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Relationship of Body Size to Metabolic Markers and Left Ventricular Hypertrophy in Cats

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Background: Cats with hypertrophic cardiomyopathy (HCM) are larger and have higher insulin-like growth factor-1 (IGF-1) concentrations than cats without HCM.

Hypothesis/Objectives: The aim of this study was to assess echocardiographic findings in a colony of adult cats to determine the relationship between early growth and left ventricular hypertrophy (LVH).

Animals: Twenty-eight neutered adult cats (20 males, 8 females) from a colony ≥3 years of age for which growth curves were available.

Methods: Case–control study. Physical examination and echocardiography were performed, and body weight, body condition score (BCS), and head length and width were measured. Circulating glucose, insulin, N-terminal pro-B-type natriuretic peptide (NT-proBNP), and IGF-1 concentrations were measured and growth data were collected. Stepwise multivariate analyses were performed.

Results: Mean age was 5.2 ± 1.1 years. Current BCSs ranged from 4 to 9 (median, 6) and mean body weight was 4.88 ± 1.29 kg. Variation in body weight was apparent by 6 (mean = 3.26 ± 0.80 kg) and 12 months of age (mean = 4.02 ± 1.02 kg). Cardiac abnormalities included a cardiac murmur (n = 7; 24%), gallop (n = 3; 10%), and arrhythmia (n = 1; 4%). Fourteen of 28 cats (50%) had echocardiographic evidence of LVH. Head width (P = .017), body weight (P < .001), NT-proBNP (P = .023), and IGF-1 (P = .013–.022) were significantly associated with selected measures of LVH.

Conclusions and Clinical Importance: Potential associations between body size, IGF-1, LVH, and HCM warrant future prospective studies.

Key words: Cardiomyopathy; Feline; Growth; Insulin-like growth factor-1; Nutrition.

Hypertrophic cardiomyopathy (HCM) affects 9–15% of cats,[1,2] with an even higher prevalence in the Maine Coon cat.[3] Genetic mutations have been identified in approximately half of the human patients with HCM, but the phenotypic expression of HCM is highly variable in both people and cats and might be related to an interaction between nutrition and genetic risk (ie, nutrient-gene interactions). In this model, the phenotypic expression in people or cats with a genetic risk for HCM might vary depending on nutrition in utero and during early growth. Nutrition during early life might alter the propensity to develop more or less severe phenotypic expression of disease by altering the growth hormone/insulin-like growth factor-1 (IGF-1) axis or insulin resistance. Growth hormone and IGF-1 are primary determinants of the ventricular growth response through regulation of both overall body growth and myocyte protein synthesis. IGF-1 overproduction increases myocardial protein synthesis and causes left ventricular hypertrophy (LVH).[4–6] In addition to hemodynamic and hormonal factors, IGF-1 also is regulated by nutrients (eg, protein, certain amino acids).[4,7,8] People with HCM have elevated myocardial and circulating IGF-1 concentrations.[9,10] In addition, people with heart failure and HCM have insulin resistance which can be the result of the heart reverting to fetal metabolic pathways[11,12] or to alterations in glucose transporters.[13]

Alterations in early nutrition of sheep can result in fetal LVH, increased myocardial IGF-1, insulin resistance, and upregulation of myocardial alpha-cardiac actin, caveolin-1, and titin.[14–16] In cats, supporting studies are more limited. Results from 1 study showed elevated growth hormone concentrations in cats with

Abbreviations:

2D	2-dimensional
A	late diastolic velocity of mitral inflow
A′	late diastolic myocardial velocity
BCS	body condition score
CHF	congestive heart failure
DCM	dilated cardiomyopathy
E	early diastolic velocity of mitral inflow
E′	early peak diastolic myocardial velocity
EPA	eicosapentaenoic acid
HCM	hypertrophic cardiomyopathy
HOMA	homeostasis model assessment
hs-troponin I	high-sensitivity cardiac troponin I
IVSd/s	interventricular septal thickness in diastole/systole
LA : Ao	left atrial to aortic root ratio
LVH	left ventricular hypertrophy
LVIDd/s	left ventricular internal dimension in diastole/systole
LVWd/s	left ventricular free wall thickness in diastole/systole
MR	mitral regurgitation
NT-proBNP	N-terminal pro B-type natriuretic peptide

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HCM,[17] but interpretation is difficult since growth hormone concentrations fluctuate dramatically throughout the day. Cats with HCM are skeletally larger and have higher glucose concentrations than cats without HCM, but IGF-1 concentrations were not different between the groups.[18] Adult Maine Coon cats with HCM are skeletally larger and more obese as adults, and are significantly larger at 6 months and 12 months of age compared to Maine Coon cats without HCM.[19] These growth data, however, were obtained retrospectively. In addition, the Maine Coon cats with HCM had significantly higher IGF-1 concentrations than cats without HCM.[19]

To better understand the relationship between early growth and the development of HCM in later life, the objective of this study was to assess adult cats to determine whether echocardiographic findings of LVH and HCM are related to early growth patterns. We hypothesize that cats with faster early growth will have increased risk for the development of HCM in later life.

Materials and Methods

All cats in the Royal Canin colony (Aimargues, France) ≥3 years of age for which growth curves during the first year of life (beginning by at least 6 months of age) were available were eligible for the study. Both males and females were included. All cats meeting study eligibility criteria underwent echocardiography (2D, M-mode, and color flow Doppler echocardiography)[a] performed by a single board-certified veterinary cardiologist (JER). Standardized measurements of left ventricular chamber and wall thickness were obtained from a 2D guided M-mode echocardiogram in a right parasternal short-axis view at the level of the chordae tendinae using the leading-edge to leading-edge method.[20] Left ventricular wall (LVW), interventricular septum (IVS), and left ventricular chamber (LVID) were measured in systole and diastole from 2D images in a right parasternal short-axis view obtained at the midcavity level with similar positioning to the M-mode images. In addition, maximum diastolic left ventricular wall and interventricular septal thickness were evaluated from 2D short-axis and long-axis views, and if the diastolic wall thickness exceeded the 2D IVSd or LVWd as measured above, then this value was recorded as the maximum IVSd or LVWd. Cats were diagnosed with HCM if they had an M-mode or 2D IVSd or LVWd > 0.6 cm and concurrent findings indicative of HCM (ie, some combination of diffuse or focal concentric hypertrophy of the left ventricle, systolic anterior motion of the mitral valve, left atrial enlargement, or dynamic left ventricular outflow tract obstruction). Cats were categorized as having LVH if the M-mode or 2D IVSd or LVWd was greater than 0.6 cm.

Systolic blood pressure was measured on each cat (Doppler technique),[b] and all cats >6 years had T4 concentrations measured. Body weight, body condition score (BCS) (using a 9-point scale),[21] muscle condition score,[22] and head length and width[18] were measured. BCSs and muscle condition scores were assigned for all cats by a single investigator (LMF). All available body weight data during growth were collected for each cat although the time points varied among cats.

Blood was collected by venipuncture after food restriction for 12–18 hours. Blood was collected into EDTA tubes and was centrifuged and frozen at −20°C until analysis. For NT pro-B-type natriuretic peptide (NT-proBNP), the plasma was first placed into protease inhibitor tubes,[c] and then frozen at −20°C until analysis. Analysis for insulin,[d] glucose,[e] and insulin-like growth factor-1 (IGF-1)[f] were performed at a commercial laboratory in France,[g] while samples for NT-proBNP were analyzed by a commercial laboratory in the United States.[h] The homeostasis model assessment (HOMA), a calculation that has been used as an estimate of insulin sensitivity in cats, was calculated using the formula: HOMA = (insulin × glucose)/22.5].[23]

Data are presented as mean ± SD if they were normally distributed or median (range) if skewed. Multivariate analyses were performed to determine risk factors for selected measures of LVH. First, a stepwise logistic regression (LOGISTIC procedure) was performed to assess the effects of fixed effects variables (age, sex, head width, head length, current body weight, body weight at 6 months, body weight at 12 months, breed, BCS, glucose, insulin, HOMA, IGF-1, and NT-proBNP) on LVH as the binary outcome. Hosmer and Lemeshow Goodness-of-Fit tests were used to assess the quality of this model. Second, four additional stepwise linear regression analyses (REG procedure) were performed to assess the impact of the same fixed effects from the previous model on each of 4 quantitative echocardiographic variables: M-mode IVSd, M-mode LVWd, 2D maximum IVSd, and 2D maximum LVWd. Goodness-of-fit tests for normal distribution of residuals of each multivariable model and normality of raw data were performed with Kolmogorov-Smirnov, Cramer-Von Mises and Anderson-Darling tests. $P < .05$ was considered statistically significant. Stepwise regressions were set in such a way that each forward selection step could be followed by a backward elimination step if necessary. The cut off value (P value) used to enter and remove a variable was set at 10% for each step of the stepwise regressions. Commercial statistical software[i] was used for all analyses. $P < .05$ was considered statistically significant.

Results

Thirty cats met the eligibility criteria for the study. However, one cat had signs of respiratory infection on physical examination and another cat had echocardiographic changes consistent with dilated cardiomyopathy so these 2 cats were excluded from further analyses. Therefore, all subsequent data will be reported for the 28 cats completing the study.

For these 28 cats (20 male, 8 female; all neutered), mean age (±SD) at the time of the evaluation was 5.2 ± 1.1 years. Breeds included domestic short- and longhairs (n = 11), Birman (n = 5), Somali (n = 4), Maine coon (n = 4), Siamese (n = 2), and 1 each of exotic shorthair and Sphinx. Six cats were >6 years of age and T4 concentrations were within reference ranges for all 6 of these cats. Mean heart rate was 169 ± 17 per minute and systolic blood pressure was 156 ± 12 mmHg; no cats had a systolic blood pressure >180 mmHg.

Seven of the 28 cats (25%) had a cardiac murmur on auscultation (I/VI: n = 4; II/VI: n = 3). Three cats had a cardiac gallop and 1 cat had occasional premature beats on auscultation. Fourteen of the 28 cats (50%) were categorized as having LVH (ie, M-mode or 2D IVSd or LVWd > 0.6 cm; Table 1). Trace mitral regurgitation (n = 1), trace tricuspid regurgitation (n = 2), and mild tricuspid regurgitation (n = 3) were noted on echocardiography, but no cats had systolic

Table 1. Echocardiographic findings for 28 healthy colony cats. Data are presented as mean ± SD.

Variable	All Cats (n = 28)	Cats With LVH (n = 14)	Cats Without LVH (n = 14)
M-Mode (in cm)			
Interventricular septum (diastole)	0.52 ± 0.07	0.55 ± 0.06	0.48 ± 0.06
Left ventricular internal dimension (diastole)	1.47 ± 0.18	1.48 ± 0.20	1.47 ± 0.16
Left ventricular free wall (diastole)	0.55 ± 0.08	0.59 ± 0.07	0.50 ± 0.06
Interventricular septum (systole)	0.80 ± 0.10	0.80 ± 0.11	0.80 ± 0.08
Left ventricular internal dimension (systole)	0.67 ± 0.19	0.70 ± 0.20	0.64 ± 0.17
Left ventricular free wall (systole)	0.87 ± 0.09	0.90 ± 0.10	0.83 ± 0.07
Left atrium	1.33 ± 0.19	1.41 ± 0.20	1.25 ± 0.14
Aorta	1.07 ± 0.13	1.15 ± 0.12	0.99 ± 0.10
Left atrium : Aorta	1.24 ± 0.12	1.22 ± 0.13	1.26 ± 0.10
2D (in cm)			
Interventricular septum (diastole)	0.48 ± 0.08	0.52 ± 0.07	0.45 ± 0.07
Left ventricular internal dimension (diastole)	1.44 ± 0.21	1.45 ± 0.19	1.42 ± 0.24
Left ventricular free wall (diastole)	0.51 ± 0.09	0.55 ± 0.10	0.48 ± 0.06
Maximum interventricular septum (diastole)	0.55 ± 0.07	0.60 ± 0.05	0.51 ± 0.06
Maximum left ventricular free wall (diastole)	0.55 ± 0.08	0.60 ± 0.07	0.50 ± 0.05
Interventricular septum (systole)	0.64 ± 0.11	0.70 ± 0.08	0.58 ± 0.11
Left ventricular internal dimension (systole)	0.81 ± 0.18	0.81 ± 0.18	0.80 ± 0.20
Left ventricular free wall (systole)	0.68 ± 0.11	0.72 ± 0.11	0.64 ± 0.10
Left atrium	1.31 ± 0.19	1.39 ± 0.21	1.23 ± 0.13
Aorta	0.95 ± 0.13	1.01 ± 0.14	0.89 ± 0.09
Left atrium : Aorta 2D	1.39 ± 0.18	1.37 ± 0.15	1.40 ± 0.21
Doppler			
Aortic velocity (m/s)	1.02 ± 0.16	1.03 ± 0.14	1.02 ± 0.18
Pulmonic velocity (m/s)	0.93 ± 0.14	0.91 ± 0.17	0.95 ± 0.11
Early diastolic velocity of mitral inflow (E; m/s)	0.65 ± 0.15	0.66 ± 0.15	0.63 ± 0.15
Late diastolic velocity of mitral inflow (A; m/s)	0.45 ± 0.12	0.46 ± 0.11	0.45 ± 0.13
$E : A$	1.52 ± 0.58	1.49 ± 0.36	1.56 ± 0.76
Early peak diastolic myocardial velocity[a] (E'; m/s)	0.11 ± 0.03	0.14 ± 0.05	0.14 ± 0.04
Late peak diastolic myocardial velocity[a] (A'; m/s)	0.14 ± 0.04	0.11 ± 0.03	0.12 ± 0.03
E/E'	4.94 ± 1.61	5.07 ± 2.05	4.79 ± 1.03

[a]Measured at the left ventricular free wall.

anterior motion of the mitral valve or dynamic left ventricular outflow tract obstruction.

Mean body weight was 4.88 ± 1.29 kg (range, 2.70–7.22 kg) and median BCS was 6 (range, 4–9; Table 2). BCS was not ideal (ie, >5) in 16 of the 28 cats (57%). All cats had normal muscle condition scores. While some cats had body weight recorded as early as 3 months of age, the first time point at which all 28 cats had body weight recorded was 6 months of age. Variation among the cats in body weight was apparent by 6 months of age (3.26 ± 0.80 kg [range, 2.18–4.49 kg]; Table 2) and, even more so, by 1 year of age (4.0 ± 1.0 kg [range, 2.23–5.56 kg]). Median percent change in body weight between 6 and 12 months of age was +23% (range, 0 to +39%).

Results of the laboratory variables are shown in Table 3. Three of the 28 cats had an NT-proBNP concentrations >100 pmol/L[24]: Two of these cats had LVH (NT-proBNP concentrations of 148 and 162 pmol/L) but the other cat (NT-proBNP concentration of 105 pmol/L) did not have LVH. Other causes for elevated NT-proBNP (eg, hypertension, recent anesthesia) could not be identified in this cat.

There were no violations of goodness-of-fit in the models. On logistic multivariate analysis, head width (P = .017) was significantly associated with LVH

Table 2. Body weight and morphometric results for 28 healthy colony cats. Data are presented as mean ± SD or median (range, for body condition score).

Variable	All Cats	Cats With LVH	Cats Without LVH
Body weight (at time of study; kg)	4.88 ± 1.29	5.49 ± 1.45	4.26 ± 0.76
Body weight (6 months of age; kg)	3.26 ± 0.80	3.61 ± 0.80	2.85 ± 0.61
Body weight (12 months of age; kg)	4.02 ± 1.02	4.42 ± 1.07	3.60 ± 0.81
Body weight (18 months of age; kg)	4.24 ± 1.15	4.76 ± 1.26	3.73 ± 0.76
Body condition score (1–9)	6 (4–9)	6 (4–9)	6 (5–7)
Head width (cm)	7.58 ± 0.54	7.91 ± 0.53	7.25 ± 0.29
Head length (cm)	10.95 ± 1.25	11.46 ± 1.32	10.44 ± 0.96

Table 3. Laboratory results for 28 healthy colony cats. Data are presented as median (range).

Variable	All Cats	Cats With LVH	Cats Without LVH	Reference Range
N-terminal pro B-type natriuretic peptide (pmol/L)	40 (<24 to 162)	44 (<24 to 162)	26 (<24 to 105)	<100
Insulin-like growth factor-1 (μg/L)	482 (181–838)	536 (329–838)	412 (181–689)	<350
Glucose (mg/dL)	85 (70–100)	80 (70–90)	90 (80–100)	60–110
Insulin (μU/L)	7 (3–22)	8 (4–16)	6 (3–22)	10–40
Homeostasis Model Assessment[23]	0.25 (0.13–0.88)	0.28 (0.14–0.64)	0.23 (0.13–0.88)	0.00–2.84

Table 4. Results of stepwise multivariable analyses for the impact of independent variables on selected measures of LVH in 28 cats.

	P-value and Regression Coefficient [95% Confident Interval] of the Significant Independent Variables on the Related Output				
		2D		M-mode	
Independent Variables of Multivariable Models[a]	LVH	Maximum IVSd	Maximum LVWd	IVSd	LVWd
Head width	0.017 4.189 [0.8659; 7.5134]	[b]	[b]	[b]	[c]
Current body weight	[b]	[b]	<0.001 0.04125 [0.02364; 0.05887]	[b]	[b]
Body condition score	[b]	[c]	[b]	[b]	[b]
NT-proBNP	[b]	[b]	[c]	0.023 0.00082 [0.00013; 0.00152]	[b]
IGF-1	[b]	0.013 0.0002 [0.00004; 0.00035]	[b]	[c]	0.022 0.00019 [0.00003; 0.00035]

LVH, left ventricular hypertrophy; 2D, 2-dimensional,; IGF-1, insulin-like growth factor-1; IVSd, interventricular septal thickness in diastole; LVH, left ventricular hypertrophy; LVWd, left ventricular free wall in diastole; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

[a]Other variables were tested but removed in stepwise regressions (ie, age, sex, breed, head length, weight at 6 months, weight at 1 year, glucose, insulin, and Homeostasis Model Assessment).

[b]$P > .10$.

[c]$.05 < P < .10$.

(Table 4). The odds of having LVH was greater for cats with a larger head width (0.5 unit of increase, OR = 8.12 [95% CI, 1.54, 42.80]). On linear multivariate analysis, body weight (+2 units of change in body weight results in +0.08 units of change in maximum LVDd; $P < .001$), NT-proBNP (+50 units of change in NT-proBNP results in +0.04 units of change in IVSd; $P = .023$), and IGF-1 (+500 units of change in IGF-1 results in +0.10 unit of change in maximum IVSd [$P = .013$] and +0.10 units of change in LVWd [$P = .022$]) were significantly associated with selected measures of LVH (Table 4). Coefficients (and 95% CI) from logistic and linear regression analyses for the selected measures of LVH are presented in Table 4. Breed, sex, age, weight at 6 and 12 months, change in weight between 6 and 12 months, current BCS, glucose, insulin, and HOMA were not significantly associated with selected measures of LVH on multivariate analysis.

Discussion

The head size and body weight results of this study are similar to those from previous research[18,19] which showed that cats with HCM were bigger than cats without HCM. In the current study, no cats were identified with overt HCM although 50% of cats had LVH. It is unclear whether LVH could be a precursor to HCM; this potential association would require further research. However, the consistent results between this and other studies regarding body weight and head size support a potential relationship between body size and HCM.

Results of multivariate analysis also showed that IGF-1 concentrations were significantly associated with selected measures of LVH in this study, similar to a previous study of Maine Coon cats in which IGF-1 concentrations were higher in cats with HCM.[19] This might be related to the study's other finding of larger body size, since growth hormone and IGF-1 are important regulators of growth, body size, and LVH.[4–8] People with HCM also have been shown to have elevated myocardial and circulating IGF-1 concentrations.[9,10] It would be ideal to measure IGF-1 concentrations during growth in cats to determine whether elevations in IGF-1 also are present at an earlier stage and might play a primary role in the pathogenesis of HCM.

In this study, early body weight was not significantly associated with any measures of LVH on multivariate analysis, an association that was seen in a retrospective study of Maine Coon cats.[19] This lack of association might be related to a small sample size, variable breeds, or might indicate that nutrition and growth at an earlier age (ie, less than 6 months or even in utero) or nutrition throughout a cat's life plays a more important role.

Results of this study did not show an association between BCS and the presence of LVH. This might be related to a small sample size since one previous study (n = 63) showed that Maine Coon cats with HCM had a higher BCS than Maine Coon cats without HCM.[19] However, an earlier study (in 47 cats that were not Maine Coon cats) did not find a relationship between obesity and HCM.[18] The variable results for BCS in the current and previous studies make it unclear whether the association seen between body weight and HCM is related more to skeletal size, to obesity, or an interaction between the two. Although BCS at the time of examination was not related to measures of LVH, BCSs were not available during the growth period, and the presence of obesity during the growth phase might still play a role in modifying risk of LVH. Alternatively, the differences between studies might be breed related. Four of 28 cats in the current study were Maine Coon cats, while the 2 previous studies included either 0[18] or 100%[19] Maine Coon cats.

There was wide variation in cats' body weights at 6 and 12 months, as well as in growth rate. Some of the variability in body weights might be related to breed differences since this study included cats of 7 different breeds. For example, it would be expected that a Maine Coon cat would weigh more than a Persian. However, this variability also might be related to differences in growth rate or the degree of obesity. One study[25] of 5 different cat breeds (Birman, Maine Coon, Norwegian Forest, Persian, and Siamese) from birth to 3 months showed variation within each breed that was similar to that found in the current study. While there are some benefits of evaluating multiple breeds since nutrient-gene interactions might vary among different breeds, this also introduces more variability into body weights, head size, and echocardiographic measurements.[26] For echocardiography, larger cats might be expected to have larger hearts, and that the cutoff of 0.6 cm for defining hypertrophy might not be appropriate for cats of all sizes. However, the current study's findings that NT-proBNP concentrations also were significantly associated with selected measures of LVH on multivariate analysis and that breed was not associated with selected measures of LVH supports a relationship between size and true LVH. Having a single cardiologist perform all the echocardiograms excluded interobserver variability for echocardiographic measurements, but additional research is needed to identify whether there are nutrient-gene interactions in cats with HCM as a species or within individual breeds.

There are additional limitations to this study. While some cats had body weights available as early as 3 months of age, the first time point at which all cats had a body weight available was 6 months. It will be important to understand the time course of body weight changes in young cats and how this might relate to development of LVH, since results of one study suggest that growth rates and body weights are variable, even within a single breed, at an early age.[25] In people, low birth weight in children, when followed by fast growth, increases risk for later development of heart disease.[27–29] In a study of Maine Coon cats,[19] cats with HCM came from smaller litters which might suggest larger birth weight, but birth weight was not available in that study. Except at the time of the examination for the current study, BCSs were not available at the same times the body weights were obtained so, it cannot be determined whether cats' early weights represented ideal weight or if they had been overweight. The latter is likely true for at least some of the cats and for some of the time points at which weight was measured since at the time of the study, 57% of cats were above ideal body condition. The role of obesity in HCM is unclear but a recent study in 275 adult people with HCM,[30] left ventricular mass was higher in overweight and obese patients and obesity was an independent predictor of progression to New York Heart Association Class III or IV. While this relationship was attributed by the authors to being a secondary effect of HCM (ie, because people with HCM are less likely to be physically active, they are more likely to become obese), the obesity might have played a more primary role by contributing to a worse phenotypic expression of the disease and thus hastening disease progression.

Related to the issue of body size, another limitation of this study is that only one measure of skeletal size was assessed (ie, head size, as assessed by head length and width). Head size is likely to be partially related to overall body size but also can be affected by breed and sex. Nonetheless, head width, and not breed or sex, was related to LVH on multivariate analysis. Two previous studies of cats included head size (length and width), humerus length, and vertebral length.[18,19] In a study that excluded Maine Coon cats,[18] vertebral length, head length and width, and humerus length were all significantly longer in cats with HCM compared to cats without HCM. However, in a study of Maine Coon cats,[19] only humerus length was significantly longer in cats with HCM. This might be because of sample size or to studying a single breed (Maine Coon cats, which tend to be larger than average cats) compared to specifically excluding Maine Coon cats. In the current study, only head length and width were measured because it was not logistically feasible to perform radiography to obtain accurate vertebral and humerus length. However, including measures of skeletal size in future studies in addition to head size would be useful.

Sample size was small and limited the statistical power of the analysis. Finally, the mean age of cats in the current study was 5.2 years, with the oldest cat

only 6.8 years. Although this mean age is similar to that found in previous studies of HCM,[31–33] it is not possible to know if any of the cats in the current cross-sectional study would remain free of HCM later in life and if any of the cats with echocardiographic measurements of LVH would progress to develop overt HCM or clinical signs. Longitudinal studies are needed to determine the relationship between early growth and the development of HCM over the course of cats' lifetimes.

Footnotes

[a] SonoScape S8 portable digital color Doppler ultrasound system, Rome, Italy
[b] Mano Médical Vet BP Doppler, Warsaw, Poland
[c] NT-proBNP collection tube, IDEXX Laboratories, Westbrook, ME
[d] Porcine Insulin, Millipore, Billerica, MA
[e] Glucose (GOD-PAP), Randox, Crumlin, UK
[f] IGF-1 RIA CT, Mediagnost, Reutlingen, Germany
[g] LDHVet, Oniris Site de La Chantrerie, Atlanpole, Nantes, France
[h] Feline CardioPet NT-proBNP, IDEXX Laboratories, Westbrook, ME
[i] SAS 9.3 software, SAS Institute Inc, Cary, NC

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Conflict of Interest Declaration: Dr Freeman reports grants from Boehringer Ingelheim, grants and personal fees from Nestlé Purina PetCare, personal fees from The Nutro Company, personal fees from P&G Petcare, and grants and personal fees from Royal Canin outside the submitted work. Dr Rush reports grants and personal fees from Boehringer Ingelheim, grants and personal fees from IDEXX Laboratories, grants and personal fees from Nestlé Purina PetCare, and grants and personal fees from Royal Canin outside the submitted work. Drs Feugier and van Hoek are employed by Royal Canin SAS.

Off-label Antimicrobial Declaration: The authors declare no off-label use of antimicrobials.

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