Cardiomyopathy prevalence in 780 apparently healthy cats in rehoming centers (the CatScan study)

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Short title for use as a running head.

"Cardiomyopathy prevalence in healthy cats"

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Conflict of Interest

The authors have no conflict of interest to declare with regard to this study.

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Abstract

Objectives

Hypertrophic cardiomyopathy (HCM) appears to be common in cats and, based on pilot data, a prevalence of 15% was hypothesized. The objectives were to screen a large population of apparently healthy adult cats for cardiac disease, and identify factors associated with a diagnosis of HCM.

Animals

1,007 apparently healthy cats ≥6 months of age

Methods

Prospective cross-sectional study. Excluding known hypertensive or hyperthyroid cats, apparently healthy cats ≥6 months of age available for rehoming over a 17 month period were considered eligible at 2 rehoming centers. Body weight, body condition score, auscultation, systolic blood pressure and two-dimensional (2D) echocardiography were evaluated. Cats with left ventricular end-diastolic wall thickness ≥6mm on 2D echocardiography were considered affected with HCM.

Results

Complete data were obtained in 780 cats. Heart murmur prevalence was 40.8% (95% confidence interval (CI) 37.3-44.3%), 70.4% of which were considered functional. The prevalence of HCM was 14.7% (95% CI 12.3-17.4%), congenital disease 0.5% (95% CI 0.1-1.3%), and other cardiomyopathies 0.1% (95 % CI 0.0-0.7%). HCM prevalence increased with age. The positive predictive value of a heart murmur for indicating HCM was 17.9-42.6% (higher in old cats), and the negative predictive value 90.2-100%, (higher in young cats). The factors associated with a diagnosis of HCM in binary logistic regression models were male sex, increased age, increased body condition score and a heart murmur (particularly grade III/VI or louder).

Conclusions

HCM is common in apparently healthy cats, in contrast with other cardiomyopathies. Heart murmurs are also common, and are often functional.

Abbreviations.

2D – Two dimensional

BCS – Body condition score

CVs – Coefficients of variation

HCM – Hypertrophic cardiomyopathy

IQR – Interquartile range

IVSd – end-diastolic interventricular septum thickness

LA:Ao – ratio of diastolic LA diameter to aortic root diameter measured on the last frame prior to aortic valve opening

LAD – diameter of the left atrium measured parallel with the mitral annulus in the last frame before mitral valve opening on a right parasternal long-axis 4-chamber view

LV – Left ventricular

LVFWd – end-diastolic left ventricular free wall thickness

LVH – Left ventricular hypertrophy

LVWd – end-diastolic left ventricular wall thickness

NPV – Negative predictive value

PPV – Positive predictive value

RVC – Royal Veterinary College

SAM – Systolic anterior motion

SBP – Systolic blood pressure

SD – Standard deviation

UCM – Unclassified cardiomyopathy

Cardiomyopathies are an important group of diseases in both people and cats, with hypertrophic cardiomyopathy (HCM) being the most commonly diagnosed cardiomyopathy in both species.[1, 2] The prevalence of HCM in people has been estimated at approximately 0.2% of young healthy adults.[3, 4] The prevalence of HCM in cats is not known with certainty, but two recent studies suggested prevalence is higher than in humans (14-16%),[5, 6] although the sample size was less than 200 cats in both studies, and neither study selected subjects at random.

Echocardiography remains the principal test for diagnosing HCM in both people[7, 8] and cats.[9] In people, an HCM phenotype is most often defined by a maximum end-diastolic LV wall thickness (LVWd) that exceeds an arbitrary cut-off value.[11] In cats, LVWd ≥6 mm is most commonly cited to define HCM, either as the maximum measurement in any region[10-14] or measured in >50% of a segment.[5, 9] As with people,[11] there is a gray zone of uncertainty, which in cats may be between LVWd 5.5 mm and 6.0 mm.[6] One group of investigators have suggested that normal LVWd in cats should be <5.0 mm, using outlier analysis.[15] Left ventricular concentric hypertrophy in cats is usually assumed to be HCM, providing hyperthyroidism[16, 17] and hypertension[18] have been excluded. Other less common conditions that may be associated with increased LV wall thickness in cats include acromegaly,[19] multicentric lymphoma[20] and congenital aortic stenosis.[21]

Heart murmurs are known to be common in cats, with a prevalence reported in apparently healthy cats of between 15.5% and 33.7%, many of which are functional heart murmurs.[5, 6, 22] In general, the specificity of a heart murmur for indicating cardiomyopathy in cats has been reported to be higher (70.5 - 87%) than the sensitivity (31 – 61.3%, depending on heart murmur intensity).[5, 6] Dynamic right ventricular outflow obstruction has been reported to be one of the functional causes of a systolic heart murmur in cats[23] both with and without structural abnormalities.[5] Nevertheless, up to 22% of referred HCM cases have no heart murmur, gallop sound or arrhythmia at diagnosis, often being diagnosed as a result of clinical signs resulting from congestive heart failure, aortic thromboembolism or syncope.[24, 25] Apparently healthy cats without a heart murmur may also be diagnosed with HCM via screening.[5, 6] Disease penetrance of HCM has been shown to increase with age in people,[26] and although cats of any age can be diagnosed with HCM, it is often initially diagnosed in young to middle-aged cats.[2, 9, 24, 25] So far, the effect of age on HCM prevalence in cats has not been evaluated. Males are generally over-represented in human[27] and feline[2, 24, 25, 28] HCM populations, despite the fact that genetic mutations that cause HCM in people and in Maine Coon and Ragdoll cats are evenly distributed between males and females.

Based on our previous work and the work of others,[5, 6, 22] we hypothesized that in a population of apparently healthy cats, the prevalence of cats with a heart murmur would be around 33% and the prevalence of cats with HCM would be around 15% using the most commonly used LVWd cut-off of ≥6.0 mm. We hypothesized that older age, male sex and the presence of a heart murmur would be associated with an increased likelihood of diagnosing HCM.

The main aims of this study were to estimate the prevalence of heart murmurs and HCM in a group of apparently healthy cats and to evaluate risk factors for the diagnosis of HCM in this population.

Animals, Materials and methods

This study was approved by the Royal Veterinary College (RVC) ethics and welfare committee (URN 2010 1004). Prior to data acquisition for the main study, inter-observer repeatability was analyzed in 17 apparently healthy cats that included normal cats and cats with HCM. Each cat underwent echocardiography separately and in randomized order by two trained observers (JRP and VLF), and each observer then measured her own studies.

Two rehoming centers for cats[a] agreed to take part in the cross-sectional study ('CatScan'). Between October 2011 and February 2013, all apparently healthy cats believed to be aged ≥6 months were considered eligible for inclusion and were screened by one investigator (JRP). This investigator was not a board-certified cardiologist, but she received two years of training (October 2009-September 2011) from a board certified cardiologist (VLF) prior to data collection. The cat identification number allocated by the rehoming center was noted to prevent cats being screened more than once. Records were reviewed to determine age (or if unknown, estimated age) and medical history. For statistical analyses, cats were categorized as juvenile (6-12 months), young adult (1-3 years), adult (3-9 years) and senior (9 years or older). Cats were excluded if they had any current illness identified or known pre-existing systemic disease; had a systolic blood pressure (SBP) ≥180 mmHg[29] or were being medically managed for hypertension; were hyperthyroid (as diagnosed by the rehoming center or on blood samples collected as part of the study); had been diagnosed with diabetes mellitus by the rehoming center; were azotemic in the presence of polyuria and polydipsia; were pregnant or nursing queens; had already been selected for a new home; or were too aggressive or too nervous to allow handling.

Cats meeting the inclusion criteria were auscultated[b] in their pens and underwent echocardiography in a separate room. Prior to echocardiography, cats were allowed to acclimate to the new room until calm (or for up to 10 minutes), and then weighed. Body condition score (BCS) was assessed on a

[a] Battersea Dogs & Cats Home's central London branch and Cats Protection's National Cat Adoption Centre
[b] Harvey™ Elite® Stethoscope with pediatric diaphragm, Welch Allyn, Skaneateles Falls, NY, USA

scale of 1-9 by the same observer.[30] Cats were then auscultated a second time, SBP was measured, and echocardiography was performed. After the echocardiographic examination, cats were auscultated for a third time and were returned to their pens. Presence/absence of a heart murmur, point of maximal heart murmur intensity, minimum/maximum heart murmur intensity, and heart rate was noted at each auscultation.[31] The presence of a third heart sound or arrhythmia was also recorded. If a cat purred loudly throughout all 3 auscultation periods such that it was impossible to hear the heart sounds, attempts were made during the third auscultation period to stop purring. Methods, in order attempted, included knocking on the underside of the table; turning on a nearby source of running water; or holding rubbing alcohol under the cat's nose.[32] Ambient noise was minimal in all areas in which the cats were auscultated, with only quiet talking or sometimes low-level music in housing areas, and complete silence in the echocardiography room. Cats were classed as having a heart murmur even if not detected during all auscultation periods and the maximum heart murmur grade was considered to be the maximum detected on any auscultation period. Likewise, cats were considered to have a third heart sound or arrhythmia even if these findings were intermittent. Indirect SBP assessment was performed as recommended by the ACVIM Consensus Statement[29] using a Doppler sphygmomanometry technique,[c] noting cuff size, limb used, cat position and cat demeanor.

Following SBP assessment, hair-coat was clipped from the right axillary area and the cat restrained in a position that was well-tolerated. The positions attempted (in order of preference) were right lateral recumbency on a purpose-built table top; on the lap of the echocardiographer; or with the cat sitting or standing on the echocardiography table and lightly restrained. If adequate quality echocardiographic images could not be obtained from any of these positions, the cat was excluded from the study.

[c] Model 811-B Doppler Ultrasonic Flow Detector, Parks Medical Electronics Inc., Aloha, Oregon, USA

An echocardiography machine[d] with a 7.5 MHz transducer was used to obtain two-dimensional (2D) and M-mode images from right parasternal views. Loops were recorded of the right parasternal long-axis 4-chamber view, the right parasternal long-axis LV outflow ('5-chamber') view, the right parasternal short-axis view at the level of the papillary muscles and the right parasternal short-axis view at the level of the aortic valve. M-mode images were guided from 2D images of the right parasternal short-axis view at the level of the papillary muscles.[33]

Measurements were made off-line. All left ventricular wall thickness measurements were made from 2D images. Maximal LVWd was measured on the first frame after mitral valve closure on images where the mitral valve was visible and at the time point in the cardiac cycle of greatest LV internal diameter on images where the mitral valve was not visible. A leading edge to trailing edge method of measurement was used, being careful to exclude pericardium, false tendons or papillary muscles but including endocardial borders.[34] At least 3 measurements were made of the thickest region identified for each view of the end-diastolic interventricular septum (IVSd) and left ventricular free wall (LVFWd), recording the largest repeatable value. The maximum left ventricular wall thickness measurement of either the IVSd or LVFWd was also recorded (LVWd). Hypertrophic cardiomyopathy was defined as LVWd ≥6 mm; equivocal was defined as LVWd 5.5-5.9 mm; and normal was defined as <5.5 mm. Cats were classified as equivocal if they had LVWd <6 mm but subjective hypertrophy of the papillary muscles. Cats with systolic anterior motion of the mitral valve (SAM) but normal wall thickness were classed as normal. M-mode images were used only for measurement of left ventricular fractional shortening (FS%).

LA size was assessed using 2 separate methods: using 2D images from a right parasternal short-axis view to calculate the ratio of diastolic LA diameter to aortic root diameter (LA:Ao) measured on the last frame prior to aortic valve opening[35] and using a right parasternal long-axis 4-chamber view to measure the diameter of the left atrium measured parallel with the mitral annulus in the last frame

[d] MyLab 30 Gold, Esaote UK, Cambridge, UK

before mitral valve opening (LAD).[36, 37] At least 3 measurements were made of each variable, recording an average value for each. The presence or absence of systolic anterior motion of the mitral valve (SAM) was assessed on a 2D right parasternal long-axis LV outflow view, using cine loop played back at reduced speed. ECG leads were not routinely attached during the echocardiographic examination unless an arrhythmia was detected on auscultation or was apparent during SBP assessment or echocardiography.

At the completion of the study, medical records kept by the rehoming center were re-assessed to check whether cats had been subsequently diagnosed with a condition considered an exclusion criterion.

Statistical analysis

Statistical analysis was performed using commercially available software.[e] Normality of continuous data was assessed graphically. Normally distributed data are presented as mean ± standard deviation (SD) and non-normally distributed data are presented as median (interquartile range, IQR: 25th percentile to 75th percentile) where appropriate.

Power calculations[f] were performed based on pilot data[6] and a preliminary estimate of HCM prevalence of 15% was used to calculate that 196 screened cats were required to estimate the prevalence of HCM in the study population with a precision of ± 5.0% (confidence level 95%, power 80%) and that 783 screened cats would be needed to estimate the prevalence with a precision of ± 2.5% (confidence level 95%, power 80%).

For inter-observer repeatability analysis, agreement between the two observers for categorical classification of cats HCM status was performed using a Kappa statistic. Coefficients of variation

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[e] GraphPad Prism 5, GraphPad Software, 2007 and PASW Statistics 20, 2011
[f] Epi Info 7.0, 2013

(CVs) were used to assess inter-observer variation for continuous variables (IVSd, LVFWd, LAD and LA:Ao). Bias and 95% limits of agreement were calculated for each variable.

When comparing cats with and without a diagnosis of HCM, the Mann Whitney U Test was used to compare continuous, non-normally distributed data and the Student's independent t-test for continuous, normally distributed data. The Fisher's exact and Pearson Chi square tests were used as appropriate to compare categorical data. Binary logistic regression models were created to identify risk factors associated with a diagnosis of HCM. Variables significant at $p<0.2$ were taken forward in a manual forwards stepwise construction manner. Models were also generated in a manual backwards stepwise elimination manner to verify results. Odds ratios (OR) and 95% confidence intervals (CIs) were calculated. First order interactions were assessed between final model variables and overall model assessment was performed looking at the Hosmer-Lemeshow goodness of fit test statistic, the percentage of cases the model correctly classified as well as the percentage of affected and unaffected cases the model correctly classified and by assessment of the residuals, looking at deviance and DFBeta values.[38] A value of $p<0.05$ was considered statistically significant. A Bonferroni correction was applied to assess statistical significance for any post hoc analysis.

Results

Seventeen cats were included in the inter-observer repeatability study. Both observers classified 8 cats as normal, 1 as equivocal and 8 as HCM with perfect agreement (Kappa=1.0). Mean coefficients of variation were between 2.3-3.9% for all 2D variables (Table 1).

Data collection occurred between October 2011 and February 2013. During this time period, 1,007 cats were considered eligible for the project, 780 of which (77.5%) completed the full screening process ('CatScan population'). Cats were excluded either due to aggression (n=93, 9.2%) or being too nervous to handle (n=134, 13.3%).

Age, body weight and BCS were non-normally distributed, while heart rate was normally distributed. The median and modal age group category in the CatScan population was 1-3 years (36.1%), with 14.9% cats 6-12 months old, 35.8% were 3-9 years old and 13.1% were older than 9 years. Seventy per cent of cats were younger than 5 years old and the oldest age group was 17-19 years (Figure 1). Three hundred and thirty eight (43.3%) cats in the CatScan population were male and 623 (79.9%) cats were neutered at the time of examination. The vast majority of cats (n=758, 97.2%) were non-pedigree, but 22 (2.8%) cats of 12 different pedigree breeds were represented, with Bengal (n=3), Exotic Shorthair (n=3) and Ragdoll (n=3) the most common pedigree breeds. Five hundred and thirty five (68.6%) cats had been given up to the centers for rehoming by their previous owners, with the remainder having been found as strays. Cats were recruited almost equally from both centers: 413 (52.9%) cats from one and 367 (47.1%) from the other. Median body weight was 3.65 kg (IQR 3.11-4.46 kg) and median BCS was 5/9 (IQR 4-5). Most cats were therefore considered to be of ideal BCS, but 60 (7.7%) cats were BCS 6 and 22 (2.8%) were BCS ≥7. There was no difference between the CatScan population and the excluded cats with regard to sex (p=0.543), neutering status (p=0.088) or proportion of non-pedigree cats (p=0.657). Cats in the CatScan population had a lower median age group category (1-3 years) than the excluded cats (3-5 years, p=0.048). As it was not possible to handle many of the excluded cats, information on their weight and body condition score was not available.

All 780 cats in the CatScan population were auscultated at least once, with a total of 1630 auscultations of diagnostic quality. In-pen auscultation was successful in less than half of the cats (n=369 cats, 47.3%) mainly due to purring, whereas it was possible to auscultate 615 (78.8%) prior to echo and 646 (82.8%) after the echo. The overall prevalence of heart murmurs in the CatScan population was 40.8% (95% CI 37.3-44.3%). The majority of heart murmurs (91.2%) varied in intensity during auscultation, and the most common maximum heart murmur grade was grade II/VI (n=165, 51.9%). Most heart murmurs had a point of maximal intensity along the left sternal border. A third heart sound was heard in 3 (0.4%) cats, and an arrhythmia was detected in 10 (1.3%) cats (Table 2). All of the cats with third heart sounds were estimated to be ≥9 years old and all had HCM. Auscultated arrhythmias included 7 cats that had one or more pauses during examination, none of which showed evidence of any arrhythmia when an electrocardiogram (ECG) was performed. Two other cats had ventricular premature complexes and 1 cat had atrial premature complexes confirmed on ECG. Three of the 10 cats with arrhythmias were diagnosed with HCM.

The proportion of cats with identified heart murmurs increased with the number of auscultations performed. Of those with a heart murmur detected, the heart murmur was present during all auscultation periods in the majority of cats (Figure 2). Taking into account all auscultations, mean heart rate was 203 ± 35 bpm. Heart rate was higher (208 ± 32 bpm) during an auscultation period when a heart murmur was present compared with auscultation period in which no heart murmur was heard (200 ± 37 bpm, $p<0.001$).

Hypertension was ruled out as a cause for LV hypertrophy in all cats and hyperthyroidism and diabetes were ruled out on a case by case basis by the veterinarians in the rehoming centers.

Median (IQR) SBP for the group was 120.6 (110.4-132.4) mmHg. Thyroxine concentrations (total T4) were measured in 216 (27.7%) cats and were within normal limits for all cats.

End-diastolic left ventricular wall thickness showed a bimodal pattern (Figure 3). Using the current cut-off of ≥6 mm, the prevalence of HCM in the 780 cats was 14.7% (95% CI 12.3 – 17.4%). Twenty-five cats (3.2%) were classed as equivocal for HCM, 635 cats (81.4%) were classified as normal, and 5 cats (0.6%) had other cardiac diagnoses: peritoneal pericardial diaphragmatic hernia (n=2), ventricular septal defect (n=1), supravalvular mitral stenosis (n=1), and unclassified cardiomyopathy (UCM, n=1). This gave a prevalence for congenital disease as 0.5% (95% CI 0.1-1.3%) and 0.1% (95 % CI 0.0-0.7%) for other cardiomyopathies.

Forty-five (5.8%) cats had systolic anterior motion of the mitral valve (SAM). Of these, 41 (91.1%) had HCM, 2 (4.4%) were equivocal and 2 (4.4%) had normal LV wall thickness (LVWd of 5.3 mm and 5.4 mm, respectively) (Table 3). The proportion of cats with a heart murmur was higher ($p<0.001$) in the cats with SAM (42/45, 93.3%) than in the cats without SAM (276/735, 37.6%). Cats with SAM had greater median maximal LV wall thickness (LVWd 6.6 (IQR 6.2-7.3) mm) compared with cats without SAM (LVWd 4.7 (IQR 4.2-5.1) mm, $p<0.001$), had higher median FS% values (48 (IQR 43-53) %) than those without SAM (43 (IQR 39-47) %, $p<0.001$) and had greater median LAD (15.0 (IQR 13.9-15.8) mm) than those without SAM (14.1 (IQR 13.3-15.1) mm, $p=0.002$). LA:Ao was not significantly different between the cats with and without SAM ($p=0.824$). When only cats with HCM were considered, cats with SAM still had greater median LVWd (6.6 (IQR 6.2-7.3) mm vs. 6.3 (IQR 6.2-6.5) mm, $p<0.001$) and higher median FS% (48 (IQR 43-53) % vs. 46 (IQR 40-50) %, $p=0.040$) than those without SAM but LAD and LA:Ao was similar in both groups ($p=0.457$ and $p=0.491$, respectively). In total, 6 cats (0.8%) had LA:Ao >1.5. Of these, 4 had HCM (LA:Ao ranged from 1.54-1.77), 1 had UCM (LA:Ao 1.56) and 1 had supravalvular mitral stenosis (LA:Ao 1.72).

In univariate analysis, factors associated with a diagnosis of HCM were increased age, increased body weight, higher SBP, male neutered sex, and increased body condition score. Cats with HCM were more likely to have a heart murmur or a third heart sound auscultated than those without HCM (Table 4). For diagnosis of HCM, a heart murmur had a sensitivity of 81.7% but a specificity of only 66.3%. The PPV of a heart murmur was 29.6% and the NPV was 95.5%. 70.4% of heart murmurs were therefore functional.

Although cats of all age groups were diagnosed with HCM, the prevalence increased with increasing age ($p<0.001$) (Table 5). Using Bonferroni correction, post hoc comparisons showed a significant difference in prevalence of HCM comparing juvenile *vs.* adult ($p<0.001$), juvenile *vs.* senior ($p<0.001$), young adult *vs.* adult ($p=0.004$) and young adult *vs.* senior ($p<0.001$). The prevalence of heart murmurs and thus the PPV of detecting a heart murmur increased with increasing age group, while the NPV decreased with increasing age group. In older cats there was an increase in both the proportion of cats with a heart murmur but no HCM, and the proportion of cats with HCM but no heart murmur, so that both sensitivity and specificity of a heart murmur for detecting HCM decreased with increasing age.

Multivariable models were generated to look for risk factors associated with a diagnosis of HCM. Cats with a diagnosis of HCM were compared to a composite of cats considered normal, equivocal and those diagnosed with other cardiac diseases. The presence of a heart murmur, especially grade III/VI or louder, increasing age group, being male and being overweight were risk factors for diagnosis of HCM (Figure 4). Model fit was assessed using the Hosmer-Lemeshow test p value and analysis of the residuals, and showed good fit ($p=0.154$). The model correctly classified 87.1% cats, with a PPV of 63.0% and a NPV of 88.8%.

Discussion

There are very few reports of feline cardiac disease prevalence in the general population[39, 40, g] and only two small non-referral based studies investigating prevalence of HCM, with a suggested prevalence of 14-16%.[5, 6] Of the 780 cats that underwent echocardiography in this study, 115 cats were diagnosed with HCM compared with 5 cats with other cardiac abnormalities, only one of which was another myocardial disease (UCM). Although HCM is acknowledged to be the most common type of cardiomyopathy in cats, most previous studies have reported the prevalence in referral center populations,[2] and our study suggests that other forms of cardiomyopathy (e.g. restrictive cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy) are substantially less common than HCM in the general cat population.

The phenotype of HCM is very variable among people with a positive HCM genotype.[10] In the absence of a gold standard for the diagnosis of HCM, an arbitrary LVWd cut-off is generally used clinically to define HCM in both people and cats. Although a variety of cut-off values for LVWd have been used to define HCM in cats, we chose to use maximum wall thickness ≥ 6 mm on any 2D image,[12-14] as this is widely used and is likely to provide a conservative estimate of HCM prevalence. Despite this, the HCM prevalence in our study was 14.7%, which is much higher than reported in people.[3, 4] Visual assessment of the distribution of end-diastolic wall thicknesses seen in this population of cats showed a bimodal pattern with the likely cut-off being between 5.5 mm and 6.0 mm. If a lower cut-off were to be used, the prevalence of HCM diagnosis would be higher. Whether all of these cats truly have HCM is difficult to determine. From this analysis it is not possible to determine whether cut-off values for LV wall thickness should be variable to take account of additional factors such as age, weight and body condition score, or whether alternatively factors such as obesity might alter expression of LV hypertrophy in cats with HCM, as has been proposed in people.[41] Multi-faceted

[g] Dirven MJM, Barendse MA, vanMook MC, Sterenborg JA, vanden Wildenberg A. Prevalence of heart murmurs and congenital heart disease in 2935 young cats. J Vet Intern Med. 2012;26:1513.

longitudinal studies with pathologic, genomic and outcome components might be needed to resolve this.

Presence of a heart murmur (in particular, a grade III/VI or louder heart murmur), being male, increasing age group and being overweight were found to be risk factors for diagnosis of HCM. Heart murmurs were extremely common, and increased in prevalence with increasing age. Most heart murmurs were of low intensity (≤III/VI) and dynamic. The PPV of a heart murmur for identifying HCM was very low, though increased with age. Conversely, the NPV was very high, especially in young cats. As PPV and NPV are influenced by prevalence, these values are only applicable when populations of similar prevalence are assessed. The prevalence of heart murmurs in cats in this population (40.8%) was higher than has been previously reported, with previous reports suggesting a prevalence of 15.5–33.7%.[5, 6, 22] In this study, however, the prevalence was calculated over multiple auscultation periods. Repeated auscultation has been shown to increase the overall prevalence of heart murmurs, both in this population and a previous study,[6] possibly due to the variable nature of heart murmurs in cats. The majority (70.4%) of heart murmurs were considered functional. This is a higher proportion of functional heart murmurs than in previous reports.[5, 6] Functional heart murmurs are also common in people, particularly in children and young adults.[42, 43] In people, functional heart murmurs are often heard in states associated with increased cardiac output such as fever, hyperthyroidism, hypertension, anemia and exercise.[31] Dynamic right ventricular outflow obstruction has been reported as a cause of systolic heart murmurs in cats[23] both with and without structural abnormalities[5] but the presence or absence of this was not routinely recorded in this population. The mean heart rate was significantly higher when a heart murmur was present than in auscultation periods in which there was no heart murmur, although the difference was arguably not clinically significant.

Males were more likely than females to be diagnosed with HCM. This has been found previously in a number of other studies of cats,[2, 24, 25, 28] and a smaller male bias has been described in people.[27] No gender bias is expected with a classic Mendelian pattern of inheritance as described for HCM in both people and cats.[12, 44] In human HCM patients with the MYBPC3 mutation, an abnormal phenotype develops earlier in males than in females,[26] and this has also been reported in Maine Coons with HCM.[12] It is possible that there are multiple factors influencing the expression of LVH in HCM that have not yet been identified. These could include modifying genes or environmental factors. Cats in our study were diagnosed with HCM in all age groups, but HCM prevalence increased with increasing age, suggesting that there is a similar age-related increase in expression of an abnormal phenotype, as seen in people. [26]

We had not anticipated that increased body condition score would be associated with LV hypertrophy in this population. Obesity has recently been proposed to be an environmental factor associated with increased LV mass in human HCM patients, although no increase in maximum LVWd was identified.[41] Being overweight has only recently been suggested as a risk factor for HCM in cats.[45] Dogs with obesity have been shown to have increased maximum LVWd compared to lean control dogs[46], and obese people have been shown to have increased LV mass and increased LVWd compared to those without obesity.[47, 48] There are many structural and functional cardiac changes associated with obesity in people, which may variously be due to the presence of metabolic syndrome, a pro-inflammatory state, or atherosclerotic changes, amongst other factors. In addition, obese individuals may have increased ventricular stiffness in the face of an expanded central blood volume and increased cardiac output, which might create a state of volume overload that could result in eccentric hypertrophy.[47] There may be similar pathophysiological processes involved in obese cats.[49] In the absence of a gold standard test for HCM, it is impossible to determine whether the cardiac changes seen in this population of cats associated with being overweight represent true HCM or whether they are load-related LVH.

Third heart sounds were uncommon and all 3 cats with a third heart sound in this study had HCM and were ≥9 years old. Without phonocardiography it is difficult to determine whether these third heart sounds were gallop sounds or systolic clicks. The predictive value of a third heart sound should be further investigated in an older population of cats. The presence of a third heart sound was not predictive of HCM in the multivariable model, possibly because few cats with HCM had a third heart sound.

Arrhythmias were also very uncommon in this population. Most of the arrhythmias described in this population consisted of single pauses on auscultation or during blood pressure assessment and were not documented during ECG recordings which makes it difficult to categorize them, although premature complexes of either atrial or ventricular origin were suspected. There was no association between arrhythmias and the presence of LV hypertrophy (Table 4). Ventricular premature complexes have been found in people that are free of cardiac disease[50] and while a study investigating prognostic indicators suggest that cats with HCM and arrhythmias have a poorer outcome than those without arrhythmias,[51] the specific prognostic implications of ventricular or supraventricular arrhythmias in cats without structural heart disease is not known.

SAM was found in cats considered normal, equivocal, and affected with HCM, although it was rare in normal and equivocal cats. As has been previously reported,[52] cats with HCM and SAM had greater LVWd than those without SAM and there was no difference in measures of left atrial size. Very few cats had left atrial enlargement. As left atrial enlargement is considered to be an important risk factor for cardiac death in cats with HCM, one might speculate that only a small proportion of the cats in this study were at imminent risk of life-threatening complications of their disease, but longitudinal studies would be required to confirm this.

If our current diagnostic criteria for diagnosing HCM are appropriate, then HCM is extremely common in cats compared with other species,[3, 4 49, 53-55] and the reasons for this are not clear. Although causative mutations in myosin binding protein C have been identified in Maine coon[56] and

Ragdoll[57] cats with HCM, and HCM has been reported to be familial in other pedigree breeds[12, 58, 59, h, i, j] and in some non-pedigree cats,[60, 61] the true prevalence of sarcomeric mutations in cats with HCM is unknown. If there is a genetic basis for most HCM in cats, it is possible that the prevalence might be high if selection pressures against HCM are weak. Natural selection may not have a large effect on HCM prevalence, as most affected cats in our study had relatively mild changes and would be considered to be at low risk of a cardiac death.

Limitations

There are a number of limitations in this study. Cats were selected from rehoming centers, and although this is more representative of the general population than cats presented to referral hospitals, it is possible that other unknown bias factors may be present in cats given up for rehoming. This study represents a snapshot of the cats coming through the rehoming centers during the 17 months of the study and no cause and effect conclusions can be drawn.

As many cats were strays, ages were estimated if unknown. This opens up a potential for inaccuracy although every effort was made to provide a realistic estimate, and using age categories may have minimized this risk. Although over 100 cats were aged 9 years or older, generally this was a young population. As these data show an increasing prevalence of HCM with age, the reported prevalence of HCM may be an underestimate with respect to the general UK cat population. The proportion of overweight and obese cats may not be reflective of the general population of owned cats. The incidence of obesity in cats is reported to be >35% and is thought to be increasing with time[62] whereas only 10.5% were considered overweight in this population. It may not be possible to

[h] Martin L, VandeWoude S, Boon J, Brown D. Left ventricular hypertrophy in a closed colony of Persian cats. J Vet Intern Med. 1994;8:143.
[i] Meurs K, Kittleson MD, Towbin J, Ware W. Familial systolic anterior motion of the mitral valve and/or hypertrophic cardiomyopathy is apparently inherited in as an autosomal dominant trait in a family of American Shorthair cats. J Vet Intern Med. 1997;11:138.
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extrapolate the finding of this study to pedigree cats as very few were included in the population. Not all cats had total thyroid hormone levels measured, although this was assessed on a case by case basis so it is less likely that any hyperthyroid cat was erroneously included. Following screening, no cat was excluded for ill health reasons. It is possible that systemic disease was present but missed in some screened cats, and undetected pyrexia or anemia was not ruled out as a cause of heart murmurs as the examination did not include assessment of temperature or of a complete blood count. However, cats with ill health were often housed separately and this may have reduced the prevalence of systemic disease in the screened population. It was not possible to auscultate all cats during all time periods. Some cats only underwent auscultation once while others underwent auscultation 3 times which limits some of the interpretation of the variability of heart murmurs between auscultation periods. Neither ECGs nor ambulatory ECG monitoring were routinely recorded in the study cats and echocardiographic examinations were performed without concurrent ECG so it is possible that some infrequent arrhythmias were not detected. Cats that showed signs of aggression or were too nervous to handle were not included for safety reasons, for both the cats and the investigator, in the absence of ethical approval for sedation. This may have affected the prevalence of HCM, especially as anecdotally anger has been linked to an increase in cardiovascular disease in people.[63] As this was a cross-sectional study, no inferences about causality between the risk factors identified and the diagnosis of HCM can be drawn. A prospective study would help to identify whether or not these are causal relationships. The echocardiographic studies were not conducted by a board-certified cardiologist, and although the repeatability study showed excellent agreement between the investigator and a board-certified cardiologist for classification of HCM severity and the measurement of 2D echocardiographic values used in the CatScan study, it is possible that other cardiac diseases were missed.

Conclusion

Hypertrophic cardiomyopathy appears to be very common in cats, with an overall prevalence of 14.7%, but becoming more common with increasing age. Functional heart murmurs are also common in apparently healthy cats, but echocardiographically-evident cardiac diseases other than HCM are uncommon. Risk factors for a diagnosis of HCM include the presence of a heart murmur (especially grade III/VI or louder), being male, increasing age and being overweight.

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Table 1 – Echocardiographic inter-observer variation (including image acquisition and measurements); coefficients of variation, bias and 95% limits of agreement (n=17)

Table 2 – Auscultation data for all CatScan population cats, all data reported as number (%)

Table 3 – Echocardiographic features of screened cats

Table 4 – Univariate comparisons of cats with and without HCM (cats without HCM include those considered normal, equivocal or other cardiac disease).

BCS – Body condition score (underweight ≤4/9, ideal = 5/9, overweight ≥6/9)

SBP – Systolic blood pressure

Table 5 – heart murmur prevalence, HCM prevalence, sensitivity, specificity, positive and negative predictive value of using a heart murmur to detect HCM

Figure 1 – age of CatScan population cats (n=780)

Figure 2 - Number of cats with a heart murmur detected according to number of times auscultated

Figure 3 – Maximum left ventricular wall thickness of 780 cats

Figure 4 – Multivariable binary logistic regression model of factors associated with a diagnosis of HCM (115 cats with HCM out of 780 cats).

Juvenile = 6-12 months, Young adult = 1-3 years, Adult = 3-9 years, Senior = 9 years or older

BCS – Body condition score (underweight ≤4/9, ideal = 5/9, overweight ≥6/9)

Table 1

	CVs ± standard deviation (%)	Bias (95% limits of agreement)
IVSd	2.8 ± 2.3	0.0 (-0.5 – 0.6) mm
LVFWd	3.9 ± 3.2	-0.0 (-0.7 – 0.6) mm
LA:Ao	2.3 ± 1.7	0.0 (-0.1 – 0.1)
LAD	3.3 ± 3.7	-0.1 (-1.8 – 1.7) mm

Table 2

	n (%)
Number auscultated	780
Heart murmur present	318 (40.8%)
Grade I/VI	*49 (15.4%)*
Grade II/VI	*165 (51.9%)*
Grade III/VI	*99 (31.1%)*
Grade IV/VI	*4 (1.3%)*
Grade V/VI	*1 (0.3%)*
Variable heart murmur grade	*290 (91.2%)*
Third heart sound present	3 (0.4%)
Arrhythmia present	10 (1.3%)

Table 3

	Normal	**Equivocal**	**HCM**
n	635	25	115
LVWd (mm)	4.6 (4.2-4.9)	5.8 (5.7-5.9)	6.3 (6.2-6.6)
LAD (mm)	14.1 (13.3-15.0)	14.8 (13.8-16.3)	14.7 (13.4-15.8)
LA:Ao (end-diastole)	1.19 (1.12-1.25)	1.15 (1.08-1.19)	1.16 (1.09-1.26)
FS%	42 (39-47)	45 (40-50)	47 (41-51)
SAM	2 (0.3%)	2 (8.0%)	41 (35.7%)

Table 4

		HCM (n=115)	No HCM (n=665)	p value
Age		5-7 years	1-3 years	<0.001
Male		72 (62.6%)	266 (40.0%)	<0.001
Non-pedigree		112 (97.4%)	646 (97.1%)	1.000
Neutered		102 (88.7%)	521 (78.3%)	0.003
Weight (kg)		4.54 (3.93-5.21)	3.53 (3.04-4.23)	<0.001
BCS	Underweight	26 (22.6%)	201 (30.2%)	<0.001
	Ideal weight	61 (53.0%)	410 (61.7%)	
	Over weight	28 (24.3%)	54 (8.1%)	
SBP (mmHg)		128.8 (115.6-139.6)	120.0 (110.0-131.2)	<0.001
Heart murmur		94 (81.7%)	224 (33.7%)	<0.001
Heart murmur grade	No heart murmur	21 (18.2%)	441 (66.3%)	<0.001
	Grade I-II/VI	47 (40.9%)	167 (25.1%)	
	Grade III-IV/VI	47 (40.9%)	56 (8.4%)	
	Grade V/VI	0 (0.0%)	1 (0.2%)	
Variable heart murmur grade		78 (83.0%)	212 (94.6%)	0.001
Third heart sound		3 (2.6%)	0 (0.0%)	0.003
Arrhythmia		3 (2.6%)	7 (1.1%)	0.172

Table 5

Table 5 – murmur prevalence, HCM prevalence, sensitivity, specificity, positive and negative predictive value of using a heart murmur to detect HCM

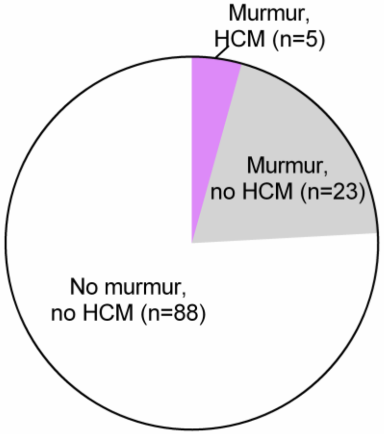
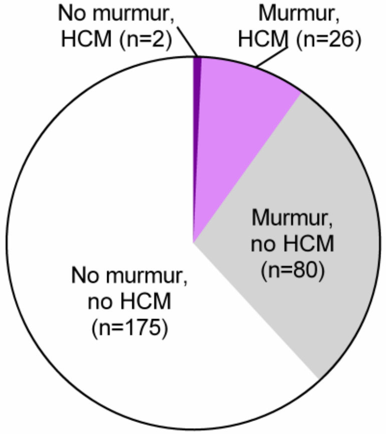
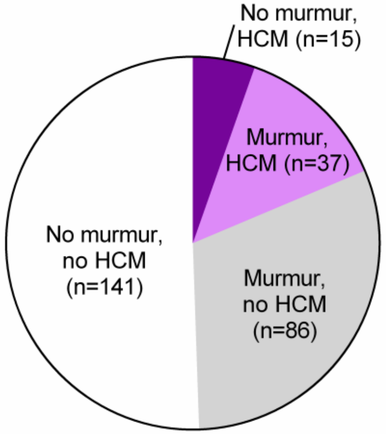
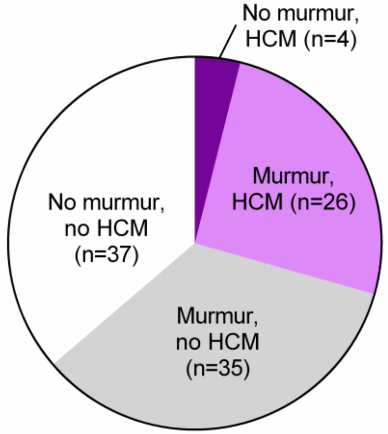
	Juvenile – 6-12 months (n=116)	Young adult – 1-3 years (n=283)	Adult – 3-9 years (n=279)	Senior – 9 years or older (n=102)
				
Heart murmur prevalence	24.1%	37.5%	44.1%	59.8%
HCM prevalence	4.3%	9.9%	18.6%	29.4%
Sensitivity	100.0%	92.9%	71.1%	86.7%
Specificity	79.3%	68.6%	62.1%	51.4%
PPV	17.9%	24.5%	30.1%	42.6%
NPV	100.0%	98.9%	90.4%	90.2%

Figure 1
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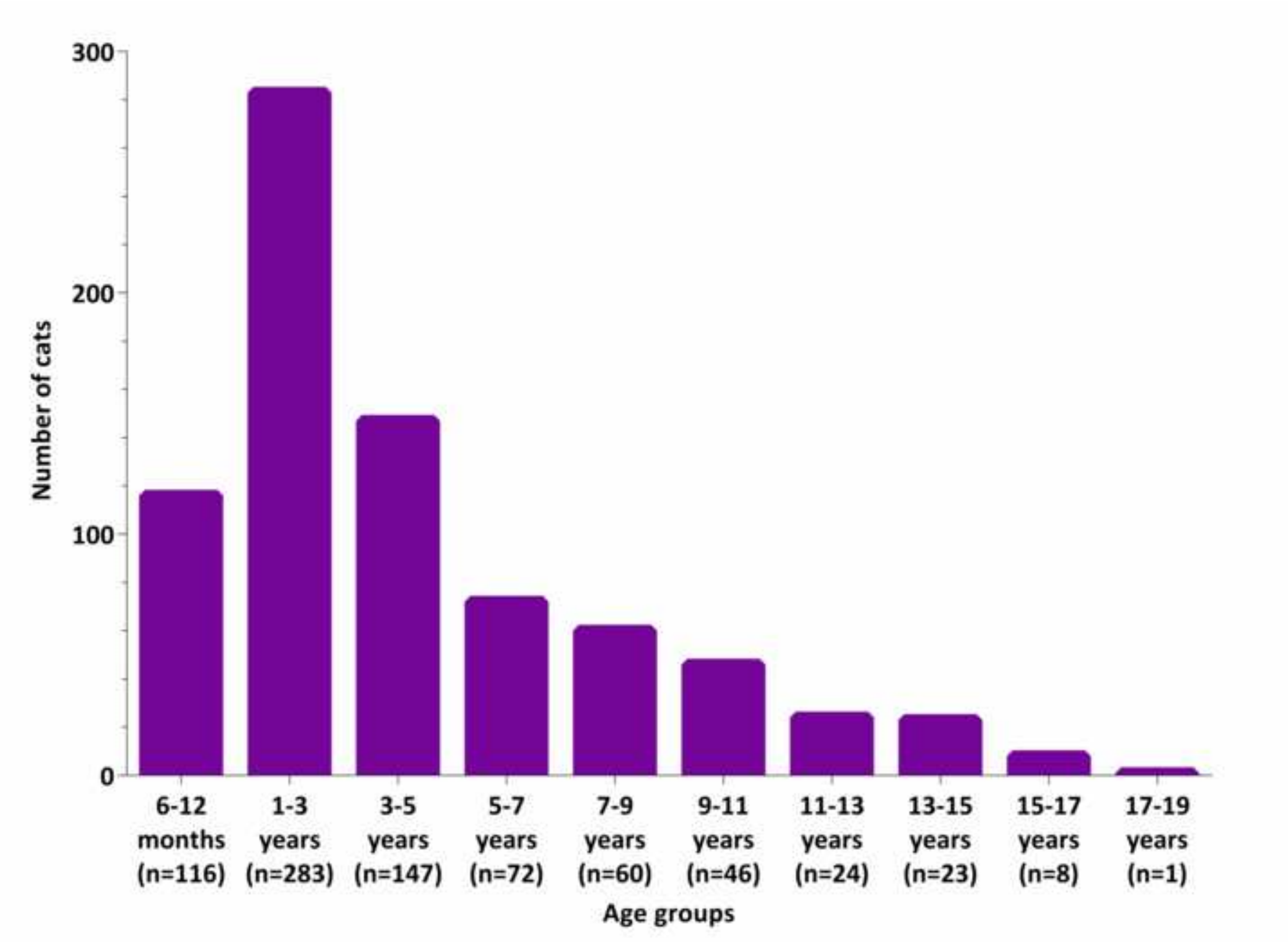

Figure 2
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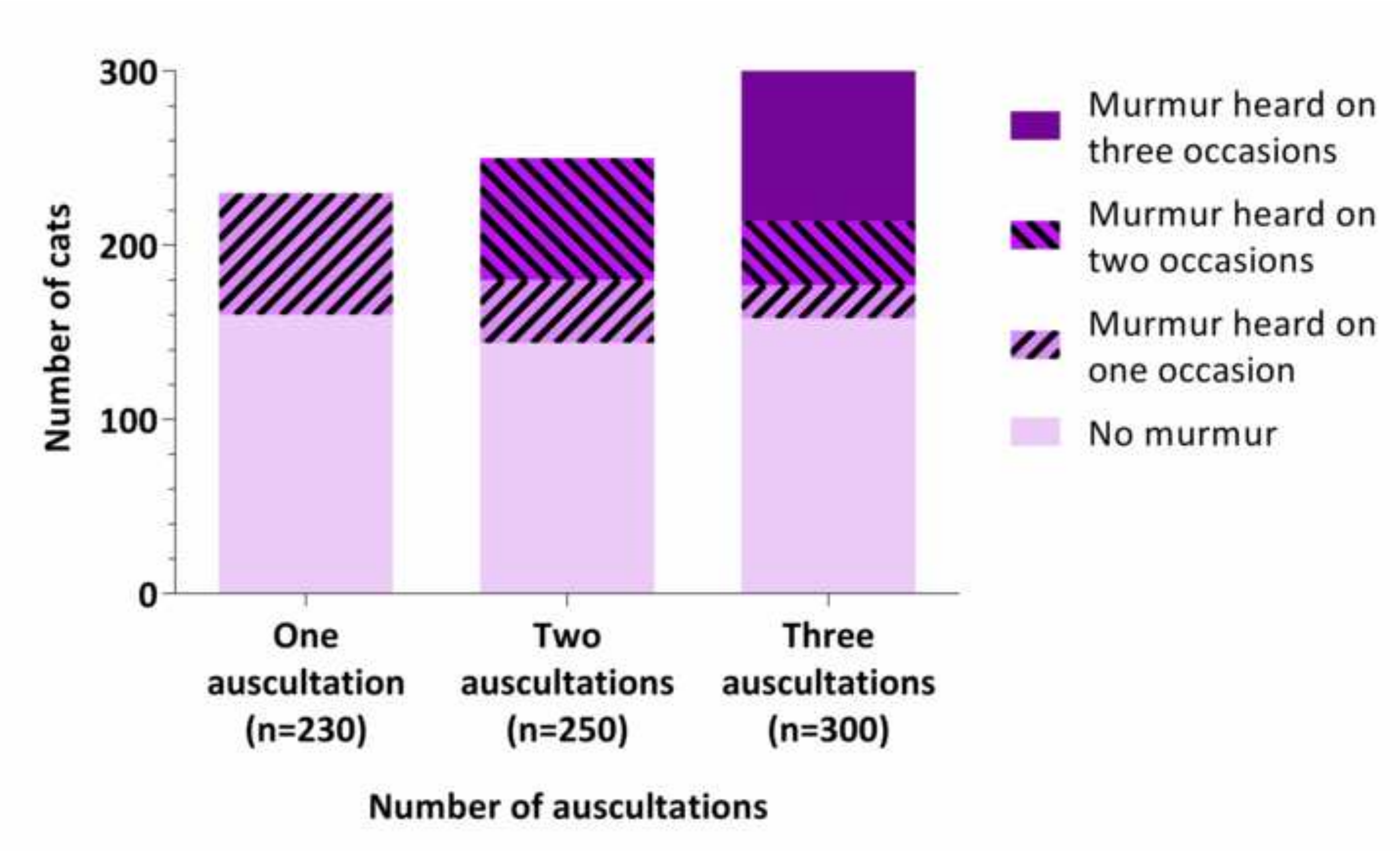

Figure 3

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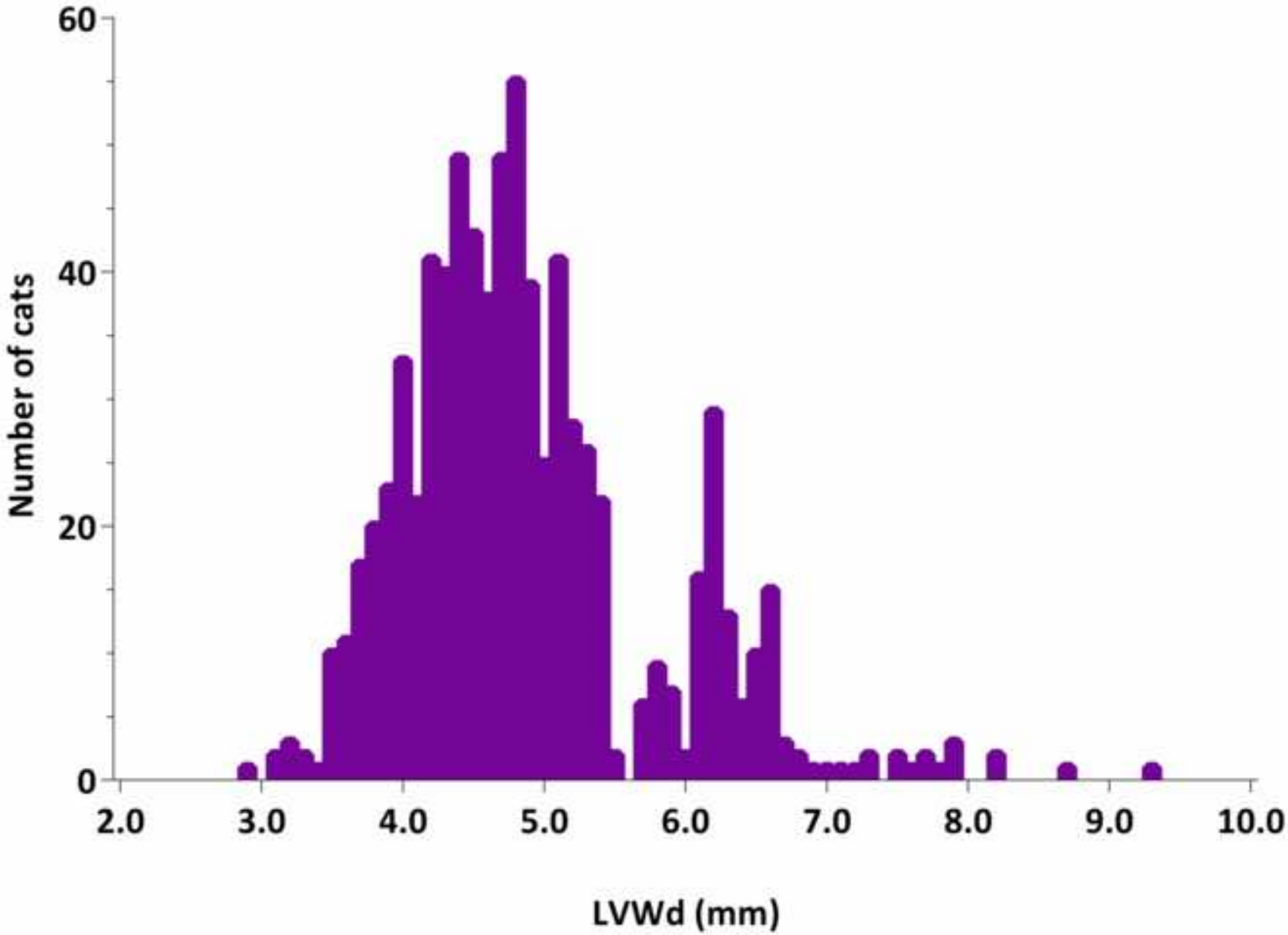

Figure 4

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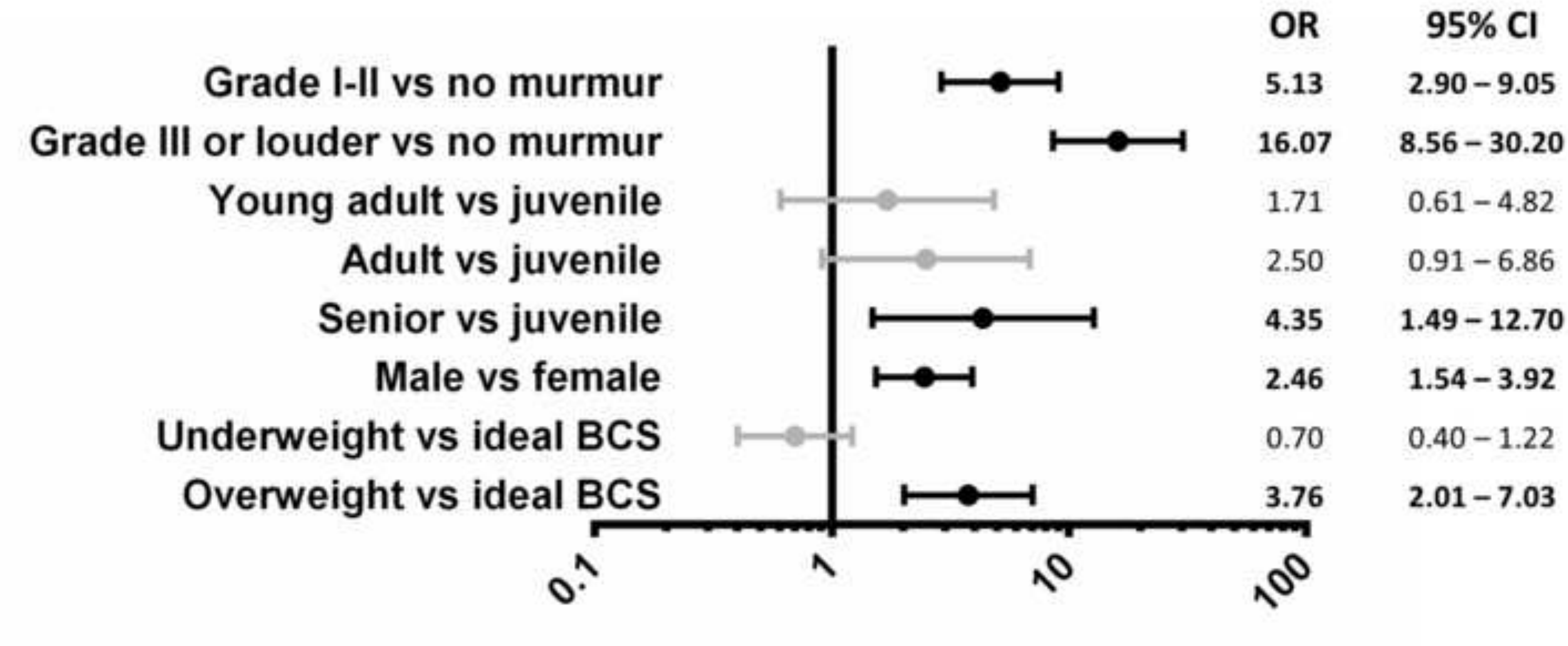

regression models were male sex, increased age, increased body condition score and a heart murmur (particularly grade III/VI or louder).

Conclusions

HCM is common in apparently healthy cats, in contrast with other cardiomyopathies. Heart murmurs are also common, and are often functional.