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1 **Exploring early life events including diet in cats presenting for gastrointestinal signs in**  
2 **later life**

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15

16

17 Abstract

18 Our study aimed to determine if certain early life events were more prevalent in cats  
19 presenting to veterinary practices specifically for gastrointestinal signs on at least 2 occasions  
20 between 6 and 30 months of age. Data from an owner-completed questionnaire for 1,212 cats  
21 before 16 weeks of age and subsequent questionnaires for the same cats between 6 and 30  
22 months of age were reviewed.

23 Of the 1,212 cats included, 30 visited a veterinary practice for gastrointestinal signs on two or  
24 more occasions. Of the early life events recorded, cats reported with vomiting, diarrhoea or  
25 both and/or those not exclusively fed commercial diet(s) that meet the WSAVA Global  
26 Nutrition Committee (GNC) guidelines before 16 weeks of age were more likely to visit  
27 veterinary practices specifically for gastrointestinal signs on at least two occasions between 6  
28 and 30 months of age ( $p < 0.001$ , odd's ratio (OR)=2.64, 95% confidence interval  
29 (CI)=1.66-4.22 and  $p = 0.030$ , OR=1.51, 95% CI=1.04-2.22, respectively).

30 Ensuring cats exclusively consume commercial diet(s) that meet the WSAVA GNC  
31 guidelines, and further studies identifying specific aetiologies for vomiting and diarrhoea  
32 before 16 weeks of age to enable prevention may reduce the number of cats subsequently  
33 presenting to primary care veterinary practices for repeated gastrointestinal signs.

## 34 Introduction

35 The exposome is a term that has been used to describe the sum of all environmental factors a  
36 human is exposed to during their lifetime, beginning *in utero* and ending at death (1). The  
37 exposome together with genetic susceptibility may impact the intestinal microbiota and  
38 mucosal immune system resulting in chronic relapsing gastrointestinal disease (2). There is  
39 increasing evidence that early life exposures in humans are important to chronic disease risk  
40 later in life (3, 4). In addition, studies have shown that a number of early life factors may  
41 influence the development of immune tolerance as well as the composition of the intestinal  
42 microbiota (5-7). Therefore, many studies have specifically focused on identifying early life  
43 risk factors for the development of chronic relapsing gastrointestinal diseases in humans,  
44 such as inflammatory bowel disease (IBD) and functional gastrointestinal disorders (8-11).  
45 Identification of such factors, particularly in early life is important to increase our  
46 understanding of disease pathogenesis as well as enable disease prevention and treatment.

47 The effect of the exposome on an animal's chronic disease risk has very rarely been studied:  
48 one study showed that dogs that survive canine parvovirus infection had a significantly  
49 higher risk of developing chronic gastrointestinal signs later in their lives (12). Currently no  
50 studies exist assessing early life events in cats that may serve as risk factors for subsequent

51 chronic gastrointestinal signs. Therefore, this study aimed to identify if certain events in early  
52 life were more prevalent in cats presenting at least twice to primary care veterinary practices  
53 specifically for gastrointestinal signs between 6 and 30 months of age compared to those cats  
54 that had never visited for gastrointestinal signs. Identification of potential early life risk  
55 factors may help in the prevention of repeated gastrointestinal signs in cats.

56

## 57 Materials and Methods

### 58 Cats

59 Cats used in this study were those that had previously been prospectively enrolled onto the  
60 Bristol Cats Study, a long-term longitudinal study of cat health, welfare and behaviour.  
61 Owners in the United Kingdom were recruited onto the study between May 1, 2010 and  
62 December 31, 2013. During 2010, enrolment was restricted to owners who lived in Bristol,  
63 and then was extended to the whole of the United Kingdom from January 1, 2011 in order to  
64 increase numbers.

### 65 Data collection

66 Owners were asked to complete a questionnaire at enrolment onto the Bristol Cats Study

67 when their cat was between 8 and 16 weeks of age (Q1). The owners of the same cats  
68 completed subsequent questionnaires when their cats reached the ages of 6 months (Q2), 12  
69 months (Q3), 18 months (Q4), 30 months (Q5), 48 months (Q6) and then at annual time  
70 intervals. Data for our study were taken from the first 5 questionnaires (Q1-5).  
71 Questionnaires were available to participating owners either in an online or in paper format.  
72 Most questions were presented in a multiple-choice format and questionnaires took  
73 approximately 10 to 15 minutes to complete. Further details regarding cohort recruitment and  
74 questionnaire design and distribution can be found in Murray et al., 2017 (13) and in the  
75 supplemental data for that manuscript.

#### 76 Cases and controls

77 Cases were defined as those cats that were reported by their owners to have visited a  
78 veterinary practice, specifically for gastrointestinal signs (vomiting, diarrhoea or both) at one  
79 or all of the 4 time-points (Q2, Q3, Q4, Q5). The questionnaires did not specifically address  
80 the diagnostic investigation, definitive or tentative diagnosis or treatment at these visits.  
81 Controls were those cats that were reported by their owners to have never visited a veterinary  
82 practice specifically for gastrointestinal signs (vomiting, diarrhoea or both) at all of the 4  
83 time-points (Q2, Q3, Q4, Q5).

84 Potential early life risk events

85 Questionnaire 1, which had been completed when the cats were between 8 to 16 weeks of age  
86 was reviewed for all cats in the case and control groups and only information on the  
87 following 4 early life events were recorded for each: 1) name of commercial diets fed and  
88 whether each complied with the World Small Animal Veterinary Association (WSAVA)  
89 Global Nutrition Committee (GNC) guidelines, 2) proportion of diet fed that consisted of raw  
90 fresh food, cooked fresh food and cow's milk or cream (owners could select one of 5 options:  
91 all of the diet,  $\geq 50\%$  of diet,  $< 50\%$  of diet, occasionally or never), 3) owner reported  
92 vomiting, diarrhoea or both and 4) presence of owner reported helminths in the faeces.

93 To determine whether the commercial diet each cat was consuming complied with the  
94 WSAVA GNC guidelines, each manufacturer was contacted and asked to reply to the 8  
95 questions outlined in section A of the web link<sup>1</sup>. Diets were considered to meet the WSAVA  
96 GNC guidelines if the manufacturer could satisfactorily address all of the questions.

97 Ethical considerations

98 The University of Bristol granted ethical approval for the study (VIN/17/049).

99 Data analysis and statistics

100 Analyses were performed using a computer software package (IBM SPSS Statistics Version  
101 23). Univariable and multivariable ordinal regression models were constructed to assess  
102 associations between the following 4 early life events, identified before 16 weeks of age: 1)  
103 whether cats exclusively consumed commercial diet(s) that complied with the WSAVA GNC  
104 guidelines, 2) proportion of diet fed that was raw fresh food, cooked fresh food and cow's  
105 milk or cream, 3) owner reported vomiting, diarrhoea or both, 4) presence of owner reported  
106 helminths in the faeces and the frequency of owner reported visits to veterinary practice  
107 specifically for gastrointestinal signs between 6 and 30 months of age. Feeding exclusively  
108 commercial diet(s) that complied with the WSAVA GNC guidelines, owner reported  
109 vomiting, diarrhoea or both and the presence of owner reported helminths in the faeces were  
110 entered into the general linear models as yes/no. The proportion of diet fed that consisted of  
111 raw fresh food, cooked fresh food and cow's milk or cream were entered into the general  
112 linear model as categorical data with 1 representing all of the diet, 2 as 50% or more of the  
113 diet, 3 as less than 50% of the diet, 4 as occasionally and 5 as never. Variables associated  
114 with the frequency of owner reported visits to veterinary practices specifically for  
115 gastrointestinal signs between 6 and 30 months of age with p-value <0.2 in the univariable  
116 analysis were entered into the multivariable analyses. In the multivariable regression models,



117 analyses were performed in a backward stepwise manner. All variables were initially  
118 included, and the variable with the highest p-value was removed until all remaining variables  
119 had a p-value  $<0.05$ . Multicollinearity was assessed by evaluating the correlation matrix.  
120 Odd's ratios (OR) with 95% confidence intervals (CI) were also calculated.

## 121 Results

### 122 Cats

123 One thousand two hundred and twelve cats that were initially enrolled onto the study between  
124 8 and 16 weeks of age had all subsequent questionnaires (Q2-Q5), from 6 to 30 months of  
125 age available for review.

126 One thousand and fourteen cats were reported to have never visited a veterinary practice  
127 specifically for gastrointestinal signs between 6 and 30 months of age. One hundred and sixty  
128 eight cats were reported by their owners to have visited a veterinary practice on one occasion  
129 specifically for gastrointestinal signs between 6 and 30 months of age. A separate 26 cats  
130 were seen twice, of which 12 cats were reported to have visited at both the 18 month and 30  
131 month questionnaire, 7 cats at both the 12 month and 18 month questionnaire, 5 cats at both  
132 the 12 month and 30 month questionnaire, of which one was reported to be diagnosed with

133 inflammatory bowel disease on intestinal histopathology, one cat at both the 6 month and 12  
134 month questionnaire and one cat at both the 6 month and 18 month questionnaire. A separate  
135 4 cats visited 3 times, with all 4 reported to have visited at the 12 month, 18 month and 30  
136 month questionnaire (figure 1).

137 Early life events associated with the frequency of visits to a veterinary practice specifically  
138 for gastrointestinal signs between 6 and 30 months of age.

139 In the univariable analyses, the proportion of diet fed that consisted of raw fresh food, cooked  
140 fresh food, cow's milk or cream and the presence of owner reported helminths in the faeces  
141 before 16 weeks of age did not significantly affect the frequency of cat visits to veterinary  
142 practices specifically for gastrointestinal signs between 6 and 30 months of age ( $p > 0.05$ , table  
143 1). Cats with reported vomiting, diarrhoea or both or those not exclusively fed commercial  
144 diet(s) that meet the WSAVA Global Nutrition Committee (GNC) guidelines before 16  
145 weeks of age were significantly associated with the frequency of visits to a veterinary  
146 practice specifically for gastrointestinal signs between 6 and 30 months of age in the  
147 univariable analyses ( $p < 0.001$ ,  $OR = 2.60$ ,  $95\% \text{ CI} = 1.64-4.26$  and  $p = 0.038$ ,  $OR = 1.49$ ,  $95\%$   
148  $CI = 1.23-2.17$ , respectively, table 1).

149 The proportion of raw fresh food fed, proportion of cooked fresh food fed, reported vomiting,  
150 diarrhoea or both and whether cats were exclusively consuming commercial diet(s) that meet  
151 the WSAVA GNC guidelines before 16 weeks of age were analysed further in the final  
152 multivariable model, as these variables had a p-value of less than 0.2 in the univariable  
153 analyses (table 1). The multivariable model showed that vomiting, diarrhoea or both and/or  
154 those not exclusively fed commercial diet(s) that meet the WSAVA Global Nutrition  
155 Committee (GNC) guidelines before 16 weeks of age were significantly associated with the  
156 frequency of visits to a veterinary practice specifically for gastrointestinal signs between 6  
157 and 30 months of age ( $p < 0.001$ , OR=2.64, 95% CI=1.66-4.22 and  $p = 0.030$ , OR=1.51, 95%  
158 CI=1.04-2.22, respectively, table 2).

## 159 Discussion

160 Environmental factors are important triggers for many chronic gastrointestinal diseases in  
161 humans, including IBD (14). Our study for the first time demonstrated early life events that  
162 may act as significant risk factors for cats that subsequently visit veterinary practices  
163 specifically for gastrointestinal signs on two or more occasions between 6 and 30 months of  
164 age. Our study identified owner-reported vomiting, diarrhoea or both and/or those not  
165 exclusively fed commercial diet(s) that meet the WSAVA Global Nutrition Committee

166 (GNC) guidelines before 16 weeks of age as being potentially significant risk factors for cats  
167 presenting to veterinary practices specifically for gastrointestinal signs on two or more  
168 occasions between 6 and 30 months of age.

169 Infectious gastroenteritis has been shown to be a significant risk factor for the subsequent  
170 development of IBD and functional gastrointestinal disorders in humans (15, 16). Similarly,  
171 dogs that survive canine parvovirus infection have a significantly higher risk of developing  
172 chronic gastrointestinal signs later in their lives (12). Unfortunately, the aetiology of  
173 vomiting and diarrhoea before 16 weeks of age in the cats in our study was unknown.  
174 However, in humans the presence of an acute inflammatory response in the gastrointestinal  
175 tract rather than a specific aetiological pathogen may be responsible for the subsequent  
176 development of IBD (15). Therefore, the presence of gastrointestinal inflammation causing  
177 episodes of vomiting and diarrhoea regardless of disease aetiology in our cats before 16  
178 weeks of age may trigger an initial over compensated response, which may then lead to over  
179 activation of the intestinal mucosal immune system leading to chronic inflammation.  
180 Alternatively, episodes of gastrointestinal inflammation before 16 weeks of age may cause  
181 lasting changes in the microbiota or gut epithelial barrier, which may subsequently increase  
182 susceptibility to gastrointestinal inflammation, resulting in these cats being frequently

183 presented to veterinary practices for their signs. Therefore, determining the aetiology of  
184 vomiting and diarrhoea in cats before 16 weeks of age may help to identify areas for  
185 prevention, which may then reduce the number of cats presenting to veterinary practices  
186 specifically for repeated gastrointestinal signs.

187 In this study, cats that were not exclusively fed commercial diet(s) that meet the WSAVA  
188 Global Nutrition Committee (GNC) guidelines before 16 weeks of age were more likely to  
189 subsequently present to veterinary practices specifically for gastrointestinal signs on two or  
190 more occasions. The WSAVA GNC guidelines outlines 8 questions for manufacturers of the  
191 diet to help ensure that a reputable and knowledgeable company that uses strict quality  
192 control measures formulates the food. According to the WSAVA GNC guidelines, if the  
193 manufacture is not able to answer the 8 questions satisfactorily, then owners should be  
194 cautious with feeding that brand. The results of our study further justify the need to ensure  
195 that cats are exclusively receiving commercial diet(s) that meets the WSAVA GNC  
196 guidelines before 16 weeks of age. Feeding a diet that does not comply with the WSAVA  
197 GNC guidelines may raise concerns regarding the source of ingredients, nutritional  
198 composition and quality control of the diet, factors which may impact on the gastrointestinal  
199 mucosal immune system, microbiota and intestinal permeability. However, further studies

200 would be needed to determine if any attributes of these diets are specifically implicated in  
201 disease pathogenesis.

202 Pre-illness dietary risk factors such as increased fat has repeatedly been shown to predispose  
203 to IBD in humans (17, 18). Unfortunately, due to the time frame of this study and the lack of  
204 detailed information regarding flavours of commercial diets fed, it was not possible to  
205 determine specific macronutrient profiles of diets fed before 16 weeks of age that may be  
206 associated with the frequency of cats presenting to veterinary practices specifically for  
207 gastrointestinal signs. In addition, as this study specifically focused on early life events,  
208 dietary changes and commercial diets that were fed prior to cats presenting to veterinary  
209 practices for gastrointestinal signs during the 30 month study period was not specifically  
210 assessed. Another limitation of this study was that the underlying definitive diagnosis for the  
211 gastrointestinal signs for which cats were presented to veterinary practices was unknown as  
212 medical records were unavailable for review for all cats. However, one owner commented on  
213 the questionnaire that their cat was diagnosed with IBD on intestinal biopsy at one of the  
214 visits. However, all cats in this study are continuing to be monitored with annual  
215 questionnaires and therefore in the future this may reveal definitive diagnoses for their  
216 gastrointestinal signs. In addition, as our study only included questionnaires until 30 months

217 of age, cats that present later in life to veterinary practices specifically for repeated  
218 gastrointestinal signs will be missed. Therefore, a follow-up study to assess these cats when  
219 they reach 10 to 12 years of age or have a definitive diagnosis for their gastrointestinal signs  
220 may give us more definitive information with regards to which early life events are  
221 significantly associated with chronic gastrointestinal disease. A follow-up study may also  
222 allow the inclusion of more cats that had presented to veterinary practices specifically for  
223 gastrointestinal signs on two or more occasions, which may allow for stronger conclusions to  
224 be made regarding early life events in these cats. Also, as the medical records were  
225 unavailable for the cats, the authors were unable to rule out any association of the significant  
226 early life events identified in this study with additional non-gastrointestinal diseases or  
227 conditions in these cats. Therefore, further studies are likely warranted to determine if owner  
228 reported vomiting, diarrhoea or both and/or not exclusively feeding commercial diet(s) that  
229 meet the WSAVA GNC guidelines before 16 weeks of age are associated with additional  
230 non-gastrointestinal diseases or conditions in cats. A final limitation of this study was  
231 additional early life risk factors that have been identified in humans with chronic  
232 gastrointestinal diseases, such as antibiotic use, early weaning and caesarean delivery were  
233 not investigated in our study. Studies have implicated antibiotic use in childhood with

234 subsequent increased risk of developing IBD (10, 19). Unfortunately, our study was unable to  
235 determine if antibiotic use in early life increased the risk of cats presenting to veterinary  
236 practices, as this information was unavailable from questionnaire 1. Therefore, future studies  
237 should specifically aim to determine if antibiotic use in early life affects the frequency of cats  
238 presenting to veterinary practices specifically for gastrointestinal signs. Determining if  
239 antibiotic use early in life predisposes to the development of repeated gastrointestinal signs in  
240 cats is important as this may ensure increased discretion of when to prescribe antibiotic  
241 therapy.

242 In conclusion, our study for the first time showed that cats that had reported vomiting,  
243 diarrhoea or both and/or those not exclusively fed commercial diet(s) that meet the WSAVA  
244 Global Nutrition Committee (GNC) guidelines before 16 weeks of age were more likely to  
245 visit veterinary practices specifically for gastrointestinal signs on two or more occasions  
246 between 6 and 30 months of age. Therefore, ensuring that cats exclusively consume a  
247 commercial diet that meets the WSAVA GNC guidelines, particularly before 16 weeks of age  
248 and further studies identifying specific aetiologies for vomiting and diarrhoea before 16  
249 weeks of age to allow for prevention may reduce the number of cats presenting to primary  
250 care veterinary practices specifically for repeated gastrointestinal signs.



251 Footnotes

252 <sup>1</sup><http://www.wsava.org/sites/default/files/Recommendations%20on%20Selecting%20Pet%20>  
253 [Foods.pdf](#).

254 Conflict of interest statement

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260 Protection.

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326 **Table 1 - Univariable ordinal regression analyses for early life events in cats**  
327 **subsequently presenting to veterinary practices for gastrointestinal (GI) signs between 6**  
328 **and 30 months of age.** Table 1 illustrates the number and percentage of cats presenting with  
329 early life events before 16 weeks of age and the frequency of subsequent visits to veterinary  
330 practices specifically for GI signs between 6 and 30 months of age. P-values are displayed for  
331 the different early life events using univariable ordinal regression analyses. For raw fresh  
332 food, cooked fresh food and cow's milk/cream: 1- all of the diet, 2 -  $\geq 50\%$  of the diet, 3 -  
333  $< 50\%$  of the diet, 4 – occasionally in the diet and 5 – never in the diet.

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Early life event before 16 weeks of age		Never visited a vet practice for GI signs between 6 and 30 months of age. Number (%)	Visited vet practice for GI signs on 1 occasion between 6-30 months of age. Number (%)	Visited vet practice for GI signs on 2 occasions between 6-30 months of age. Number (%)	Visited vet practice for GI signs on 3 occasions between 6-30 months of age. Number (%)	P-value
Vomiting, diarrhoea or both	Yes	64 (6.3)	23 (13.7)	5 (19.2)	1 (25.0)	<0.001
	No	950 (93.7)	145 (86.3)	21 (80.8)	3 (75.0)	
Helminths in faeces	Yes	43 (4.3)	12 (7.1)	0 (0.0)	1 (25.0)	0.203
	No	946 (95.7)	156 (92.9)	26 (100)	3 (75.0)	
Raw fresh food	1	6 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	-
	2	31 (3.5)	2 (1.5)	0 (0.0)	0 (0.0)	0.113
	3	81 (9.0)	11 (8.0)	3 (13.0)	1 (25.0)	0.765
	4	354 (39.5)	50 (36.5)	8 (34.8)	1 (25.0)	0.234
	5	424 (47.3)	74 (54.0)	12 (52.2)	2 (50.0)	-
Cooked fresh food	1	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	-
	2	7 (0.8)	2 (1.5)	0 (0.0)	0 (0.0)	0.660
	3	22 (2.5)	5 (3.6)	0 (0.0)	2 (50.0)	0.198
	4	145 (16.5)	18 (13.1)	2 (9.1)	0 (0.0)	0.196

	<b>5</b>	702 (80.1)	112 (81.8)	20 (90.9)	2 (50.0)	-
<b>Cow's milk/cream</b>	<b>1</b>	4 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	-
	<b>2</b>	16 (1.7)	1 (0.7)	1 (4.2)	0 (0.0)	0.569
	<b>3</b>	96 (10.5)	16 (11.0)	2 (8.3)	0 (0.0)	0.776
	<b>4</b>	379 (41.4)	57 (39.3)	11 (45.8)	1 (25.0)	0.616
	<b>5</b>	420 (46.0)	71 (49.0)	10 (41.7)	3 (75.0)	-
<b>Exclusively feeding commercial diet(s) that meet(s) the WSAVA Global Nutrition Committee Guidelines</b>	<b>Yes</b>	757 (82.1)	118 (75.6)	18 (75.0)	3 (75.0)	0.038
	<b>No</b>	165 (17.9)	38 (24.4)	6 (25.0)	1 (25.0)	

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347 **Table 2 - Multivariable ordinal regression analyses for early life events in cats**  
348 **subsequently presenting to veterinary practices for gastrointestinal (GI) signs between 6**  
349 **and 30 months of age.** Table 2 illustrates the P-values with odd's ratio (OR) and 95%  
350 confidence intervals (CI) for those early life events before 16 weeks of age that were  
351 significantly associated with the frequency of visits to a veterinary practice specifically for GI  
352 signs between 6 and 30 months of age following multivariable ordinal regression analyses.

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<b>Early life event before 16 weeks of age</b>		<b>Never visited a vet practice for GI signs between 6 and 30 months of age. Number (%)</b>	<b>Visited vet practice for GI signs on 1 occasion between 6-30 months of age. Number (%)</b>	<b>Visited vet practice for GI signs on 2 occasions between 6-30 months of age. Number (%)</b>	<b>Visited vet practice for GI signs on 3 occasions between 6-30 months of age. Number (%)</b>	<b>P-value (OR, 95% CI)</b>
<b>Vomiting, diarrhoea or both</b>	<b>Yes</b>	64 (6.3)	23 (13.7)	5 (19.2)	1 (25.0)	<0.001 (2.64, 1.66-4.22)
	<b>No</b>	950 (93.7)	145 (86.3)	21 (80.8)	3 (75.0)	
<b>Exclusively feeding commercial diet(s) that meet(s) the WSAVA Global Nutrition Committee Guidelines</b>	<b>Yes</b>	757 (82.1)	118 (75.6)	18 (75.0)	3 (75.0)	0.030 (1.51, 1.04-2.22)
	<b>No</b>	165 (17.9)	38 (24.4)	6 (25.0)	1 (25.0)	

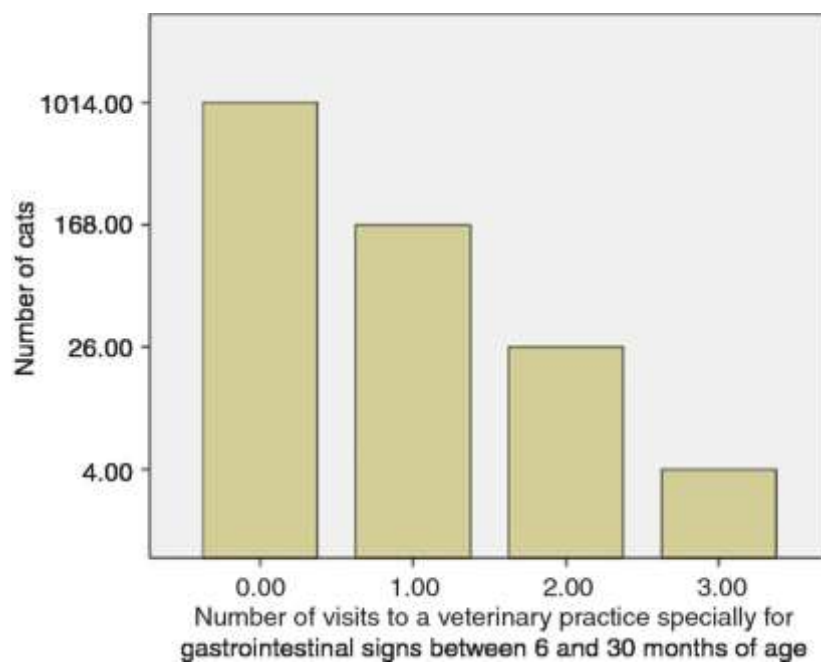
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368 **Figure 1 - A bar chart illustrating the number of cats that visited a veterinary practice**  
369 **specifically for gastrointestinal signs according to the owner between 6 and 30 months**  
370 **of age.**



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