

1 **Chronic kidney disease in cats attending primary-care practice in the UK: A VetCompass™ study**

2 Author Contribution:

3 MC: Conception, design, analysis, manuscript writing and revision

4 DB: Conception, design, interpretation, manuscript revision

5 DON: Conception, design, manuscript revision

6 YC: Conception, design, interpretation, manuscript revision

7 JE: Conception, design, interpretation, manuscript revision

8

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19 This work conforms to the STROBE guidelines for reporting observational epidemiological studies.

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25 INTRODUCTION

26 Chronic kidney disease (CKD) is a commonly recognised heterogeneous disease syndrome in cats,
27 with previous studies estimating a prevalence of 1.7% to 3.6% in cats attending primary-care
28 practice in the UK ^{1,2}. Prevalence increases with age, with up to 80% of cats aged over 15 years
29 estimated to have CKD in some studies ³⁻⁵. Kidney disease has also been reported as the most
30 common cause of death in cats over 5 years of ages in the UK, with almost 1 in 7 animals dying of
31 this condition⁶. Previously reported median survival time estimates ranged from 21 days to 1151
32 days depending on severity of renal dysfunction at diagnosis ⁷⁻⁹.

33 It has previously been reported that CKD does not become clinically apparent until around 75% of
34 the renal function has been lost ¹⁰. Though as the condition progresses, considerable morbidity has
35 been reported, with cats experiencing a range of clinical signs as the disease progresses. The most
36 commonly described clinical signs were polydipsia, weight loss, anorexia, polyuria, depression, and
37 vomiting ^{8,11,12}, with anorexia, weight loss and depression all reported to negatively impact on the
38 quality of life of the cat ¹³.

39 Previously reported risk factors for CKD diagnosis include age ^{8,11,14}, sex ^{15,16}, breed ^{11,15},
40 hyperthyroidism ^{17,18}, feline leukaemia virus (FeLV) ^{19,20} and feline immunodeficiency virus (FIV) ^{21,22}.
41 Vaccination ²³ and incomplete recovery from acute kidney injury ²⁴ have additionally been
42 hypothesised as other potential risk factors. Useful prognostic indicators following diagnosis include
43 proteinuria ²⁵⁻²⁷, the feeding of a low protein, low phosphate diet ^{9,28}, anaemia ^{25,27,29} and serum
44 phosphate levels ^{25,27,29}. No single variable has been identified that reliably predicts survival following
45 diagnosis of CKD. This may be due to the heterogeneous nature of CKD in cats and the variable rates
46 of progression observed ²⁷.

47 Clinically apparent CKD causes considerable morbidity and mortality in cats. Additionally, up to 15%
48 of apparently healthy cats aged 10 years or older are found to have undiagnosed CKD at a routine

49 health check^{30,31}, suggesting that CKD may result in morbidity to a substantial proportion of the
50 geriatric cat population. Previous research on risk factors for CKD diagnosis and survival following
51 diagnosis of CKD has been limited mainly to referral populations, prospective research following
52 standard protocols focussing on one region (London) and questionnaire based studies, with little
53 work undertaken using general primary-care data. This may reduce the generalisability of the results
54 to the wider cat population³². This study aimed to estimate prevalence and risk factors for CKD
55 diagnosed in cats attending VetCompass™ practices in the UK, to document the current standard of
56 care applied in these practices and to evaluate survival following CKD diagnosis. By comparison with
57 published expert recommendations (guidelines), these data should assist primary practitioners
58 identify ways in which diagnosis and management of feline CKD could be improved.

59 MATERIALS AND METHODS

60 Ethics approval was provided by the Royal Veterinary College Clinical Research Ethical Review Board
61 (URN M2015 0050).

62 Data collection and management

63 VetCompass™ collects and collates anonymised electronic patient records (EPR) from enrolled
64 primary-care veterinary practices in the UK. Patient demographic (species, breed, date of birth, sex,
65 neutering status, bodyweight) and clinical data (free clinical text, VeNom³³ diagnosis terms and
66 treatment fields) are uploaded for use in research studies^{1,34}.

67 A stratified prevalence study derived from the cohort of cats attending 244 participating
68 VetCompass™ practices from 1st January 2012 to 31st December 2013 was used to estimate the
69 two-year period prevalence³⁵. A frequency matched case control study, nested within the study
70 cohort, was used to investigate risk factors for diagnosis of CKD and a retrospective cohort study was
71 used to explore survival following CKD diagnosis. The sampling protocol for the three studies is
72 illustrated in Figure 1. Potential cases of CKD were identified by searching the EPR for VeNom
73 diagnosis codes (renal failure, renal disorder, renal disease, chronic renal failure, renal insufficiency),

74 treatment (KD, RCW feline renal, renal food, renalzin, ipakitine, alucap, semintra, tumil K, renal
75 profile, UPC) and free text clinical terms (CKD, CRD, CRF, chronic renal/kidney
76 failure/disease/insufficiency, kidney disease, renal disease, iris stage). The results from all searches
77 were merged and duplicates removed. A random sample of 20% of potential cases was selected to
78 review in detail the EPRs manually. The case definition required a diagnosis of CKD (or synonym)
79 recorded within the EPR, or a diagnosis of kidney disease (or synonym) within the EPR with evidence
80 of chronicity of disease, with chronicity defined as the presence of clinical signs or azotaemia for ≥ 3
81 months. 'Pre-existing cases' were those first diagnosed prior to the study period and 'incident cases'
82 were those first diagnosed during the study period. Controls were identified by examining EPR
83 records of a random sample of cats not identified as potential cases in the EPR CKD searches.
84 Controls were required to have not had CKD suspected at any time within the EPR. Controls selected
85 that were hyperthyroid needed to have been non-azotaemic when total T4 levels were less than
86 40nmol/l³⁶ to be included in the study. Cases and controls were frequency matched by age (< 9
87 years and ≥ 9 years) to control for the effect of age.

88 Demographic data were extracted automatically from the database, and further clinical data were
89 extracted manually from the EPR (date of diagnosis, death, reason for presentation at diagnosis,
90 clinical signs and physical exam results, laboratory results, imaging results, blood pressure
91 measurement, vaccination history, historical exposure to potential nephrotoxic drugs and toxins,
92 treatments prescribed and co-morbidities). Data were exported to Microsoft Excel 13 for cleaning
93 and then further exported to Stata 11 (StataCorp LP, College Station, TX) for statistical analysis.

94 Sample size calculations indicated that at least 290 cases and 290 controls would be required to be
95 sampled to detect an odds ratio of 2 or greater for a risk factor present in 10% of controls, assuming
96 80% power and 95% confidence³⁷

97 Medians and interquartile ranges (IQR) were calculated for continuous variables. Age was
98 categorised as < 9 years or ≥ 9 years. Bodyweight was categorised into quintiles and also maintained

99 as a continuous variable. Breed was categorised into crossbred and purebred, with purebred being a
100 recorded breed name recognised by International Cat Care³⁸. Reason for presentation at CKD
101 diagnosis was categorised as clinical signs, geriatric health check (apparently healthy cats aged ≥ 7
102 years presented for a health check) and monitoring of pre-existing disease. Serum creatinine and
103 serum phosphate at diagnosis were categorised based on IRIS guidelines³⁹ and maintained as
104 continuous variables. Vaccination was categorised as annual, kitten only or non-annual and no
105 recorded vaccination in the full EPR. Non-steroidal anti-inflammatory drug (NSAID) use was
106 categorised into one-off treatment, repeated one-off treatment and long term treatment recorded
107 in the full EPR. Days since last anaesthetic was categorised into 0 – 179 days, 180 – 364 days and no
108 anaesthetic recorded in 365 days prior to CKD diagnosis.

109 Statistical Analysis

110 The prevalence of CKD was estimated from the cohort of cats attending VetCompass™ practices
111 during the study period. A stratified analysis was used to describe the incidence risk and prevalence
112 of CKD in the VetCompass™ cat population, with the estimates adjusted for the random sampling of
113 20% of potential CKD cases (Fig. 1)³⁵. Stratum 1 contained the cats that had been identified with the
114 search terms and had their EPR read in detail and had a confirmed case/ non-case status. Stratum 2
115 contained all the cats that were not identified with the search terms, and were assumed to be non-
116 cases. A probability weighting was ascribed to each stratum (1/the proportion of the group that had
117 a confirmed case or non-case status) to account for the different proportions of all cats included⁴⁰.
118 All 'pre-existing' and 'incident' cases were included in prevalence estimates.

119 In the case-control study all incident cases were included in the analysis and compared to frequency
120 age-matched controls. Multivariable logistic regression was used to identify risk factors associated
121 with CKD diagnosis. Cats that had no age recorded were removed from the analysis. Variables that
122 were broadly associated with diagnosis of CKD ($p < 0.2$) in the univariable analysis were carried
123 forward to the multivariable model. Age was forced into the model to control for the frequency

124 matched sampling strategy. Model fit was assessed using the Hosmer-Lemeshow test ⁴¹ and
125 predictive ability was assessed by examining the area under the ROC curve ⁴². The model was
126 adjusted for veterinary group attended as a confounder by inclusion as a variable in the final model.
127 Statistical significance was set at the 5% level.

128 All incident cases identified had their clinical notes followed until 31st December 2015. Cats with one
129 day or more follow up were included in the survival analysis. Median survival time and mortality
130 rates were estimated. Multivariable Cox proportional hazards modelling was used to investigate risk
131 factors associated with survival following CKD diagnosis. Variables broadly associated with survival at
132 the univariable level ($p < 0.2$) were carried forward to the multivariable model assessment.
133 Proportionality of hazards was confirmed by assessing the Schoenfeld residuals and the Kaplan-
134 Meier curve. Model fit was assessed by examining the Cox-Snell residuals and predictive ability of
135 the model was assessed using Harrell's C concordance statistic ⁴². The model was adjusted for
136 veterinary group attended as a confounder by inclusion as a variable in the final model. Statistical
137 significance was set at the 5% level.

138 RESULTS

139 The denominator population included 353,448 cats attending 244 VetCompass™ clinics during the
140 study period. EPR searches identified 11,836 potential cases, of which 2,368 (20%) were reviewed in
141 detail and 625 were classified as incident and 336 pre-existing cases. Overall CKD prevalence was
142 estimated at 1.2% (95% confidence interval (CI) 1.1% - 1.3%). Prevalence increased with age: 0.1%
143 (95% CI 0.1% - 0.2%) in cats < 9 years and 3.6% (95% CI 3.3% - 3.8%) in cats aged ≥ 9 years (Table 1).
144 CKD prevalence by breed was highest in Burmese cats (5%, see Table 1).

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148 Descriptive statistics

149 Sex was recorded in 98.3% of cats, neuter status in 72.0% of cats and bodyweight in 43.8% of cats.

150 Age was not recorded in 8 cases and 8 controls. Median age at diagnosis of CKD was 14.8 years (IQR
151 12.1 – 16.7).

152 Cats were most commonly diagnosed with CKD following presentation to the veterinary surgeon due
153 to clinical signs compatible with CKD (66.6%; 416). Diagnosis followed a geriatric health or pre-
154 anaesthetic check in only 10.6% (66) and 7.0% (44) of cases respectively. Weight loss (49.9%; 311),
155 polydipsia (38.6%; 241) and polyuria (24.5%; 153) were the most frequently reported clinical signs.
156 At diagnosis, over half of cats (56.6%; 354) had two or more compatible clinical signs recorded, and
157 24.8% (155) cats had no clinical signs recorded. Diagnosis was confirmed using combined
158 biochemistry and urine analysis in 52.6% (329) of cats, with 33.9% (212) confirmed with
159 biochemistry, 3.5% (21) confirmed with urinalysis and 10.1% (63) diagnosed following clinical
160 examination alone. At diagnosis, 14.4% (90) had urine protein: creatinine ratio (UPC) performed and
161 11.4% (71) had imaging. IRIS staging³⁹ was recorded in the EPR of 19.8% (124), with 22.6% (28) in
162 stage one, 46.8% (58) in stage two, 26.3% (74) in stage three and 14.6% (41) in stage four. Serum
163 creatinine was recorded in the EPR of 45.0% (281). When categorised by serum creatinine
164 concentration, 5.3% (15) were in IRIS stage one, 53.7% (151) in stage two, 26.3% (74) in stage three
165 and 14.6% (41) in stage four at diagnosis. During monitoring, repeated biochemistry was carried out
166 in 32.6% (204) of cats and blood pressure measured in 25.6% (160). Just over half (51.2%; 83) of
167 those CKD cases where blood pressure was measured were co-morbidly diagnosed with
168 hypertension.

169 The most common treatment prescribed to cats diagnosed with CKD was a proprietary renal diet
170 (63.2%; 395) (Table 2). Just over a fifth of cats (22.8%; 142) had no recorded treatment for CKD, with
171 over half of these (54.9%; 78) being euthanised within 7 days of CKD diagnosis.

172 Risk factor analysis

173 The following variables were found to be broadly associated ($p < 0.2$) with incident CKD diagnosis
174 and carried forward to the multivariable analysis: bodyweight, breed, heart auscultation
175 abnormality, presence of goitre, vaccination, NSAID treatment, days since previous anaesthetic,
176 hyperthyroidism, arthritis, cystitis, and hepatopathy (all diagnosed prior to CKD).

177 Cats with no age recorded were excluded from multivariable analysis (8 cases and 8 controls). Table
178 3 reports the risk factors associated with diagnosis of CKD in the multivariable analysis. Hyperthyroid
179 cats, purebred cats, the absence of a recorded goitre, the presence of a heart auscultation
180 abnormality, long term NSAID treatment, no cardiomyopathy diagnosis, no anaesthetic within one
181 year of diagnosis and a bodyweight $< 3.5\text{kg}$ at diagnosis were all associated with increased risk of
182 CKD diagnosis (Table 3). The model had good fit (Hosmer-Lemeshow $p=0.46$) and good predictive
183 ability (area under the ROC curve 0.81).

184 Survival analysis

185 Three hundred and eighty (60.8%) cats had death recorded in the EPR during the follow up to the
186 end of 2015; with 90.3% (343) of these cats being euthanised. The most frequently recorded reason
187 for euthanasia included CKD (37.9%; 144) and poor quality of life (22.6%; 86). A third (35.8%; 224) of
188 cats were lost to follow up. Ninety two cats were not seen by a vet following first diagnosis of CKD,
189 most of which (82.6%; 76) were euthanised at diagnosis. Of these cats, 40.8% (31) had biochemistry
190 performed. Of the 15 cats with serum creatinine concentration recorded in their EPR, 66.7% (10)
191 were in IRIS stage 4 CKD.

192 All-cause mortality rate was calculated as 8.1 deaths per 10.0 CKD cat years at risk (95% CI 7.3 – 9.0).

193 The 92 cats that were not seen after diagnosis were excluded from further analysis as, from a clinical
194 perspective, they would not aid any further understanding of prediction of disease progression or
195 treatment effectiveness.

196 Median survival time in cats with at least one day follow up was 388 days following diagnosis of CKD
197 (IQR 88 – 1042 days) (Fig. 2). The following variables were broadly associated ($p < 0.2$) with survival
198 of at least one day following CKD diagnosis at the univariable level: neuter status, breed,
199 bodyweight, reason for presentation, method of diagnosis, heart auscultation, blood pressure, IRIS
200 stage at diagnosis, serum phosphate at diagnosis, UPC at diagnosis, treatments used (renal diet,
201 phosphate binders, potassium supplementation, amlodipine, anabolic steroids, IVFT) , and diagnosis
202 of; periodontal disease, cystitis, cardiomyopathy, hepatopathy, constipation and diabetes mellitus.

203 Table 4 details the associations identified with survival of at least one day following CKD diagnosis in
204 the multivariable Cox proportional hazards model. Serum phosphate at diagnosis, UPC at diagnosis,
205 breed, proprietary diet prescription, IVFT, diagnosis of constipation, body-weight, phosphate binder
206 prescription and cystitis diagnosis were all associated with survival. An interaction with time was
207 identified with the association between serum phosphate at diagnosis and survival. The association
208 of serum phosphate with survival was only identified in the first 400 days following diagnosis of CKD.
209 Proportionality of hazards was met (Scaled schoenfeld residuals $p=0.22$) and the model had good
210 predictive ability (Harrell's C = 0.85).

211 DISCUSSION

212 This study is the largest to date investigating the prevalence of, and risk factors for, CKD diagnosis
213 and survival following diagnosis in cats attending primary-care practices in the UK. Prevalence of CKD
214 in cats attending VetCompass™ practices was estimated as 1.2% (95% CI 1.1% - 1.3%) increasing to
215 3.6% (95% CI 3.3% - 3.8%) in cats aged ≥ 9 years. The large size of the study population suggests that
216 this prevalence value is likely to be reasonably generalizable to the UK primary-practice attending
217 cat population. The overall prevalence was 6 times higher than the prevalence previously reported in
218 dogs from the same database, and the median survival time following diagnosis in cats was found to
219 be 1.7 times that in dogs, suggesting that CKD results in a greater burden of disease in cats than dogs
220 in primary-care practice due to both higher prevalence and duration³⁴.

221 In the current study, most cats (66%) were diagnosed with CKD once clinical signs were present, with
222 many cats showing two or more clinical signs at diagnosis. It has previously been reported that
223 clinical signs of CKD do not occur until at least 75% of kidney function has been lost ¹⁰. This suggests
224 that CKD is underdiagnosed in this population, as those cats with sub-clinical disease may be missed.
225 This conclusion is supported by the limited number of diagnoses made during geriatric health
226 checks, despite previous evidence that up to 15% of apparently healthy geriatric cats have evidence
227 of CKD after biochemistry and urinalysis ³¹ and up to 30% of geriatric cats develop azotaemia within
228 12 months ^{14,23}. The limited proportion of cats diagnosed following a health check suggests that
229 these are not carried out routinely, indicating there may be many older cats that have undiagnosed
230 subclinical CKD. This could impact on morbidity and cause a reduction in quality of life associated
231 with CKD, as earlier diagnosis allows for early implementation of treatments that can slow
232 progression of disease, limiting development of clinical signs ⁴³.

233 Monitoring of cats diagnosed with CKD was limited in the current study, with a minority of cats
234 receiving repeated biochemistry tests, UPC analyses or BP measurements. This is consistent with
235 findings from a study on monitoring of hyperthyroidism in cats in the UK and a questionnaire
236 response from owners of cats with CKD ^{12,44}, despite recommendations to monitor azotaemia, BP
237 and UPC following CKD diagnosis ^{39,45}. Cats with CKD have been found to have 5 times the risk of
238 developing hypertension in comparison to cats without CKD ⁴⁶. It is important to identify
239 hypertension early to instigate treatment to reduce the risk of target organ damage and its
240 associated morbidity ⁴⁷. The limited use of blood pressure measurement indicates that this group of
241 CKD cats may be at increased morbidity risk from hypertension secondary to CKD. It was not possible
242 to extract information from the EPR on whether the decision to not perform these investigations
243 was owner or veterinary dependent, or both. Further study into the decision-making process would
244 aid targeted education for improved monitoring of CKD.

245 In the current study, risk factors associated with CKD diagnosis were similar to those previously
246 identified in other populations, with purebred status^{11,15} and hyperthyroid status^{18,48} found to be
247 associated with CKD diagnosis. The current study is the first to identify long-term NSAID therapy as a
248 risk factor for CKD. A possible explanation for this is chronic low-level nephrotoxicity causing kidney
249 injury that leads to CKD^{49,50}. It is also possible that cats on long-term NSAID therapy represents a
250 form of diagnostic bias because these cats are more likely to receive blood tests than cats not
251 receiving therapy. The protective association found in the current study between a recent
252 anaesthetic and CKD diagnosis is inconsistent with previous research¹⁵. It is plausible that this
253 association is a form of reverse causality whereby veterinary surgeons opt to avoid anaesthesia on
254 cats they consider to be at risk of CKD. The association identified between low bodyweight and CKD
255 diagnosis is likely to indicate reverse causality, as cats diagnosed with CKD are likely to have lost
256 weight in the months leading up to diagnosis⁸.

257 Vaccination²³, periodontal disease^{15,23} and cystitis¹⁵ have previously been reported as risk factors
258 for CKD diagnosis, but were not identified as such in the current study. Differences in study design,
259 study population and methods of data collection and recording are likely to explain why these
260 previously identified risk factors for CKD were not identified by the present study.

261 Similarly to the risk factor analysis, a number of variables found to be associated with survival have
262 been previously identified, including serum phosphate concentration^{7,27}, proteinuria^{25,26} and the
263 use of a proprietary renal diet^{9,28,43}. Serum phosphate concentration was only predictive in the first
264 400 days following diagnosis. This is logical given the mainstay of CKD treatment is reduction of
265 phosphate through proprietary diets and oral phosphate binders, so a single measurement of serum
266 phosphate concentration at diagnosis of CKD is unlikely to be predictive of survival once is
267 successfully implemented.

268 The other variables associated with survival were likely related to disease severity at diagnosis
269 (bodyweight⁸, IVFT⁸ and constipation^{51,52}), or were related to owner management of the cat. It is

270 possible that owners of purebred cats are more likely to pursue investigations and treatments for
271 their cats in comparison to owners of crossbred cats, or that purebred cats may be more likely to be
272 insured, although insurance status has not been shown to be associated with longevity in previous
273 studies⁶. As cystitis is usually a chronic disease in cats, cystitis cases may have more frequent
274 veterinary visits and therefore receive improved veterinary care compared to cats that visited less
275 frequently.

276 There were limitations to the present study. The data were not collected for research purposes, so
277 information may have been inconsistently recorded in all EPRs (i.e. high missing-ness). This was
278 particularly evident for blood test results and possibly resulting in serum creatinine levels and PCV
279 not being associated with survival, despite being previously identified as strong risk factors^{25,26,29}. To
280 ensure adequate power, cats with missing data for these variables were retained in the analyses.
281 The case definition relied on the veterinary surgeons to correctly diagnose CKD rather than a strict
282 definition based on biochemical markers. It is possible that some misclassification of cases could
283 have occurred. Insurance data were not available for this study. Insurance status has been identified
284 as a risk factor for diagnosis of other conditions, so may be a confounder for some of the variables in
285 the final models^{34,53}. As a third of cats were lost to follow up, it is possible that there was bias
286 within the survival estimates. Some of the cats lost to follow up may have died at home or were
287 euthanised at another practice, although it is common for owners to notify veterinary practices of
288 death as most practices send notifications for routine check-ups required.

289 In conclusion, CKD appears to be diagnosed relatively late in the course of the disease in primary
290 care practice. Most cats are diagnosed once clinical signs are present, while monitoring following
291 CKD diagnosis is limited. Increased uptake of routine screening of higher risk cats using urinalysis and
292 biochemistry may identify cats with pre-clinical CKD before clinical signs appear, allowing earlier
293 intervention and a reduction in morbidity and mortality associated with CKD by the application of
294 treatments aimed at slowing progression of the disease. Improved BP monitoring could aid

295 reduction in co-morbidity associated with hypertension and target organ damage. These findings can
296 aid the improved [m](#)anagement, health and welfare of CKD cats in primary-care practice.

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311 REFERENCES

- 312 1. O'Neill DG, Church DB, McGreevy PD, Thomson PC, Brodbelt DC. Prevalence of disorders
313 recorded in cats attending primary-care veterinary practices in England. *Vet J.* 2014
314 Nov;202(2):286–91.

- 315 2. Sanchez-Vizcaino F, Radford A., Newman J, Jones P., Batchelor D, Menacere T, et al.
316 Preliminary characterisation of the cat consultations presenting with renal disease in small
317 animal practices of the UK through SAVSNET, the Small Animal Veterinary Surveillance
318 Network. In: Boehringer Ingelheim: International Renal and Renovascular Symposium. 2015.
319 p. 52.
- 320 3. Bartges JW. Chronic Kidney Disease in Dogs and Cats. *Vet Clin North Am - Small Anim Pract*
321 [Internet]. 2012;42(4):669–92. Available from: <http://dx.doi.org/10.1016/j.cvsm.2012.04.008>
- 322 4. Krawiec DR, Gelberg HB. Chronic Renal Disease in Cats. In: Kirk R, editor. *Current Veterinary*
323 *Therapy X* [Internet]. Philadelphia: Saunders Elsevier; 1989. p. 1170–3. Available from: Lib
324 scanned
- 325 5. Marino CL, Lascelles BDX, Vaden SL, Gruen ME, Marks SL. Prevalence and classification of
326 chronic kidney disease in cats randomly selected from four age groups and in cats recruited
327 for degenerative joint disease studies. *J Feline Med Surg* [Internet]. 2014 Jun 1;16(6):465–72.
328 Available from: <http://jfm.sagepub.com/lookup/doi/10.1177/1098612X13511446>
- 329 6. O'Neill DG, Church DB, McGreevy PD, Thomson PC, Brodbelt DC. Longevity and mortality of
330 cats attending primary care veterinary practices in England. *J Feline Med Surg*. 2015 Feb
331 1;17(2):125–33.
- 332 7. Boyd LM, Langston C, Thompson K, Zivin K, Imanishi M. Survival in Cats with Naturally
333 Occurring Chronic Kidney Disease (2000-2002). *J Vet Intern Med* [Internet]. 2008
334 Sep;22(5):1111–7. Available from: <http://doi.wiley.com/10.1111/j.1939-1676.2008.0163.x>
- 335 8. Elliott J, Barber PJ. Feline chronic renal failure: clinical findings in 80 cases diagnosed between
336 1992 and 1995. *J Small Anim Pract* [Internet]. 1998 Feb [cited 2015 Oct 12];39(2):78–85.
337 Available from: <http://doi.wiley.com/10.1111/j.1748-5827.1998.tb03598.x>

- 338 9. Elliott J, Rawlings JM, Markwell PJ, Barber PJ. Survival of cats with naturally occurring chronic
339 renal failure: effect of dietary management. *J Small Anim Pract* [Internet]. 2000 Jun [cited
340 2016 Jan 21];41(6):235–42. Available from: [http://doi.wiley.com/10.1111/j.1748-](http://doi.wiley.com/10.1111/j.1748-5827.2000.tb03932.x)
341 5827.2000.tb03932.x
- 342 10. Brown SA, Crowell WA, Brown CA, Barsanti JA, Finco DR. Pathophysiology and Management
343 of Progressive Renal Disease. *Vet J*. 1997;154:93–109.
- 344 11. Lulich JP, Osborne CA, O'Brien TD, Polzin DJ. Feline renal failure: Questions, Answers,
345 Questions. *Compend Contin Educ*. 1992;14(2):127–52.
- 346 12. Caney SM. An online survey of dietary and phosphate binder practices of owners of cats with
347 chronic kidney disease. *J Feline Med Surg* [Internet]. 2016 Oct 17; Available from:
348 <http://jfm.sagepub.com/lookup/doi/10.1177/1098612X16672999>
- 349 13. Bijmans ES, Jepson RE, Syme HM, Elliott J, Niessen SJM. Psychometric Validation of a General
350 Health Quality of Life Tool for Cats Used to Compare Healthy Cats and Cats with Chronic
351 Kidney Disease. *J Vet Intern Med* [Internet]. 2016 Jan [cited 2016 Nov 30];30(1):183–91.
352 Available from: <http://doi.wiley.com/10.1111/jvim.13656>
- 353 14. Jepson RE, Brodbelt D, Vallance C, Syme HM, Elliott J. Evaluation of predictors of the
354 development of azotemia in cats. *J Vet Intern Med*. 2009;23(4):806–13.
- 355 15. Greene JP, Lefebvre SL, Wang M, Yang M, Lund EM, Polzin DJ. Risk factors associated with the
356 development of chronic kidney disease in cats evaluated at primary care veterinary hospitals.
357 *J Am Vet Med Assoc* [Internet]. 2014 Feb;244(3):320–7. Available from:
358 <http://avmajournals.avma.org/doi/abs/10.2460/javma.244.3.320>
- 359 16. White J, Norris J, Baral R, Malik R. Naturally-occurring chronic renal disease in Australian cats:
360 a prospective study of 184 cases. *Aust Vet J* [Internet]. 2006 Jun [cited 2016 Jan

361 21];84(6):188–94. Available from: <http://doi.wiley.com/10.1111/j.1751-0813.2006.tb12796.x>

362 17. van Hoek I, Lefebvre HP, Peremans K, Meyer E, Croubels S, Vandermeulen E, et al. Short- and
363 long-term follow-up of glomerular and tubular renal markers of kidney function in
364 hyperthyroid cats after treatment with radioiodine. *Domest Anim Endocrinol*. 2009;36(June
365 2008):45–56.

366 18. Williams TL, Peak KJ, Brodbelt D, Elliott J, Syme HM. Survival and the development of
367 azotemia after treatment of hyperthyroid cats. *J Vet Intern Med*. 2010;24(4):863–9.

368 19. Beatty J. Viral causes of feline lymphoma: retroviruses and beyond. *Vet J* [Internet]. 2014 Aug
369 [cited 2016 Feb 3];201(2):174–80. Available from:
370 <http://www.sciencedirect.com/science/article/pii/S1090023314002238>

371 20. Glick AD, Horn RG, Holscher M. Characterization of feline glomerulonephritis associated with
372 viral-induced hematopoietic neoplasms. *Am J Pathol* [Internet]. 1978 Aug [cited 2016 Jan
373 14];92(2):321–32. Available from:
374 [http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2018289&tool=pmcentrez&ren](http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2018289&tool=pmcentrez&rendertype=abstract)
375 [dertype=abstract](http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2018289&tool=pmcentrez&rendertype=abstract)

376 21. Baxter KJ, Levy JK, Edinboro CH, Vaden SL, Tompkins MB. Renal Disease in Cats Infected with
377 Feline Immunodeficiency Virus. *J Vet Intern Med*. 2012;26(2):238–43.

378 22. Poli A, Tozon N, Guidi G, Pistello M. Renal Alterations in Feline Immunodeficiency Virus (FIV)-
379 Infected Cats: A Natural Model of Lentivirus-Induced Renal Disease Changes. *Viruses*
380 [Internet]. 2012;4(12):1372–89. Available from: <http://www.mdpi.com/1999-4915/4/9/1372/>

381 23. Finch NC, Syme HM, Elliott J. Risk Factors for Development of Chronic Kidney Disease in Cats.
382 *J Vet Intern Med* [Internet]. 2016 Mar;30(2):602–10. Available from:
383 <http://doi.wiley.com/10.1111/jvim.13917>

- 384 24. Reynolds BS, Lefebvre HP. Feline CKD: Pathophysiology and risk factors - what do we know? J
385 Feline Med Surg. 2013;15(S1):3–14.
- 386 25. King JN, Tasker S, Gunn-Moore D a, Strehlau G. Prognostic factors in cats with chronic kidney
387 disease. J Vet Intern Med [Internet]. 2007;21(5):906–16. Available from:
388 papers2://publication/uuid/841BE806-ABD9-4680-9B58-6FE81FF9E296
- 389 26. Syme HM, Markwell PJ, Pfeiffer D, Elliott J. Survival of cats with naturally occurring chronic
390 renal failure is related to severity of proteinuria. J Vet Intern Med. 2006;20:528–35.
- 391 27. Chakrabarti S, Syme HM, Elliott J. Clinicopathological Variables Predicting Progression of
392 Azotemia in Cats with Chronic Kidney Disease. J Vet Intern Med. 2012;26(2):275–81.
- 393 28. Plantinga E a, Everts H, Kastelein a MC, Beynen a C. Retrospective study of the survival of
394 cats with acquired chronic renal insufficiency offered different commercial diets. Vet Rec.
395 2005;157:185–7.
- 396 29. Kuwahara Y, Ohba Y, Kitoh K, Kuwahara N, Kitagawa H. Association of laboratory data and
397 death within one month in cats with chronic renal failure. J Small Anim Pract [Internet]. 2006
398 Aug [cited 2015 Dec 17];47(8):446–50. Available from:
399 <http://www.ncbi.nlm.nih.gov/pubmed/16911112>
- 400 30. Lundbol S. Prevalence study on chronic kidney disease in apparently healthy middle-aged and
401 geriatric cats. In: Boehringer Ingelheim: International Renal and Renovascular Symposium.
402 2015. p. 50.
- 403 31. Paepe D, Verjans G, Duchateau L, Piron K, Ghys L, Daminet S. Routine health screening:
404 findings in apparently healthy middle-aged and old cats. J Feline Med Surg [Internet].
405 2013;15(1):8–19. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23254237>
- 406 32. O'Neill DG, Church DB, McGreevy PD, Thomson PC, Brodbelt DC. Approaches to canine health

- 407 surveillance. *Canine Genet Epidemiol* [Internet]. 2014;1(1):2. Available from:
408 <http://www.cgejournal.org/content/1/1/2>
- 409 33. Venom Coding Group. *Veterinary Nomenclature* [Internet]. 2016 [cited 2016 Oct 31].
410 Available from: <http://www.venomcoding.org/VeNom/Welcome.html>
- 411 34. O'Neill DG, Elliott J, Church DB, McGreevy PD, Thomson PC, Brodbelt DC. Chronic kidney
412 disease in dogs in UK veterinary practices: prevalence, risk factors, and survival. *J Vet Intern
413 Med* [Internet]. 2013;27(4):814–21. Available from:
414 <http://www.ncbi.nlm.nih.gov/pubmed/23647231>
- 415 35. Pearce N. Classification of epidemiological study designs. *Int J Epidemiol* [Internet]. 2012 Apr
416 [cited 2016 Nov 30];41(2):393–7. Available from:
417 <http://www.ncbi.nlm.nih.gov/pubmed/22493323>
- 418 36. Wakeling J, Moore K, Elliott J, Syme H. Diagnosis of hyperthyroidism in cats with mild chronic
419 kidney disease. *J Small Anim Pract* [Internet]. 2008 Jun [cited 2016 Aug 23];49(6):287–94.
420 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18422499>
- 421 37. Centers for Disease Control and Prevention. *Epi Info V 7.1.4.0* [Internet]. 2014. Available
422 from: <http://wwwn.cdc.gov/epiinfo/7/>
- 423 38. International Cat Care. *Cat Breeds* [Internet]. 2015 [cited 2016 Aug 1]. Available from:
424 <http://icatcare.org/advice/cat-breeds>
- 425 39. IRIS. *International Renal Interest Society* [Internet]. 2015 [cited 2015 Oct 26]. Available from:
426 <http://www.iris-kidney.com/>
- 427 40. Birnbaum ZW, Sirken MG. *Design of Sample Surveys to Estimate the Prevalence of Rare
428 Diseases : Three Unbiased Estimates*. Washington, D.C; 1965.
- 429 41. Hosmer DW, Lemeshow S. *Applied Logistic Regression*. 2nd ed. Hoboken, New Jersey: John

- 430 Wiley & Sons, Inc; 2000.
- 431 42. Dohoo IR. *Veterinary Epidemiologic Research*. 2nd ed. Charlottetown, Canada: VER Inc; 2010.
- 432 43. Ross SJ, Osborne C a, Kirk C a, Lowry SR, Koehler L a, Polzin DJ. Clinical evaluation of dietary
433 modification for treatment of spontaneous chronic kidney disease in cats. *J Am Vet Med*
434 *Assoc* [Internet]. 2006;229(6):949–57. Available from: [papers2://publication/uuid/A785DF61-](https://pubmed.ncbi.nlm.nih.gov/16444444/)
435 [4AAA-43F9-83CA-4E2ED2E2D058](https://pubmed.ncbi.nlm.nih.gov/16444444/)
- 436 44. Higgs P, Murray JK, Hibbert A. Medical management and monitoring of the hyperthyroid cat:
437 a survey of UK general practitioners. *J Feline Med Surg* [Internet]. 2014;16(10):788–95.
438 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24423813>
- 439 45. Brown SA. Management of chronic kidney disease. In: Elliott J, Grauer GF, editors. *BSAVA*
440 *manual of canine and feline nephrology and urology*. 2nd ed. Gloucester, UK: British Small
441 *Animal Veterinary Association*; 2009. p. 223–30.
- 442 46. Bijsmans ES, Jepson RE, Chang YM, Syme HM, Elliott J. Changes in Systolic Blood Pressure
443 over Time in Healthy Cats and Cats with Chronic Kidney Disease. *J Vet Intern Med* [Internet].
444 2015 May;29(3):855–61. Available from: <http://doi.wiley.com/10.1111/jvim.12600>
- 445 47. Brown S, Atkins C, Bagley R, Carr A, Cowgill L, Davidson M, et al. Guidelines for the
446 Identification, Evaluation, and Management of Systemic Hypertension in Dogs and Cats. *J Vet*
447 *Intern Med* [Internet]. 2007 May;21(3):542–58. Available from:
448 <http://doi.wiley.com/10.1111/j.1939-1676.2007.tb03005.x>
- 449 48. Van Hoek I, Daminet S. Interactions between thyroid and kidney function in pathological
450 conditions of these organ systems: A review. *Gen Comp Endocrinol* [Internet].
451 2009;160(3):205–15. Available from: <http://dx.doi.org/10.1016/j.ygcen.2008.12.008>
- 452 49. Khan TM, Khan KNM. Acute kidney injury and chronic kidney disease. *Vet Pathol* [Internet].

453 2015 May 1 [cited 2015 Nov 13];52(3):441–4. Available from:
454 <http://vet.sagepub.com/content/52/3/441>

455 50. Papich M. Drugs and the kidneys: Preventing and managing their potential adverse effects. In:
456 Proceedings of the NAVC North American Veterinary Conference [Internet]. Orlando, Florida:
457 Internation Veterinary Information Service; 2005. p. 857–60. Available from:
458 <http://www.ivis.org/proceedings/navc/2005/SAE/357.pdf?LA=1>

459 51. Birchard SJ, Sherding RG, Sherding RG. Chapter 74 – Constipation and Anorectal Diseases. In:
460 Saunders Manual of Small Animal Practice. 2006. p. 831–44.

461 52. Korman RM, White JD. Feline CKD: Current therapies - what is achievable? J Feline Med Surg
462 [Internet]. 2013;15 Suppl 1(2013):29–44. Available from:
463 <http://www.ncbi.nlm.nih.gov/pubmed/23999184>

464 53. Mattin M, O’Neill D, Church D, McGreevy PD, Thomson PC, Brodbelt D. An epidemiological
465 study of diabetes mellitus in dogs attending first opinion practice in the UK. Vet Rec
466 [Internet]. 2014 Apr 5;174(14):349–349. Available from:
467 <http://veterinaryrecord.bmj.com/cgi/doi/10.1136/vr.101950>

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475 TABLES AND FIGURES

476 Figure 1: Flow chart showing case and control selection and inclusion in each study.

477 EPR: Electronic Patient Record

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479 Figure 2: Kaplan-Meier survival curve of all cats diagnosed with CKD in UK primary-care practice from
480 1/1/2012 – 31/12/2013 with at least 1 day of follow up (n=533)

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484 Table 1: Prevalence of chronic kidney disease in cats attending primary-care practice in the UK from

485 1st January 2012 to 31st December 2013

		Denominator	Cases	Prevalence ¹	95% Confidence interval
Overall		353448	961	1.2%	1.1% - 1.3%
Age (years)	0 - < 4.5	118136	17	0.1%	0.02% - 0.07%
	4.5 - < 9	67842	58	0.4%	0.3% - 0.5%
	9 - < 13.5	45597	212	1.9%	1.6% - 2.1%
	13.5 - < 18	30586	478	4.7%	4.3% - 5.1%
	18 - < 22.5	7672	186	6.5%	5.6% - 7.4%
	22.5 - < 27	317	1	1.1%	0% - 3.2%
Breed	Crossbreed	341791	800	1.1%	1.05% - 1.20%
	Burmese	3173	44	5.0%	3.54% - 6.35%
	British Shorthair	7057	14	0.9%	0.42% - 1.33%
	Bengal	4167	3	0.3%	0% - 0.73%
	Persian	4202	25	2.3%	1.44% - 3.24%
	Siamese	2990	22	2.9%	1.72% - 4.08%
	Main Coon	2428	4	0.8%	0.02% - 1.48%
	Other pedigree	11531	38	1.5%	1.00% - 1.92%
	Unknown	3081	11	1.6%	0.66% - 2.51%

486 ¹ Calculated using stratified analysis

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492 Table 2: Treatments prescribed to 549 cats attending primary-care practice in the UK and diagnosed
 493 with chronic kidney disease and not euthanased at diagnosis.

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Treatment	N (%)
Proprietary renal diet	395 (63.2%)
Antiproteinuric treatment	
Benazepril	221 (35.4%)
Telmisartan	23 (3.7%)
Ramipril	2 (0.3%)
Imidapril	1 (0.2%)
Intravenous fluid therapy	121 (19.4%)
Oral Phosphate binder	91 (14.6%)
Amlodipine	66 (10.6%)
Anabolic steroid	61 (9.8%)
Multivitamin injections	61 (9.8%)
Subcutaneous fluid therapy	19 (3.0%)
Potassium supplementation	10 (1.6%)
Anti-nausea medication	
H ₂ blocker	29 (4.6%)
Maropitant	20 (3.2%)
Metoclopramide	4 (0.6%)

520 Table 3: Multivariable logistic regression analysis for diagnosis of chronic kidney disease in cats
 521 attending primary-care practice in the UK from 1st January 2012 to 31st December 2013. Adjusted for
 522 vet group effects.

	Variable	Case N (%)	Control N (%)	Odds Ratio	95% Confidence Interval	p-value	
						Walds test	Likelihood ratio test
Age	< 9 years	58 (9.3)	89 (9.3)	Reference			0.2
	≥ 9 years	559 (89.4)	559 (89.4)	0.75	0.48 - 1.15	0.18	
Purebred status	Crossbred	530 (84.8)	553(88.5)	Reference			0.03
	Purebred	87 (13.9)	59(9.4)	1.72	1.15 - 2.58	0.008	
	Unknown	8 (1.3)	13(2.1)	1.07	0.38 - 2.93		
Goitre	No	189 (30.2)	33 (5.3)	Reference			0.04
	Yes	61 (9.8)	17(2.7)	0.42	0.21 - 0.85	0.02	
	Not recorded	375 (60.0)	575(92.0)	0.13	0.08 - 0.19		
Heart auscultation abnormal	No	307 (49.1)	266 (45.6)	Reference			0.08
	Yes	113 (18.1)	57 (9.1)	1.64	1.06 - 2.54	0.03	
NSAID¹	Not Recorded	205 (32.8)	302 (48.3)	1.12	0.83 - 1.52		
	No treatment recorded	389 (62.2)	350 (56.0)	Reference			0.02
	One off treatment recorded	142 (22.7)	182 (29.1)	0.81	0.60 - 1.11	0.19	
	Repeated one off treatment recorded	51 (8.2)	79 (12.6)	0.7	0.44 - 1.10	0.12	
Hyperthyroidism	Long term treatment recorded	43 (6.9)	14 (2.2)	2.34	1.12 - 4.88	0.02	
	No	554 (88.6)	615 (98.4)	Reference			<0.0001
	Yes	71 (11.4)	10 (1.6)	5.7	2.78 - 11.68	<0.001	
Cardiomyopathy	No	612 (97.9)	606 (97.0)	Reference			0.003
	Yes	13 (2.1)	19 (3.0)	0.26	0.10 - 0.65	0.004	
Days since last recorded anaesthetic	0-179 days	40 (6.4)	71 (11.4)	Reference			0.005
	180 - 364 days	20 (3.2)	32 (5.12)	1.21	0.55 - 2.70	0.63	
	No anaesthetic recorded within 1 year	565 (90.4)	522 (83.5)	2.07	1.28 - 3.36	0.003	
Body weight (kg)	0 - 3	51 (8.2)	66 (10.6)	Reference			<0.0001
	3.01 - 3.5	51 (8.2)	58 (9.3)	1.03	0.57 - 1.85	0.92	
	3.51 - 4.05	53 (8.5)	53 (8.5)	0.84	0.46 - 1.54	0.58	
	4.07 - 4.78	82 (13.1)	31 (5.0)	0.36	0.19 - 0.67	0.001	
	4.85 - 9.6	81 (13.0)	22 (3.5)	0.26	0.13 - 0.51	<0.001	
	No weight recorded	307 (49.1)	395 (63.2)	0.7	0.40 - 1.3		

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524 ¹NSAID: Non-steroidal anti-inflammatory drug

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531 Table 4: Multivariable Cox proportional hazards model for survival of at least one day following
 532 chronic kidney disease diagnosis in 533 cats attending primary-care practice in the UK from 1st
 533 January 2012 to 31st December 2013 with follow up. Adjusted for vet group effects.

Variable		N	Deaths	Hazard Ratio	95% Confidence Interval	Walds test	p-value Likelihood ratio test	
Purebred status	Crossbred	446	261	Reference			0.001	
	Purebred	80	40	0.57	0.40 - 0.81	0.002		
	Unknown	7	3	0.3	0.09 - 0.96			
Serum phosphate at diagnosis	0-400 days after diagnosis	<1.5mmol/l	20	4	Reference		<0.0001	
	>400 days after diagnosis	1.5mmol/l +	68	47	5.78	1.91 - 17.32		0.002
		Not recorded	445	190	4.35	1.49 - 12.71		
		<1.5mmol/l	12	7	Reference			
	UPC ¹	1.5mmol/l +	Not recorded	11	6	0.47		0.15 - 1.44
Not recorded			159	50	0.45	0.20 - 1.01		
0-0.2			28	6	Reference		0.01	
0.21-0.4			19	8	3	1.02 - 8.34	0.05	
Renal diet	No	>0.4	15	11	4.96	1.78 - 13.81	0.002	
		Not recorded	471	279	2.77	1.21 - 6.35		
Phosphate Binder	No	Yes	143	94	Reference		0.0009	
		Yes	390	210	0.58	0.45 - 0.75	<0.001	
IVFT ²	No	Yes	442	257	Reference		0.02	
		Yes	91	47	0.68	0.48 - 0.95	0.02	
Cystitis	No	Yes	419	222	Reference		<0.0001	
		Yes	114	82	1.97	1.48 - 2.62	<0.001	
Constipation	No	Yes	440	262	Reference		0.02	
		Yes	93	42	0.69	0.49 - 0.97	0.02	
		Before CKD diagnosis	8	8	Reference		0.01	
		At CKD diagnosis	3	2	0.35	0.07 - 1.78	0.2	
Body weight (kg)	No constipation	After CKD diagnosis	10	5	0.15	0.05 - 0.50	0.002	
		1.65 - 2.78	512	289	0.23	0.11 - 0.51	<0.001	
		2.8 - 3.23	39	31	Reference		0.0003	
		3.25 - 3.65	37	25	0.87	0.50 - 1.51	0.62	
		3.67 - 4.3	45	30	0.54	0.32 - 0.92	0.02	
		4.3 - 7.5	43	29	0.47	0.28 - 0.80	0.005	
		No weight recorded	44	25	0.48	0.27 - 0.83	0.009	
		325	164	1.4	0.82 - 2.41			

534 ¹ Urine protein: creatinine ratio ²IVFT: Intravenous fluid therapy

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