent blindness is a well-documented secondary consequence of taurine deficiency in cats, and retinal changes have been reported to appear after approximately 6 to 9 months of depletion.[6,37,38] Although further progression of retinal degeneration is prevented with normalized B-TauC, the retinal lesions are not reversible and typical retinal lesions in an individual with nB-TauC may indicate previous taurine deficiency.[12,39] The dog in our study population displaying retinal changes but nB-TauC may, accordingly, have had a history of taurine deficiency, explaining the retinal abnormalities. Such a scenario, however, cannot be confirmed retrospectively. Retinal lesions also were found in 3 of the 11 American cocker spaniels with taurine-responsive CM investigated in a previous study of taurine deficiency in dogs.[8,35]

Heparinized plasma analyses identified more dogs with concentrations below specified reference values than EDTA-plasma analyses in our study population. On the other hand, EDTA-plasma analyses identified more dogs with plasma concentrations considered critically low (<40 nmol/mL) than heparinized plasma analyses. This discrepancy could, at least partly, be explained by the different cutoff values used by the analyzing laboratories (IDEXX EDTA-TauC <44 nmol/mL and UC Davis AAL Hep-TauC <60 nmol/mL) and emphasizes the importance of validated reference values for the method and additive used. Amino acid concentrations also have been shown to vary across analytic methods.[40] In addition, B-TauC has been observed to have significant daily intraindividual variation in both plasma and WB, further complicating the interpretation of results.[27,28]

Seventy-nine percent of the dogs with low B-TauC and all <TauC:CHF+ dogs consumed diets with D-TauC below the median value of the 60 diets analyzed. Furthermore, diets composed of red meats were associated with lower EDTA-TauC and lower D-TauC, D-CysC, and D-MetC compared with diets composed of white meats. The protein source is essential in a diet's amino acid content, and different protein sources contain different amounts of taurine. Shellfish, fish, and chicken generally contain more taurine than lamb, beef, and pork,[41-43] but D-TauC also differs depending on which part of the animal is used in the diet. Chicken legs contain, for example, almost twice as much taurine as chicken breast.[41,42] Plant-based proteins such as soy and vegetables do not naturally contain taurine, whereas insect-based protein may be comparable with animal protein sources if the most taurine-rich insect species are used.[34] There are no official recommendations for minimum taurine content in dog food, and it is currently unknown how preparation and heat processing may affect the taurine bioavailability of the end product, further complicating the assessment of adequate supplementation requirements.[42,44]

Although the association between red meat and low TauC was observed in both blood and diets, it cannot be concluded that the protein source alone provides insufficient taurine concentrations without knowing whether the various diets are taurine supplemented by the manufacturer. Disparities between diets with the highest and lowest D-TauC exceeded 500 mg/100 g (as fed) of feed in our study, corresponding to the daily dose of taurine supplementation (250 mg q12h) given to dogs with low B-TauC in our study population. Although it is not possible to state with certainty, it is likely that the discrepancy is not solely due to the choice of protein source, and that some food manufacturers supplement their diets whereas others do not. In addition, plant-based diets analyzed in our study all had D-TauC well above median concentrations. Neither the packaging ingredient lists nor the European manufacturers' websites provided any information regarding the taurine content in the diets, whether taurine was sourced from the original ingredients, or if the diets included supplementary taurine.

It is noteworthy that dietary TauC, CysC, and MetC were covariates and that dietary MetC was the variable that remained associated with EDTA-TauC in the multivariable regression analyses. Dietary methionine and cysteine serve as precursors for taurine synthesis, and inadequate amounts have been reported as a causative factor for taurine deficiency in dogs.[13] In addition to serving as rate-limiting factors for taurine synthesis in individuals with adequate enzymatic activity, methionine and cysteine also function as precursors for glutathione, thereby playing crucial roles in the body's antioxidant defenses.[45-47]

Established recommended daily requirement guidelines for methionine and cysteine in dog diets vary with different life stages, depend on digestibility or bioavailability, and have been observed to differ among various breeds.[33,48] In addition, methionine and cysteine are interdependent, meaning that the necessary amount of 1 may change depending on the level of the other.[49] In our study, 8% and 5% of the

analyzed diets failed to meet the established requirements for D-MetC and D-MetC+D-CysC, respectively. All of these diets were associated with dogs having <B-TauC. However, >90% of the diets associated with <B-TauC had D-MetC and D-MetC+D-CysC with recommended dietary requirements or allowances, as defined by the NRC.[32] This observation suggests that adequate intake of the precursors methionine and cysteine may not be sufficient for maintaining adequate taurine concentrations in some individuals. Differences in enzymatic activity, gastrointestinal absorption, or losses, and various metabolic processes also may affect bioavailability.

Dietary grain content was weakly associated with EDTA-TauC in univariable regression analyses ($P = .05$), but the association did not remain significant in the final multivariable regression model. This finding corresponds with a previous study in ECS, where dogs fed a lamb-based diet exhibited lower B-TauC, regardless of whether the diets contained grains.[50] Grain-free diets have been suggested as a potential cause of suspected cases of nutrition-associated DCM in dogs, regardless of confirmed taurine deficiency.[17] Nevertheless, this association is debated, because several subsequent studies have failed to establish a definitive connection between grain content in the diet and the development of CM or <B-TauC.[14,50,51]

More recently, diets rich in pulses (peas, lentils, beans, and chickpeas) or various forms of potatoes, or both, have been reported as a potential causative factor in diet-associated CM in dogs of various breeds, regardless of B-TauC.[16] A weak association between potato and pulse content and B-TauC also was seen in the univariable analyses in our study. The association, however, did not remain in the multivariable analyses.

## 5 | LIMITATIONS

Heparin-TauC and WB-TauC were not assessed in 7 and 5 dogs, respectively, presenting with CHF out of hours at the emergency clinic of 1 of the study hospitals. Nevertheless, EDTA concentrations in all of these dogs were consistently <7.99 nmol/mL, strongly indicating that both Hep-TauC and WB-TauC would likely fall well below normal reference ranges had they been analyzed.

All of the dogs in our study were privately owned and were fed diets based on the individual decisions of their owners. This factor resulted in a varied distribution of diets among the dogs. Nearly all dogs included in the study (97%) had routine access to treats and leftovers, which adds complexity when assessing the impact of diets on our research outcomes. However, the diets registered in the study represented the primary diet for each dog and accounted for a majority of their daily dietary intake, according to their owners.

## 6 | CONCLUSIONS

Twenty-nine percent of the included ECS had B-TauC below the normal reference range. Signs of CHF were seen in 25% of dogs with low B-TauC and retinal abnormalities in 9% of these dogs. EDTA-TauC was associated with dietary TauC, MetC, and protein source (red/-white meat). Additionally, dogs with B-TauC below the normal reference range were on average older than dogs with normal concentrations. Low B-TauC suggests that taurine deficiency may play a role in the development of CHF in ECS. As a result, measuring and supplementing taurine in ECS with DCM phenotype seems to be a prudent and relatively low-cost strategy.

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## CONFLICT OF INTEREST DECLARATION

Dr. Fascetti is the Scientific Director and Dr. Yu is the Technical Director of the Amino Acid Laboratory at the University of California, Davis (UCD) that provides amino acid analysis on a fee-for-service basis. Dr. Fascetti advised Synergy Food Ingredients, Clorox, and received a grant from Nutro and remuneration for lectures, or as an advisor on behalf of Nestlé Purina PetCare, Mars Petcare, and the Pet Food and Mark Morris Institutes. A nutrition resident received funds from the Hill's Pet Nutrition Resident Clinical Study Grants program; AJF collaborated on the resulting research project. The Veterinary Medical Teaching Hospital at University of California, Davis receives partial support for a Nutrition Technician from Nestlé Purina PetCare and its veterinary nutrition program from Nestlé Purina, Mars Petcare, and Hill's Pet Care.

## OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

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

Approved by the Ethical Committee for Animal Welfare in Stockholm, Sweden (5.8.18-01548/2017, 5.8.18-21508/2021, and 5.8.18-04682/2020).

## HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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