Body weight, gonadectomy, and other risk factors for diagnosis of osteoarthritis in companion dogs.

Jessica L Graves, MS[1][†].; Brennen A McKenzie, VMD[1][†][*]; Zane Koch, BS[1]; Alexander Naka, PhD[1]; Nathaniel Spofford, MPH[2]; JoAnn Morrison, DVM, DACVIM[2]

[1]Loyal, San Francisco, CA, Unites States
[2]Banfield Pet Hospital, Portland, OR, United States

† These authors contributed equally to this work.

*Correspondence:
Brennen McKenzie
brennen@loyalfordogs.com

Keyword: dogs, osteoarthritis, degenerative joint disease, risk factors, incidence

Abstract

OBJECTIVE
To evaluate age, sex, body weight, breed, neuter status, and age at neutering as risk factors for diagnosis of osteoarthritis in companion dogs

ANIMALS
Dogs seen as patients at Banfield Pet Hospital in the United States from 1998-2019 with a date of death in 2019. The final cohort consisted of 131,140 dogs.

METHODS
In this retrospective cohort study, Cox proportional hazard models were used to test for associations between osteoarthritis incidence and age at baseline, sex, maximum body weight, maximum body condition score, neuter status, and age at neutering. The same model was used to test these associations in 12 representative breeds, chosen based on breed weight and sample size.

RESULTS
Older age, higher adult body weight, gonadectomy, and younger age at gonadectomy were significantly associated with higher risks of osteoarthritis in the total cohort and in all 12 breeds evaluated. Higher body condition score and sex were also significantly associated with osteoarthritis but with minimal effect sizes in the overall cohort, and these risk factors were not consistently significant in all breeds tested.

CLINICAL RELEVANCE
These results will assist veterinarians in identifying dogs at higher risk for osteoarthritis and applying appropriate diagnostic, preventative, and treatment interventions. An understanding of

45 potentially modifiable risk factors, such as body condition, and neutering, will support evidence-
46 based discussions with dog owners about risk management in individual patients.

47 **Introduction**

48   Musculoskeletal pain and lameness are among the most common clinical problems seen
49 in companion dogs.(1–3) A large proportion of these cases involve osteoarthritis (OA), the most
50 common joint disorder in dogs. There is inconsistency in literature regarding the terminology for
51 this condition. Terms such as "osteoarthritis," osteoarthrosis, and "degenerative joint disease"
52 may be used interchangeably, or some authors may use different terms for conditions with
53 specific etiology or pathogenesis. In this report, we use the term "osteoarthritis" to refer to a
54 diagnosis of one of the following structured diagnostic codes: osteoarthritis, arthritis or
55 degenerative joint disease – excluding rheumatoid, septic or immune mediated arthritic
56 conditions.
57
58   Prevalence of OA ranges from 2.5% to over 80% depending on study methods and
59 population characteristics.(1,4,5) This variation likely reflects both true differences in prevalence
60 between populations, related to differences in breed, age, husbandry, and other causal factors, as
61 well as differences in diagnostic methods and case definitions between studies.(6)
62
63   As a progressive, incurable condition, OA can affect comfort and quality of life for a
64 substantial proportion of a patient's life.(4) This condition compromises the welfare of affected
65 dogs and places a significant burden on human caregivers.(7) Musculoskeletal pain and
66 locomotor dysfunction, often due to OA, are also among the most frequent reasons for euthanasia
67 in dogs.(8–11)
68
69   Currently, the primary approach to mitigating the negative impact of canine OA is
70 treatment once clinical signs have manifested. Earlier detection and interventions to prevent or
71 delay the development of OA could have significant benefits. Effective approaches for
72 preventing or delaying the development of OA depend on a clear understanding of relevant risk
73 factors and identifying individuals at increased risk.
74
75   Many putative risk factors have been associated with development and progression of
76 canine OA.(6) There is strong evidence for the role of genetic factors influencing both individual
77 risk and breed differences in susceptibility to OA. These factors are often associated indirectly
78 with OA, causing predisposition conditions such as hip or elbow dysplasia or a propensity for
79 cranial cruciate ligament rupture, which then lead to development of arthritis.(6,12)
80
81   Body weight is another factor associated with OA risk. However, studies often do not
82 clearly distinguish between body size and body condition. Larger breeds appear to be at greater
83 risk, as do individuals who are overweight or obese, but the relationship between these different
84 body-size variables is not always clear.(6,13–15)
85
86   Osteoarthritis is considered a disease of aging, and increased age is often associated with
87 increased OA prevalence. This association is potentially complicated, however, by the lack of
88 surveillance and diagnostic markers of early, pre-clinical joint disease. Predisposing conditions
89 and early OA may be present undetected in young dogs while older individuals may be more

90　likely to be diagnosed with OA because of greater diagnostic attention or because the condition
91　has progressed to more apparent clinical signs.(6)
92

93　　　The evidence is limited and conflicting for many potential OA risk actors. Sex, for
94　example, is often associated with OA prevalence, but both males and females have been reported
95　to be at increased risk and the potential for confounding by body size, activity, and neuter status
96　is high.(6)
97

98　　　One of the most debated risk factors for OA is neuter status.(6,16–19) While most reports
99　indicate neutered dogs are at higher risk than intact dogs, the details of the relationship between
100　neuter status and OA are unclear. For example, this association seems to be consistently true for
101　large-breed dogs and less often found in smaller breeds.(18) Neutered dogs are also at greater
102　risk for obesity, so the degree to which the relationship between neutering and OA is mediated or
103　confounded by body condition is uncertain.(6,20–22)
104

105　　　Some studies find that age at neutering influences the impact of gonadectomy on the risk
106　of OA and predisposing conditions, such as cruciate ligament disease.(19,23) This suggests
107　gonadal hormones are protective primarily through effects of skeletal development, and
108　neutering after puberty or skeletal maturity may be less likely to promote OA. However, other
109　studies report residual increased risk in dogs neutered after skeletal maturity and suggest that
110　gonadal hormones may have an ongoing protective effect.(24) There is also significant variation
111　in the existence and strength of associations between neutering and orthopedic disease found in
112　different breeds and different research studies.(18) Many other factors, including diet, activity
113　patterns, and even birth month have been associated with the risk of OA, but detailed causal links
114　have not been clearly identified.(6)
115

116　　　From a preventative-medicine perspective, risk factors for OA can be considered
117　modifiable or non-modifiable. Most genetic factors are not directly modifiable in individuals,
118　and the risk presented by specific genotypes, breed, and conformation are fixed at birth or during
119　development. Recent advances in the study of epigenetics suggest it may be possible to mitigate
120　the impact of some genes through environmental modification of the regulation of gene activity,
121　but clinical interventions for doing so have not yet been validated.(25,26) On a population level,
122　genetic factors which influence the occurrence of OA can potentially be modified by selective
123　breeding targeting both individual genes associated with increased OA risk as well as
124　conformations that predispose to the disease.(25,26)
125

126　　　Other factors associated with OA are clearly modifiable in individuals, including body
127　weight and body condition, diet, activity patterns, and neutering practices.
128

129　　　Common dietary recommendations to delay or prevent OA include reduced feeding to
130　prevent obesity and modulate skeletal development in growing puppies. Lifelong caloric
131　restriction in a cohort of Labrador retrievers delayed the onset of hip OA and reduced the
132　severity of the disorder.(27,28) Less definitive effects were reported for elbow and shoulder
133　OA.(29,30) Whether these effects were due solely to differences in body condition or other
134　influences of caloric restriction is uncertain.
135

136   Experimental studies have also shown that reduction in caloric and calcium content of
137 diets can reduce the risk of developmental abnormalities in giant-breed dogs, such as hip
138 dysplasia, that frequently lead to OA later in life.(31,32) Other nutritional interventions may also
139 influence development of OA and predisposing conditions,(33) but there is still significant
140 uncertainty about the efficacy of most dietary approaches.
141
142   Greater clarity about the role of key risk factors in development of canine OA would be
143 useful for informing preventative strategies. The purpose of this study was to examine selected
144 risk factors for development of OA in a large, retrospective cohort study of companion dogs
145 using medical record data from primary care veterinary practices. We examined previously
146 reported risk factors including age, sex, breed, body weight, and body condition. We also sought
147 to further investigate the relationships between OA, neuter status and age at neutering as well as
148 the variability of these relationships among breeds.

Materials and Methods

Data summary and processing

151   By the end of 2019 the Banfield Pet Hospital network included 1,084 primary care small
152 animal hospitals in 42 U.S. states, the District of Columbia and Puerto Rico. All hospitals used
153 the same proprietary practice information management system (PIMS; PetWare®) to enter
154 patient and visit information and the resulting electronic medical records were uploaded nightly
155 to a central data warehouse. The PIMS contained both structured and unstructured fields for data
156 entry. Structured data included diagnoses and clinical signs, physical examination findings, and
157 invoiced services and medications; unstructured data included narrative text related to subjective
158 and objective observations, patient assessment and treatment plan.
159
160   All in-network visits from dogs with a death date in 2019 were extracted from the data
161 warehouse, with visit information ranging from 1998-2019. Patient information for each visit
162 included breed, sex, neuter status, visit age, and visit weight. Visit information included the
163 location and reason for the visit, all structured clinical signs and diagnoses, examination findings
164 related to musculoskeletal issues and body condition, and any invoiced items or services related
165 to the diagnosis or treatment of osteoarthritis. Invoiced items or services related to in-hospital
166 euthanasia were also extracted in order to more accurately identify patient death date.
167
168   To improve data quality the visit-level data was cleaned and evaluated for data entry
169 errors. First, only visits in which the dog received a physical examination by a veterinarian were
170 included. Some data were removed due to likely data entry errors. These include visits in which
171 there were discrepant entries, visit dates occurring after 2019 or weights recorded over 300 lbs,
172 or dogs who had implausible data values (e.g., negative age). To minimize cohort effects, only
173 dogs born after 1997 were included for analysis. Lastly, the body condition score (BCS)
174 assessment has changed over time (e.g., the use of 3-point (clinician-based assessment), 5-point
175 and 9-point BCS scales), scores were harmonized and converted into a single 9-point scale
176 (**Table 1**).
177
178   Osteoarthritis was defined as the earliest diagnosis of the following structured diagnostic
179 codes: osteoarthritis, arthritis or degenerative joint disease – excluding rheumatoid, septic or

180 immune mediated arthritic conditions. Follow-up time was calculated as the number of years
181 between a dog's age at their first visit and their age at OA diagnosis or death, whichever
182 occurred first – dogs with follow-up times greater than 20 years were removed. In order to
183 capture incidence of aging-related OA, dogs who were not observed into maturity (2 years and
184 up) or who already had OA at their first visit were not included for analysis.
185
186 Desexing status was defined based on veterinarian assessment and if the dog was
187 gonadectomized at a Banfield clinic. Age at desexing was defined as age during a visit with a
188 desexing procedure. Age at desexing was only ascertained for dogs desexed at a Banfield clinic.
189 To preserve temporality between desexing as a risk factor and OA incidence, dogs desexed after
190 being diagnosed with OA were treated as intact. Dogs desexed after 5 years of age were not
191 included in age at desexing analyses, as desexing later has a higher likelihood of being a
192 therapeutic rather than an elective procedure.
193
194 Multiple weight and BCS metrics were created. To estimate the effects of maximum body
195 size or condition, the 75th-percentile of adult (2+ years of age) body weights and BCS were used
196 to approximate a 'maximum' weight or BCS. 75th percentiles were used to minimize the
197 influence of outliers. Median weight and BCS between ages 1.5 and 2.5 years of age were used
198 to approximate the weight and BCS at developmental maturity. Not all dogs were seen between
199 1.5 and 2.5 years of age. In these cases, weight or BCS at desexing (so long as desexing occurred
200 after full development, e.g., 2+ years of age) was used.
201
202 To estimate effects of weight gain after desexing, weight and BCS after desexing was
203 defined as the 75th-percentile of weight and BCS after desexing and 2+ years of age. Percent
204 change in weight and BCS after desexing was calculated as 100*(observation after desexing -
205 observation at maturity)/observation at maturity.
206
207 The majority of dogs seen at Banfield are on a wellness plan (a set of pre-paid services
208 meant to enhance the provision of preventive care services). Wellness plan data is structured
209 within the system so the wellness plan variable was converted to a binary variable encoding if a
210 dog ever was on a wellness plan. Dogs whose wellness plan started at or after OA diagnosis were
211 treated as "never" having been on a plan.
212
213

214 **Table 1**: Body condition score conversion methodology

Point scale	Original BCS value	New BCS value	Classified as
5-point & 9-point	Body Condition Score - Thin 1	1	Too thin
5-point	Body Condition Score - Underweight 2	2	Too thin
3-point	Nutrition/Weight Control Advice - Thin 1	2	Too thin
9-point	Body Condition Score - Too Thin 2	2	Too thin
9-point	Body Condition Score - Too Thin 3	3	Too thin
9-point	Body Condition Score - Ideal 4	4	Ideal
3-point	Nutrition/Weight Control Advice - Normal 2	4	Ideal
5-point	Body Condition Score - Ideal 3	5	Ideal
9-point	Body Condition Score - Ideal 5	5	Ideal
9-point	Body Condition Score - Above Ideal 6	6	Overweight
5-point	Body Condition Score - Overweight 4	7	Overweight
9-point	Body Condition Score - Overweight 7	7	Overweight
3-point	Nutrition/Weight Control Advice - Heavy 3	7	Overweight
5-point	Body Condition Score - Obese 5	8	Obese
9-point	Body Condition Score - Obese 8	8	Obese
9-point	Body Condition Score - Obese 9	9	Obese

215
216
217   ***Statistical methods***

218   *Descriptive statistics*

219   Mean, standard deviation (SD), median, 25th and 75th percentiles, and ranges were
220   calculated for continuous measures: age at baseline, mature and maximum weight, age at OA or
221   censorship/death and duration of follow up (years). Observation counts and proportions were
222   calculated for categorical variables: sex (Female or Male), mature and maximum BCS (1-3=Too
223   thin; 4-5=Ideal; 6-7=Overweight, 8-9=Obese), gonadectomy status (desexed or intact), age at
224   desexing (<6 months, 6-12 months, 12-24 months, 24-60 months), and ever had a Banfield
225   wellness plan (Yes or No). For all variables, the number of missing values were reported. All
226   descriptive statistics are reported for the total cohort as well as stratified by OA diagnosis.
227
228   *Cox proportional hazards*

229   Survival analysis was used to characterize the incidence of OA in companion dogs. The
230   analyses were conducted using duration of follow-up as the measure of survival time, calculated
231   as the years between a dog's first visit and their OA onset or death. This choice of follow-up
232   time as the survival time scale enables easier estimation of age as a risk factor for OA onset.
233   Dogs were right-censored at death.
234
235   A Cox proportional hazards model(34) was used to test joint associations of OA risk
236   factors. In particular, age at baseline, max weight, max BCS, desexing status and sex were used
237   as risk-factors. The Cox model was stratified, separating dogs on (76.3%) and not on (23.7%)
238   wellness plans (**Table 2**). As the dogs on wellness plans were more closely observed on average,
239   the likelihood of OA diagnosis in these dogs was higher (**Supplemental Figure 1**), mostly
240   likely due potential detection bias, and for this reason a stratified Cox proportional hazards

241 model was used. This stratified model accounts for this wellness plan-associated surveillance
242 bias by allowing the baseline hazard of dogs in these groups to be different.(35) On average,
243 dogs on wellness plans visited Banfield 25.06 times (SD 18.54) while dogs not on a wellness
244 plan visited only 4.67 times (SD 6.85).

246 After fitting the Cox proportional hazards model, using the *coxph* function from the
247 *survival* package(36) in R, the proportional hazards assumption was assessed using *cox.zph* and
248 visualization of residuals. The assumption being met, hazard ratios (HR) and their 95%
249 confidence intervals (CI) were estimated to test the magnitude and direction of each risk-factor
250 on time to OA diagnosis. To account for the risk-factors having varying scales of values,
251 standardized HRs were calculated for continuous risk factors (e.g., age at baseline) by
252 standardizing the risk factor (mean centering and dividing by the standard deviation). For all
253 models, both the natural scale and standardized HRs and 95% CIs are reported, along with
254 concordance index and number of observations.

256 The marginal effects of each risk-factor on OA-free survival time were plotted to better
257 understand the magnitude of effect sizes. Marginal effects reflect the average effect of a given
258 risk factor, holding all other covariates in the model constant. To visualize effects of continuous
259 risk factors, predicted OA-free survival curves were estimated based on quartile values or
260 clinical relevance. To visualize marginal effects of categorical variables, each level was used to
261 predict OA-free survival curves. For risk factors not being directly visualized, continuous values
262 were assigned as cohort median values (e.g., median weight) and categorical variables were
263 assigned as a proportion (e.g., proportion male). As the majority of dogs were on wellness plans,
264 strata were assigned to being on a wellness plan. For all interaction models, median survival
265 times and their 95% CIs are also reported.

267 ***Breed-specific analyses***

268 For breeds with at least 500 observations, binomial tests of proportion were used to
269 compare breed-specific OA incidence rates against the cohort-wide incidence rate, using
270 Bonferroni adjusted p-value to adjust for multiple comparisons. Given the diversity and size of
271 the cohort, risk factors of OA were also evaluated in 12 representative breeds, chosen based on
272 breed weight and sample size. First, the maximum body weight of all dogs in the cohort was split
273 into quartiles and then breeds were assigned to a weight quartile based on the mean maximum
274 weight of all dogs of that breed. Then, the top three breeds within each quartile with the most
275 samples were chosen for further analysis. This ensures representation of a wide range of dog
276 weights while not including breeds lacking sufficient sample size to make substantive
277 conclusions. The same stratified Cox regression model used to test primary risk factors of OA
278 was applied to each of these 12 breeds.

280 All analyses were performed in R version 4.1.2. Type I error was set to $\alpha = 0.05$ for all
281 statistical tests.

282

283

284 **Results**

285 *Descriptive statistics*

286   Descriptive statistics of the final cohort resulting from the data processing steps outlined
287 are reported in **Table 2.** The final cohort included 131,140 dogs, 31,365 (23.9%) of which were
288 diagnosed with OA during the course of the study. The cohort of dogs had an average age
289 entering the study of 5.12 years (SD = 4.33), average mature weight of 41.8 lbs (SD=31.0), and
290 63,541 (48.5%) dogs were female. There were 318 unique breeds present in the study, with
291 Labrador Retrievers (n=11,718), Chihuahuas (n=10,147) and Yorkshire Terriers (n=6,570) as the
292 most frequent breeds observed.
293

294   Not all variables generated during the data processing steps outlined above contain
295 observable data. The relatively high proportion of missing data in mature BCS are due to strict
296 construct definitions to generate this variable. Mature BCS was defined as the median BCS score
297 between 1.5 to 2.5 years – many dogs did not have visits during this window in which BCS was
298 assessed. Similarly, age at desexing could only be quantified for dogs who were gonadectomized
299 at a Banfield hospital, which could be confidently matched to a visit date. Approximately 20% of
300 dogs in this cohort were desexed at Banfield, of which 1% were desexed after receiving an OA
301 diagnosis and 9.4% were desexed > 5 years of age. To preserve temporality and capture patterns
302 of voluntary desexing, age at desexing > 5 years of age or after OA were set to missing and are
303 therefore not included in age at desexing analyses.
304

305   In order to fully leverage all available data, only observed data of relevant variables were
306 included in statistical analyses.
307

308 **Table 2.** Cohort descriptive statistics

		Osteoarthritis	
	Total (N=131,140)	**Diagnosed (N=31,365)**	**Never diagnosed (N=99,775)**
Age (years) at baseline			
Mean (SD)	5.12 (4.33)	4.61 (4.04)	5.29 (4.41)
Median (Q1, Q3)	4.41 (0.906, 8.24)	4.00 (0.523, 7.77)	4.73 (0.999, 8.79)
Range	0.00274 - 21.0	0.00274 - 20.0	0.00274 - 21.0
Sex			
Female	63,541 (48.5%)	15,461 (49.3%)	48,080 (48.2%)
Male	67,574 (51.5%)	15,904 (50.7%)	51,670 (51.8%)
Missing	25 (0.0%)	0 (0%)	25 (0.0%)
Mature[1.] weight (lbs)			
Mean (SD)	41.8 (31.0)	50.9 (30.7)	38.5 (30.5)
Median (Q1, Q3)	35.8 (14.0, 64.6)	52.7 (21.4, 71.8)	26.7 (12.6, 61.1)
Range	2.10 - 224	2.20 - 194	2.10 - 224
Missing	85,898 (65.5%)	19,419 (61.9%)	66,479 (66.6%)
Max[2.] weight (lbs)			
Mean (SD)	42.0 (32.4)	52.3 (33.0)	38.8 (31.5)
Median (Q1, Q3)	29.6 (14.6, 66.6)	52.8 (20.8, 76.6)	24.8 (13.5, 62.0)
Range	2.00 - 262	2.44 - 230	2.00 - 262
Mature[1.] BCS			

Too thin (1-3)	429 (0.3%)	79 (0.3%)	350 (0.4%)
Ideal (4-5)	8,626 (6.6%)	480 (1.5%)	8,146 (8.2%)
Overweight (6-7)	4,672 (3.6%)	1,223 (3.9%)	3,449 (3.5%)
Obese (8-9)	219 (0.2%)	47 (0.1%)	172 (0.2%)
Missing	117,194 (89.4%)	29,536 (94.2%)	87,658 (87.9%)
Max[2.] BCS			
Too thin (1-3)	2,279 (1.7%)	153 (0.5%)	2,126 (2.1%)
Ideal (4-5)	60,734 (46.3%)	13,564 (43.2%)	47,170 (47.3%)
Overweight (6-7)	52,596 (40.1%)	15,947 (50.8%)	36,649 (36.7%)
Obese (8-9)	5,433 (4.1%)	1,658 (5.3%)	3,775 (3.8%)
Missing	10,098 (7.7%)	43 (0.1%)	10,055 (10.1%)
Desexed			
Yes	112,704 (85.9%)	29,046 (92.6%)	83,658 (83.8%)
No	18,411 (14.0%)	2,319 (7.4%)	16,092 (16.1%)
Missing	25 (0.0%)	0 (0%)	25 (0.0%)
Age at desexing grouped			
<6 mos	13,178 (10.0%)	4,060 (12.9%)	9,118 (9.1%)
6-12 mos	7,956 (6.1%)	2,029 (6.5%)	5,927 (5.9%)
12-24 mos	1,590 (1.2%)	342 (1.1%)	1,248 (1.3%)
24-60 mos	1,862 (1.4%)	387 (1.2%)	1,475 (1.5%)
Missing	106,554 (81.3%)	24,547 (78.3%)	82,007 (82.2%)
Age (years) at OA or death			
Mean (SD)	11.2 (3.49)	10.7 (2.91)	11.4 (3.64)
Median (Q1, Q3)	11.5 (9.05, 13.7)	10.9 (8.88, 12.8)	11.7 (9.12, 13.9)
Range	0.353 - 22.0	0.353 - 20.5	1.34 - 22.0
Duration of follow up (years)			
Mean (SD)	6.10 (4.07)	6.11 (3.82)	6.10 (4.15)
Median (Q1, Q3)	5.79 (2.62, 9.27)	6.03 (2.83, 9.07)	5.71 (2.55, 9.34)
Range	0.00274 - 20.0	0.00274 - 18.5	0.00274 - 20.0
Had wellness plan			
Yes	100,086 (76.3%)	28,389 (90.5%)	71,697 (71.9%)
No	31,054 (23.7%)	2,976 (9.5%)	28,078 (28.1%)

[1.] 75th percentile of observations > 2 years of age

[2.] Median of observations within 1.5 and 2.5 years of age where available, if not, observation at desexing used

SD=Standard deviation; Q1=25th percentile; Q3=75th percentile

Primary risk factors

To explore if effects of previously reported risk factors were recapitulated in this expansive cohort, we fit stratified Cox proportional hazards model using age at baseline, desexed status (desexed/intact), sex (male/female), adult weight and adult BCS as our primary risk factors, and treated wellness plan as a stratifying variable. Stratification along the presence of being on a wellness plan was supported by evidence of a surveillance (or detection) bias in dogs who were on wellness plans **(Supplemental Figure 1)**.

Table 3 and **Figure 1** show that older age (Std. HR=3.70 (3.64-3.76)), higher adult body weight (Std. HR=1.83 (1.81-1.85)), and desexing (Std. HR=1.37 (1.31-1.43)) are statistically significantly associated with higher risks of OA in this cohort. While hazard ratios for adult BCS and sex were both statistically significant, these effect sizes are minimal (**Figure 1**).

325

326 **Table 3.** Stratified Cox proportional hazard model testing the associations of primary risk factors

327 on OA-free survival.

Variable	HR (95% CI)	Std. HR (95% CI)	p-value	Concordance	N obs
Age at baseline	1.35 (1.35-1.36)	3.70 (3.64-3.76)	<0.001***	0.79	121,035
Max weight	1.02 (1.02-1.02)	1.83 (1.81-1.85)	<0.001***		
Max BCS	1.02 (1.01-1.03)	1.02 (1.01-1.03)	<0.001***		
Desexed	1.37 (1.31-1.43)	1.37 (1.31-1.43)	<0.001***		
Male	0.91 (0.89-0.93)	0.91 (0.89-0.93)	<0.001***		

328 *Std. HR= Standardized continuous variables (mean centered, scaled by standard deviation).

329 Wellness plan treated as stratifying variable.

330
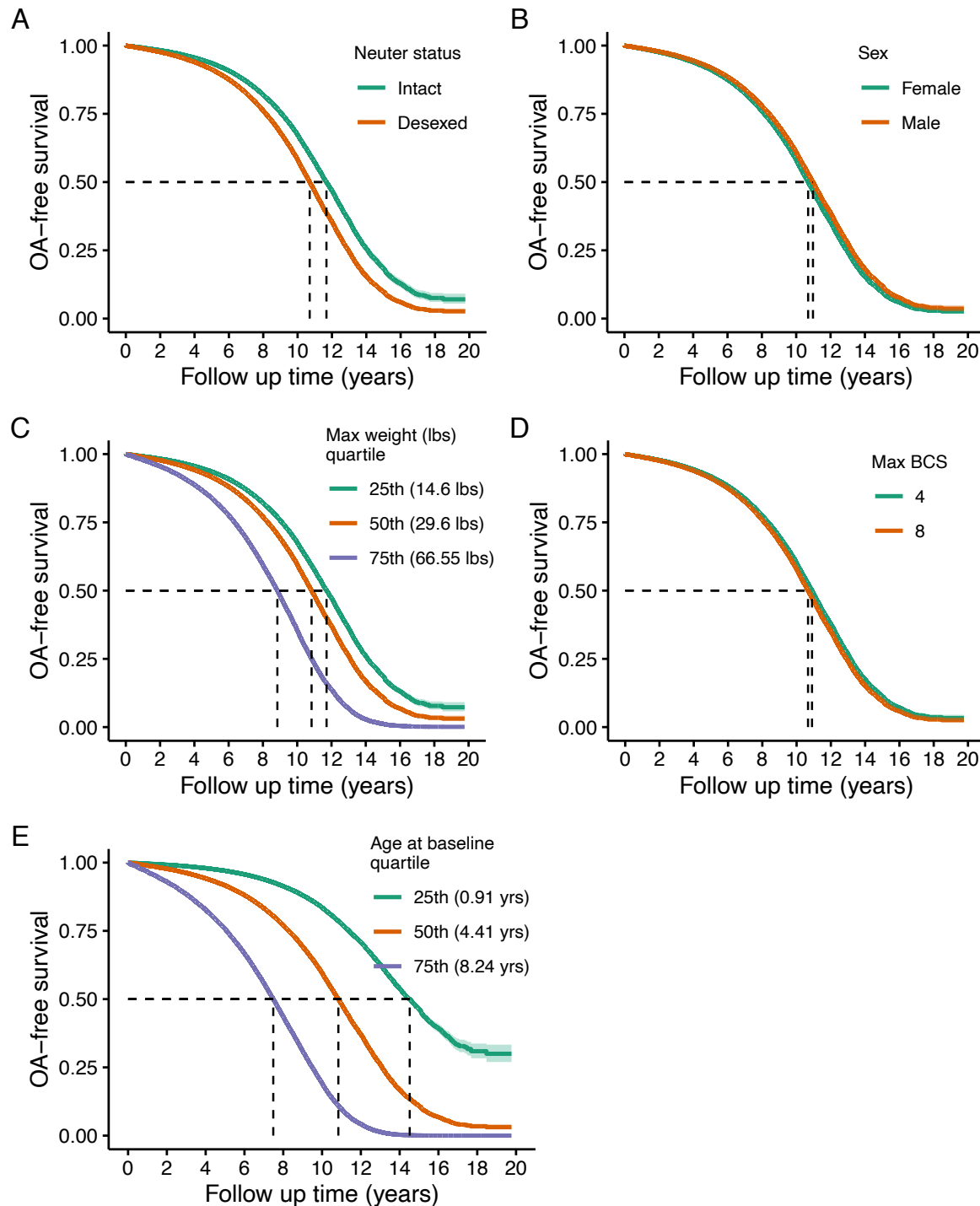
Figure 1. Predicted marginal OA-free survival curves of primary risk factors of OA. Assignments for generating predicted survival curves: median values for continuous covariates not being directly tested, proportions for binary variables, and assuming presence of a wellness plan. Quantiles were used for continuous variable groupings being visualized, except for BCS, which were determined based on clinical relevance.

338

Breed-specific risk factors: Are risk factors consistent within breeds?

340 To explore if the effects of these risk factors were consistent across breeds, the same
341 primary risk factor model was fit to a subset of breeds. The top three most frequent breeds within
342 each weight quartile were selected as an analysis subset (see **Statistical Methods: Breed-**
343 **Specific Analyses** section for more information). **Supplemental Table 1, Supplemental Figure**
344 **2** and **Supplemental Figure 3** the 12 representative breeds as well as breed-specific OA
345 incidence tested against the overall cohort OA incidence rate.

346

347 **Figure 2** summarizes these results using a dot-and-whisker plot of the standardized HR
348 and 95% CI for each of the risk factors within each breed. Higher weight and older age are
349 consistently associated with higher risks of OA across breeds. However, the effect of desexing
350 on OA incidence shows variability across breeds, where desexing does not appear to be a risk
351 factor for Yorkshire Terriers, Maltese, Shih Tzus, Pugs, Dachshunds and Beagles. The effects of
352 BCS also differ across breeds, where effects are more pronounced in smaller breeds. HRs and
353 95% CIs reported in **Supplemental Table 2.**
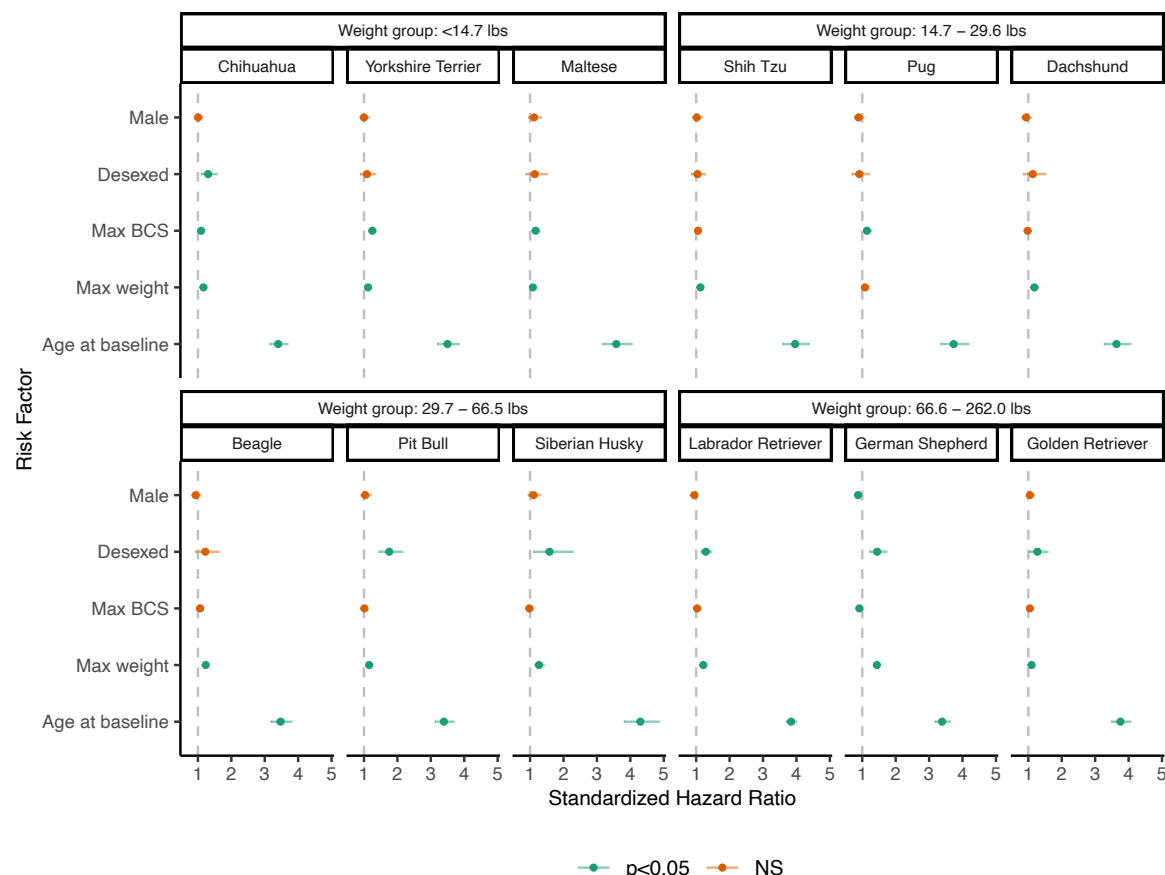
354

355
356 **Figure 2.** Dot-and-whisker plot results of breed-specific analysis of primary risk factors of OA.
357 Dots and whiskers reflect the standardized HR and 95% CIs associated with each risk factor,
358 respectively. Each panel reflects the model fit to an individual breed, where panels are grouped
359 by weight groups. Color assignments designate statistical significance of the HR.

360

361   *Does desexing moderate the effect of max body weight on OA?*

362

363   Both weight and desexing are independent risk factors of OA. However, it has been
364 reported that dogs who are desexed may be more likely to develop obesity,(21,22,37) which may
365 increase the risk of OA. To test if the influence of higher body weight on OA-free survival
366 differed by desexing status, the interaction between adult weight and desexing status was tested.

367

368   There was a statistically significant interaction between desexing and adult weight (Std.
369 HR=1.07 (1.03, 1.11), **Table 4**), suggesting that the increased risk of OA in larger dogs is greater
370 in those that are desexed compared to intact dogs. **Figure 3** shows the predicted survival curves
371 as well as the predicted median survival times for each weight class and desexing group. Both
372 desexed and intact dogs show that higher body weight is associated with higher OA risk;
373 however, this risk appears slightly larger in desexed dogs compared to intact dogs.

374

375 **Table 4.** Stratified Cox proportional hazard model testing the interaction between desexing and
376 maximum adult weight and BCS.

Model	Variable	HR (95% CI)	Std. HR (95% CI)	p-value	Concordance	N obs
Desexing x Weight	Age at baseline	1.35 (1.35-1.36)	3.70 (3.64-3.76)	<0.001***	0.79	121,035
	Max weight	1.02 (1.02-1.02)	1.73 (1.67-1.79)	<0.001***		
	Max BCS	1.02 (1.01-1.03)	1.02 (1.01-1.03)	<0.001***		
	Desexed	1.23 (1.15-1.32)	1.34 (1.29-1.40)	<0.001***		
	Male	0.91 (0.89-0.93)	0.91 (0.89-0.93)	<0.001***		
	Desexed x max weight	1.00 (1.00-1.00)	1.07 (1.03-1.11)	<0.001***		
Desexing x BCS	Age at baseline	1.35 (1.35-1.36)	3.70 (3.64-3.76)	<0.001***	0.79	121,035
	Max weight	1.02 (1.02-1.02)	1.83 (1.81-1.85)	<0.001***		
	Max BCS	1.02 (0.99-1.06)	1.03 (0.99-1.07)	0.186		
	Desexed	1.42 (1.14-1.76)	1.37 (1.31-1.43)	0.002**		
	Male	0.91 (0.89-0.93)	0.91 (0.89-0.93)	<0.001***		
	Desexed x max BCS	0.99 (0.96-1.03)	0.99 (0.95-1.04)	0.754		

377 *Std. HR= Standardized continuous variables (mean centered, scaled by standard deviation).
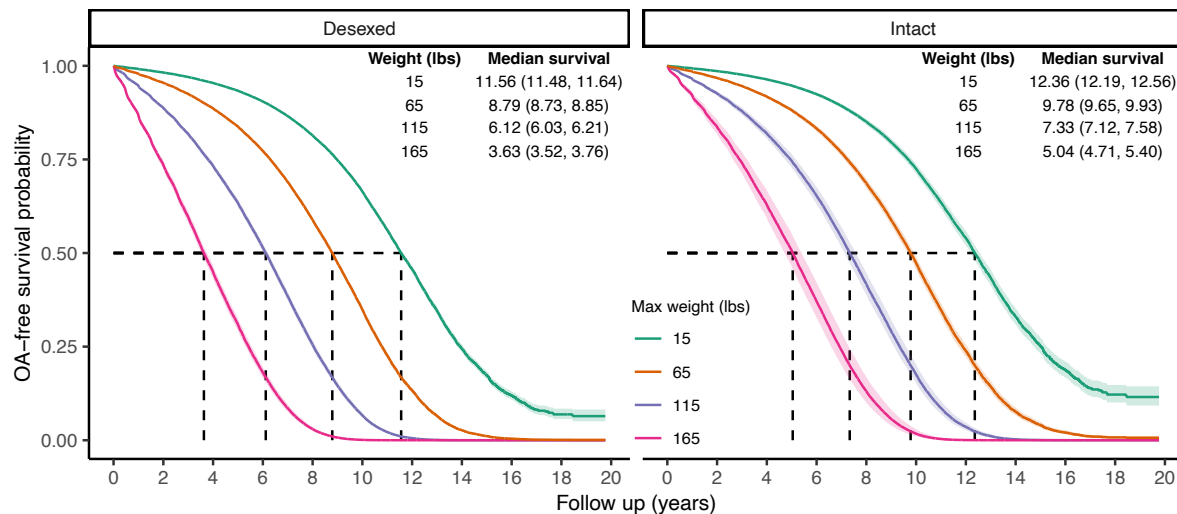378 Wellness plan treated as stratifying variable.

Figure 3. Predicted marginal OA-free survival curves to visualize interaction effects between weight and desexing status. Color indicates maximum weight values. Median survival times and 95% CIs are reported. To generate predictions, median values were used for continuous covariates, proportions for binary variables, and the presence of wellness plan were used.

Does weight gain increase risk of developing OA?

Limitations of the modeling approach used in **Table 2** and **Figure 1** include the lack of temporal precedence – specifically, the inability to test subsequent weight gain after desexing and its influence on OA incidence. To test this hypothesis, percent changes in maximum weight within desexed dogs (calculated as 100*[maximum weight - mature weight]/mature weight) was tested as a risk factor for OA.

Both main effects of percent weight change as well as the interaction with mature body weight were tested in the full cohort and in a sensitivity analysis restricting to dogs whose age at desexing was ≤ 2 years of age. Mature body weight was treated as a covariate as larger-breed dogs are less likely to have larger percent changes in body weight compared to smaller-breed dogs. To determine if weight changes were independent of desexing status, these analyses were performed in intact dogs as well, where percent changes in weight reflected overall changes from mature body weight to maximum body weight.

Results in **Table 5** show that positive percent change in body weight was associated with higher risk of OA (full cohort Std. HR=1.12 (1.09-1.15); age desexing ≤ 2 Std. HR=1.12 (1.09-1.15)). There was also a significant interaction effect between percent change in body weight after desexing and mature body size (Std. HR=1.09 (1.05-1.12)), which held in the dogs desexed ≤ 2 years of age. These results suggest that percent increases in body weight after desexing may have stronger deleterious effects in larger dogs, compared to smaller dogs.

In order to illustrate these effects in more interpretable units, **Figure 4** shows the main effects of percent changes in body weight after desexing, where every 50% increase in body weight after desexing was associated with an approximately 1 year decrease in median time to OA. **Figure 5** visualizes the finding that percent increases in body weight after desexing was

411 associated with higher OA risks in larger dogs compared to smaller dogs. It is important to note
412 that 50% increases in body weight become less likely as mature body size increases and the use
413 of 50% increments are used only to facilitate interpretation of the direction and magnitude of
414 effects.

415

416 **Table 5**. Stratified Cox proportional hazard model testing both the main effects and interaction
417 effects of percent change in body weight in desexed dogs, dogs desexed $\leq$ 2 years of age, and
418 intact dogs, respectively. For dogs who were desexed, percent change in body weight is based on
419 weight change exclusively after desexing.

Subset	Model	Variable	HR (95% CI)	Std. HR (95% CI)	p-value	Concordance	N obs
All desexed dogs	Main effect	Age at baseline	1.20 (1.15-1.26)	2.23 (1.82-2.74)	<0.001***	0.69	23,099
		Male	0.86 (0.82-0.90)	0.86 (0.82-0.90)	<0.001***		
		% change in weight after desexing	1.01 (1.01-1.01)	1.12 (1.09-1.15)	<0.001***		
		Mature weight	1.02 (1.02-1.02)	1.95 (1.91-2.00)	<0.001***		
	Interaction	Age at baseline	1.21 (1.15-1.26)	2.25 (1.83-2.76)	<0.001***	0.69	23,099
		Male	0.86 (0.82-0.91)	0.86 (0.82-0.91)	<0.001***		
		% change in weight after desexing	1.00 (1.00-1.01)	1.05 (1.01-1.09)	0.027*		
		Mature weight	1.02 (1.02-1.02)	1.86 (1.80-1.92)	<0.001***		
		% change in weight after desexing x mature weight	1.00 (1.00-1.00)	1.09 (1.05-1.12)	<0.001***		
Dogs desexed $\leq$ 2 years old	Main effect	Age at baseline	1.12 (0.98-1.28)	1.02 (1.00-1.05)	0.108	0.69	21,296
		Male	0.86 (0.82-0.90)	0.86 (0.82-0.90)	<0.001***		
		% change in weight after desexing	1.01 (1.01-1.01)	1.12 (1.09-1.15)	<0.001***		
		Mature weight	1.02 (1.02-1.02)	2.00 (1.95-2.05)	<0.001***		
	Interaction	Age at baseline	1.12 (0.98-1.28)	1.02 (1.00-1.05)	0.097	0.69	21,296
		Male	0.86 (0.82-0.91)	0.86 (0.82-0.91)	<0.001***		
		% change in weight after desexing	1.00 (1.00-1.01)	1.04 (1.00-1.08)	0.057		
		Mature weight	1.02 (1.02-1.02)	1.89 (1.83-1.96)	<0.001***		
		% change in weight after desexing x mature weight	1.00 (1.00-1.00)	1.09 (1.05-1.13)	<0.001***		
Intact Dogs	Main effect	Age at baseline	1.44 (1.30-1.59)	4.84 (3.12-7.50)	<0.001***	0.69	5,519
		Male	1.23 (1.04-1.44)	1.23 (1.04-1.44)	0.014*		
		% change in weight	1.01 (1.01-1.01)	1.19 (1.14-1.25)	<0.001***		
		Mature weight	1.02 (1.02-1.02)	1.70 (1.59-1.81)	<0.001***		
	Interaction	Age at baseline	1.45 (1.31-1.60)	4.97 (3.20-7.71)	<0.001***	0.69	5,519
		Male	1.26 (1.07-1.48)	1.26 (1.07-1.48)	0.006**		
		% change in weight	1.01 (1.00-1.01)	1.12 (1.05-1.20)	0.001**		
		Mature weight	1.01 (1.01-1.02)	1.57 (1.45-1.71)	<0.001***		
		% change in weight x mature weight	1.00 (1.00-1.00)	1.13 (1.05-1.22)	0.001**		

420 *Std. HR= Standardized continuous variables (mean centered, scaled by standard deviation).
421 Wellness plan treated as stratifying variable.

422
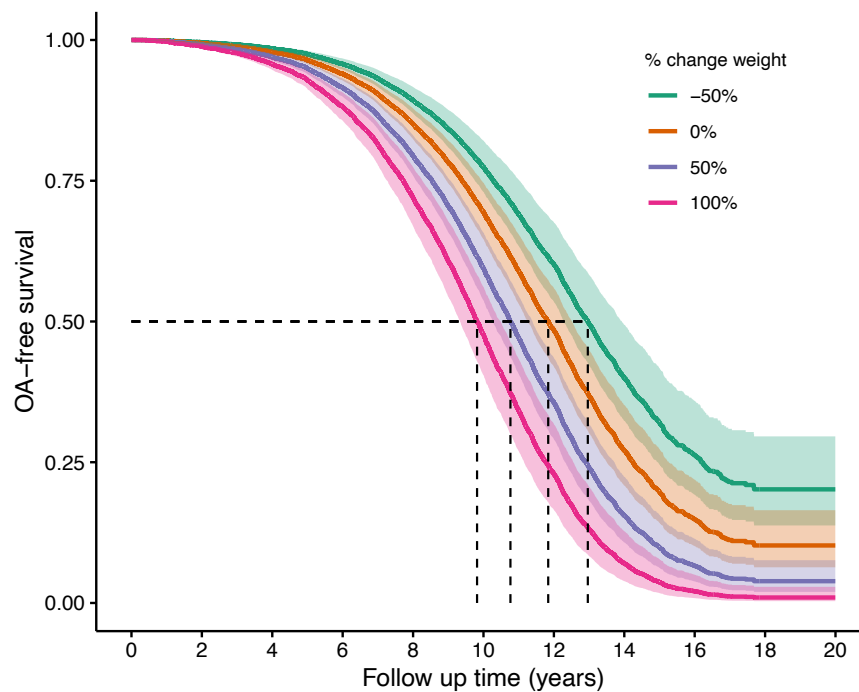
Figure 4. Predicted marginal OA-free survival curves illustrating the main effect of percent weight changes after desexing. Color indicates percent change values. To generate predictions, median values were used for continuous covariates, proportions for binary variables, and the presence of wellness plan were used.
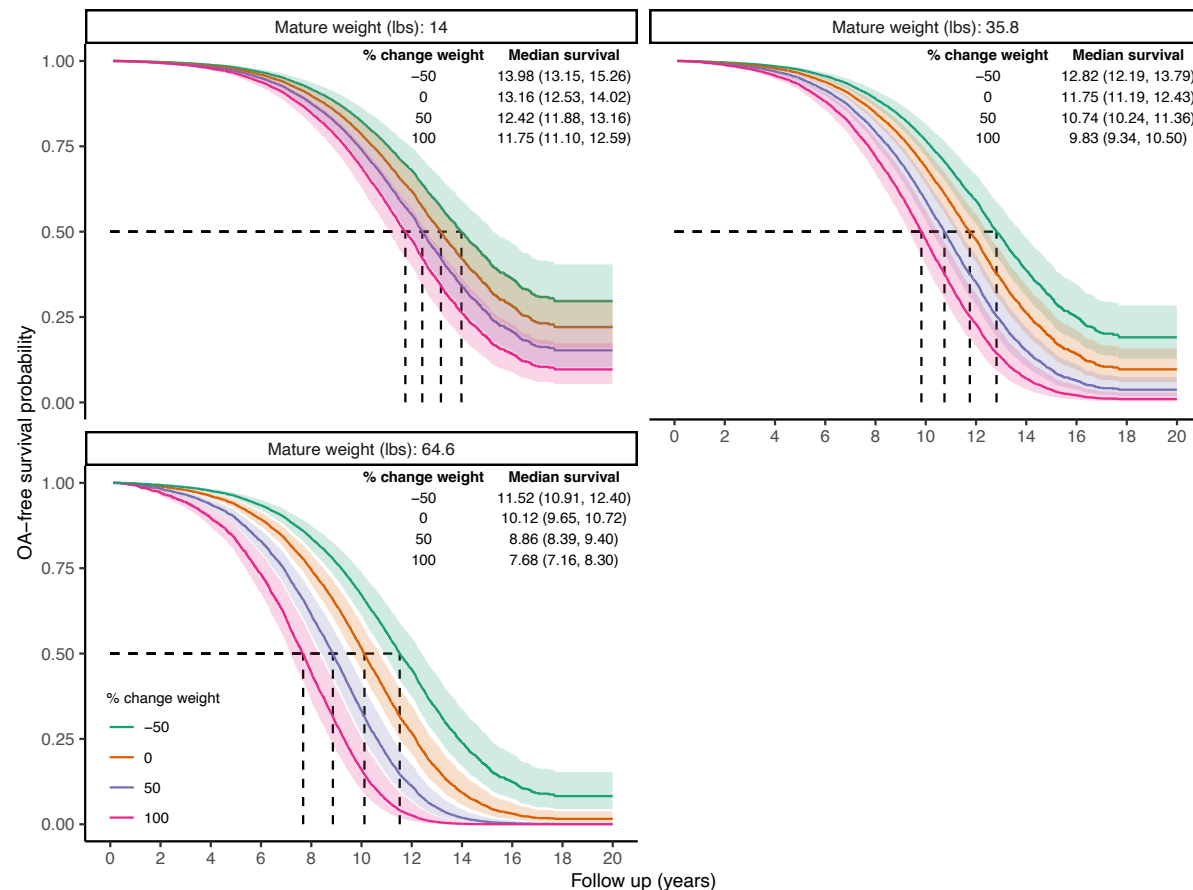
Figure 5. Predicted marginal OA-free survival curves illustrating the interaction effect between percent weight change after desexing and mature body weight. Color indicates percent change values. Median survival times and 95% CIs are reported. To generate predictions, median values were used for continuous covariates, proportions for binary variables, and the presence of wellness plan were used.

Does increased BCS influence OA risks?

As BCS is a distinct construct from weight or body size, percent changes in body condition score after desexing was also tested as a risk factor for OA. Paralleling the approach used in the percent change in weight models, both main effects of percent BCS change as well as the interaction with mature BCS were tested in the full cohort and in a sensitivity analysis restricting to dogs whose age at desexing was ≤ 2 years of age. Mature body BCS was treated as a covariate as dogs with higher BCS at maturity are less likely to have larger BCS changes in BCS compared to dogs with lower BCS at maturity. To determine if weight changes were independent of desexing status, these analyses were performed in intact dogs as well, where percent changes in BCS reflected overall changes from mature BCS to maximum BCS.

Results indicate increases in percent change in BCS are associated with higher risk of OA (Std. HR=1.12 (1.05-1.20), **Table 6**), and that these effects may be stronger in dogs with higher mature BCS (Std. HR=1.16 (1.04-1.29), **Table 6**). However, limited variability in BCS in this cohort makes determining the clinical significance of these effects difficult. As seen in **Figure 6**

451   and **Figure 7**, standard errors from model predictions show significant overlap, except in dogs

452   who have higher mature BCS, where effects begin to appear strongest. However, it is important

453   to note that due to there being a ceiling in the BCS tool, dogs with mature BCS of 7 can only

454   experience at most a percent change increase of 28% (28%=100*(9-7)/7).

455

456   These analyses were also performed in intact dogs, where percent changes in BCS reflect

457   overall changes from mature BCS to maximum BCS to identify any changes across desexing

458   status, where percent changes in BCS were not statistically significantly associated with OA

459   incidence.

460

461

Table 6. Stratified Cox proportional hazard model testing both the main effects and interaction effects of percent change in BCS in desexed dogs, dogs desexed ≤ 2 years of age, and intact dogs, respectively. For dogs who were desexed, percent change in BCS is based on BCS change exclusively after desexing.

Subset	Model	Variable	HR (95% CI)	Std. HR (95% CI)	p-value	Concordance	N obs
All desexed dogs	Main effect	Age at baseline	1.25 (1.12-1.39)	2.60 (1.64-4.12)	<0.001***	0.67	7,484
		Male	0.92 (0.82-1.04)	0.92 (0.82-1.04)	0.186		
		% change in BCS after desexing	1.00 (1.00-1.01)	1.12 (1.05-1.20)	<0.001***		
		Mature weight	1.02 (1.02-1.02)	1.69 (1.61-1.78)	<0.001***		
		Mature BCS	1.16 (1.08-1.24)	1.18 (1.09-1.29)	<0.001***		
	Interaction	Age at baseline	1.24 (1.12-1.38)	2.56 (1.61-4.05)	<0.001***	0.67	7,484
		Male	0.92 (0.82-1.04)	0.92 (0.82-1.04)	0.166		
		% change in BCS after desexing	1.00 (1.00-1.00)	1.01 (0.90-1.13)	0.831		
		Mature weight	1.02 (1.02-1.02)	1.69 (1.60-1.78)	<0.001***		
		Mature BCS	1.16 (1.08-1.25)	1.19 (1.09-1.29)	<0.001***		
		% change in BCS after desexing x mature BCS	1.00 (1.00-1.00)	1.16 (1.04-1.29)	0.008**		
Dogs desexed ≤ 2 years old	Main effect	Age at baseline	1.16 (0.80-1.66)	1.03 (0.96-1.11)	0.432	0.67	6,921
		Male	0.91 (0.81-1.03)	0.91 (0.81-1.03)	0.135		
		% change in BCS after desexing	1.00 (1.00-1.01)	1.14 (1.06-1.21)	<0.001***		
		Mature weight	1.02 (1.02-1.02)	1.72 (1.63-1.81)	<0.001***		
		Mature BCS	1.15 (1.07-1.24)	1.17 (1.08-1.27)	<0.001***		
	Interaction	Age at baseline	1.14 (0.80-1.64)	1.03 (0.95-1.11)	0.471	0.67	6,921
		Male	0.91 (0.81-1.03)	0.91 (0.81-1.03)	0.124		
		% change in BCS after desexing	1.00 (1.00-1.01)	1.03 (0.92-1.14)	0.647		
		Mature weight	1.02 (1.02-1.02)	1.71 (1.62-1.81)	<0.001***		
		Mature BCS	1.16 (1.07-1.25)	1.18 (1.08-1.28)	<0.001***		
		% change in BCS after desexing x mature BCS	1.00 (1.00-1.00)	1.16 (1.05-1.29)	0.005**		
Intact dogs	Main effect	Age at baseline	2.07 (1.52-2.82)	23.46 (6.15-89.40)	<0.001***	0.67	2,153
		Male	1.21 (0.73-2.01)	1.21 (0.73-2.01)	0.467		
		% change in BCS	1.00 (1.00-1.01)	1.13 (0.98-1.30)	0.085		
		Mature weight	1.02 (1.01-1.02)	1.67 (1.39-2.00)	<0.001***		
		Mature BCS	1.00 (0.82-1.21)	1.00 (0.80-1.25)	0.981		
	Interaction	Age at baseline	2.07 (1.51-2.82)	23.16 (6.02-89.13)	<0.001***	0.67	2,153
		Male	1.21 (0.73-2.02)	1.21 (0.73-2.02)	0.463		
		% change in BCS	1.00 (1.00-1.01)	1.12 (0.92-1.36)	0.267		
		Mature weight	1.02 (1.01-1.02)	1.66 (1.39-2.00)	<0.001***		
		Mature BCS	1.00 (0.81-1.24)	1.00 (0.79-1.28)	0.971		
		% change in BCS x mature BCS	1.00 (1.00-1.00)	1.02 (0.76-1.39)	0.876		

*Std. HR= Standardized continuous variables (mean centered, scaled by standard deviation).

Wellness plan treated as stratifying variable.
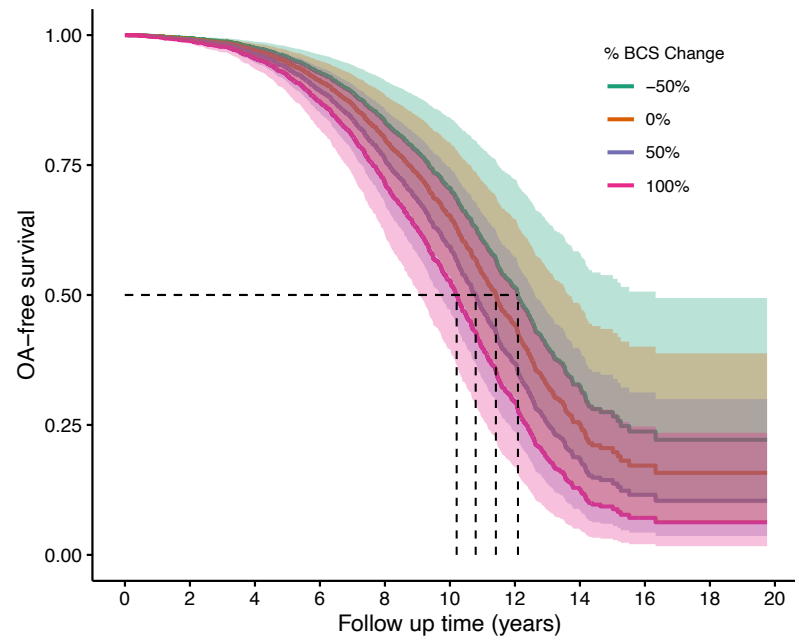
470
471
Figure 6. Predicted marginal OA-free survival curves illustrating the main effect of percent BCS after desexing. Color indicates percent change values. To generate predictions, median values were used for continuous covariates, proportions for binary variables, and the presence of wellness plan were used.
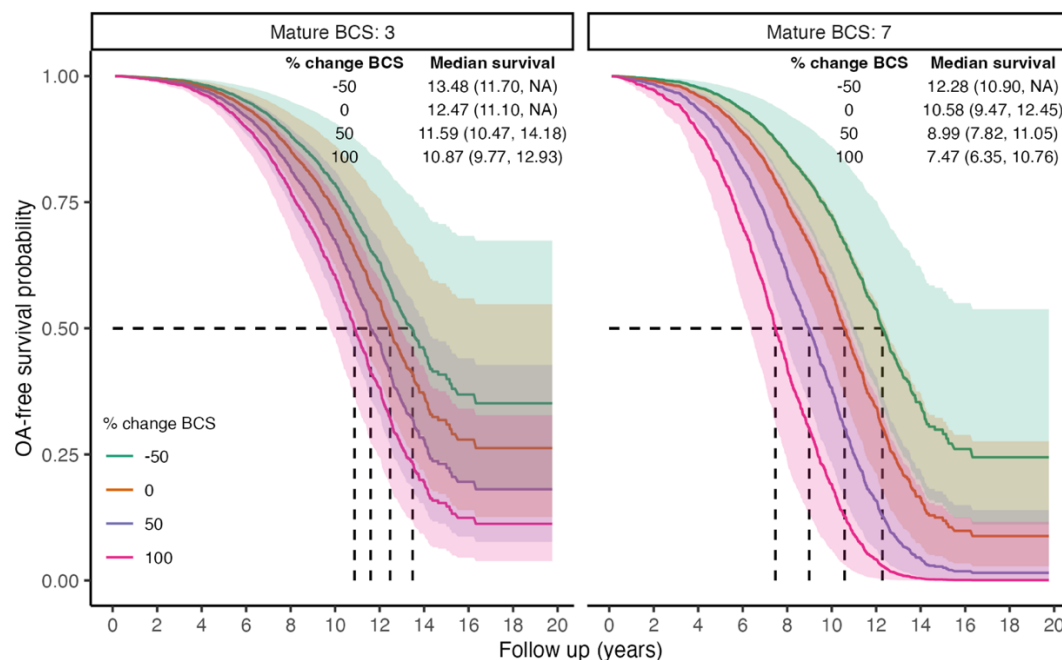

476
Figure 7. Predicted marginal OA-free survival curves illustrating the interaction effect between percent BCS after desexing and mature BCS. Color indicates percent change values. Median survival times and 95% CIs are reported. To generate predictions, median values were used for continuous covariates, proportions for binary variables, and the presence of wellness plan were used.

482
483
484   *Does age at desexing influence OA risks?*

485   To test the hypothesis that age at desexing is a risk factor for OA, age at desexing was
486   added into the primary risk factor model. Age at desexing was tested as a continuous variable as
487   well as a categorical variable (<6 months, 6-12 months, 12-24 months, and 24-60 months). Age
488   at desexing was significantly inversely associated with OA risk (Std. HR=0.90 (0.86-0.94) **Table**
489   **7**). Categorical analysis shows that relative to dogs desexed before 6 months of age, dogs
490   desexed 6-12 months are 13% less likely to develop OA, while dogs who are desexed 12-24 or
491   24-60 months are 28% and 32% less likely to develop OA, respectively. This categorical model
492   suggests a potential non-linear relationship between age at desexing and OA risk, such that the
493   effects of age at desexing diminish as dogs get older. To test this, a sensitivity analysis was
494   performed adding a quadratic term in the continuous age at desexing model. The quadratic term
495   for age at desexing was statistically significant (Std. HR=1.35 (1.22-1.49) **Table 7**)). Predictions
496   from all models are presented in **Figure 8**. Results from this quadratic model more closely relate
497   to the categorical model, providing additional evidence that the magnitude of the OA-related risk
498   associated with age at desexing diminishes with age.
499
500   **Table 7**. Stratified Cox proportional hazard model testing the role of age at desexing as a risk
501   factor for OA. Age at desexing is treated as a continuous measure and as a categorical variable.

Desexing variable	Variable	HR (95% CI)	Std. HR (95% CI)	p-value	Concordance	N obs
Continuous	Age at baseline	1.42 (1.32-1.53)	1.42 (1.32-1.53)	<0.001***	0.70	24,159
	Max weight	1.02 (1.02-1.02)	1.83 (1.79-1.87)	<0.001***		
	Max BCS	1.05 (1.02-1.07)	1.05 (1.03-1.08)	<0.001***		
	Male	0.88 (0.84-0.93)	0.88 (0.84-0.93)	<0.001***		
	Age at desexing	0.87 (0.82-0.92)	0.90 (0.86-0.94)	<0.001***		
Quadratic	Age at baseline	1.42 (1.32-1.52)	1.42 (1.32-1.52)	<0.001***	0.70	24,159
	Max weight	1.02 (1.02-1.02)	1.82 (1.79-1.86)	<0.001***		
	Max BCS	1.05 (1.02-1.07)	1.06 (1.03-1.08)	<0.001***		
	Male	0.89 (0.84-0.93)	0.89 (0.84-0.93)	<0.001***		
	Age at desexing	0.61 (0.53-0.69)	0.67 (0.61-0.75)	<0.001***		
	Age at desexing^2	1.09 (1.06-1.13)	1.35 (1.22-1.49)	<0.001***		
Grouped	Age at baseline	1.41 (1.31-1.51)	4.39 (3.26-5.90)	<0.001***	0.70	24,159
	Max weight	1.02 (1.02-1.02)	1.82 (1.78-1.86)	<0.001***		
	Max BCS	1.05 (1.02-1.07)	1.06 (1.03-1.08)	<0.001***		
	Male	0.89 (0.85-0.93)	0.89 (0.85-0.93)	<0.001***		
	Desexed <6 mos	*Reference*				
	Desexed 6-12 mos	0.87 (0.82-0.92)	0.87 (0.82-0.92)	<0.001***		
	Desexed 12-24 mos	0.72 (0.64-0.80)	0.72 (0.64-0.80)	<0.001***		
	Desexed 24-60 mos	0.68 (0.58-0.79)	0.68 (0.58-0.79)	<0.001***		

502   *Std. HR= Standardized continuous variables (mean centered, scaled by standard deviation).
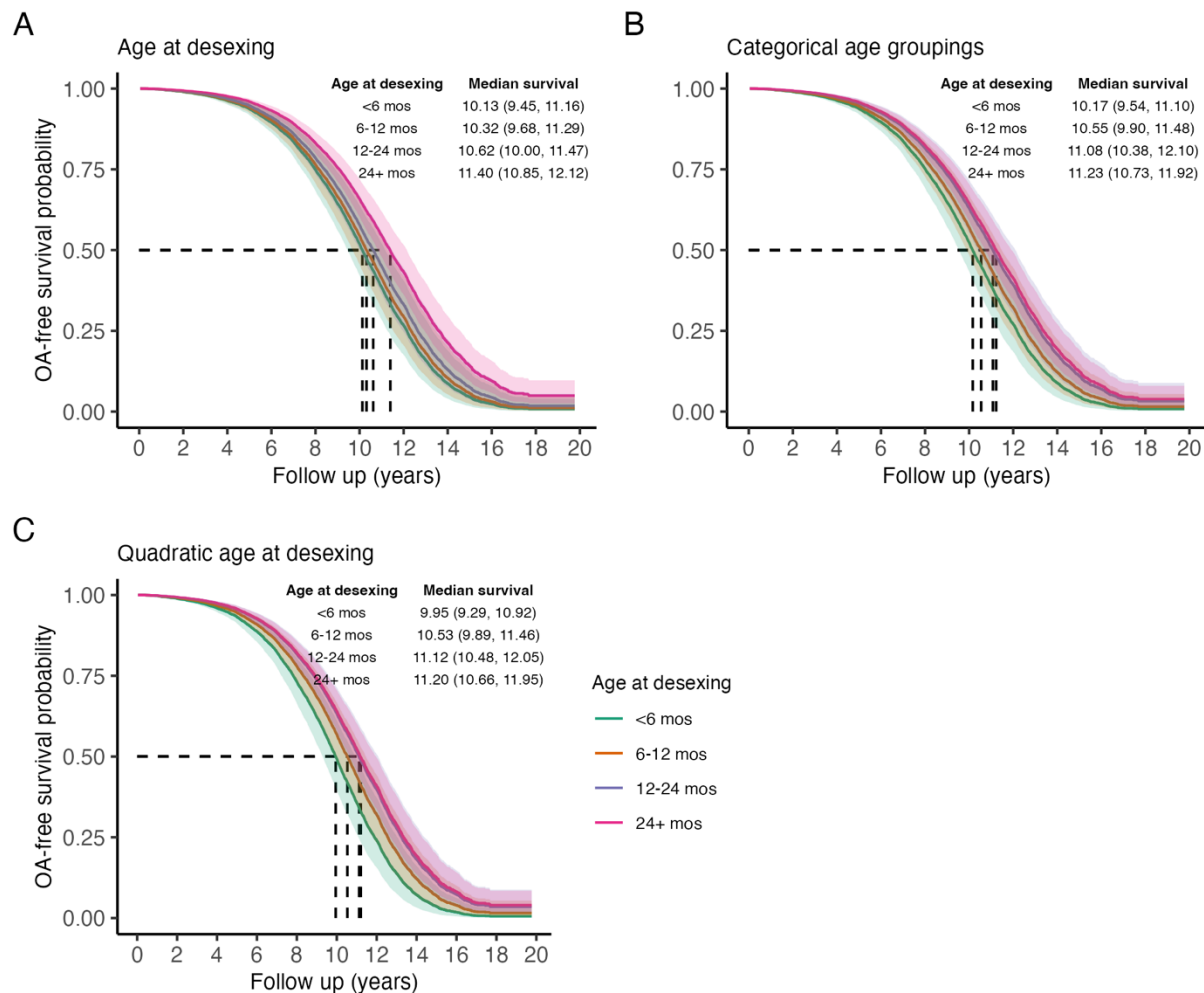503   Wellness plan treated as stratifying variable.
504

Figure 8. Predicted marginal OA-free survival curves illustrating the effect of age at desexing on OA incidence, treating age as a linear continuous variable, a categorical variable, or quadratic variable. Color indicates ages at desexing. Median survival times and 95% CIs are reported. To generate predictions, median values were used for continuous covariates, proportions for binary variables, and the presence of wellness plan were used.

Discussion

The proportion of dogs in this population that developed OA was 24.9%. It is difficult to compare this to occurrence data from other studies due to differences in study populations, case definitions, and other methodological factors. Previous analyses of primary practice databases in the UK, for example, reported a one-year period prevalence of OA in dogs of any age of 2.34%(1) and 2.5%.(4) An owner survey, also in the UK, reported an overall prevalence of 2.23%.(38)

In contrast, a proprietary industry survey of 200 veterinarians in the U.S. reported an overall prevalence of 20%(5) in dogs over 1 year of age, a figure frequently cited in reviews and other articles discussing the condition. A more recent study involving dogs 5-12 years of age and

over 11 kg in weight presenting for dental prophylaxis found 68% of dogs had radiographic evidence of OA in one or more joints.(39) However, owner surveys from a subset of the population reported no clinical signs in 71% of the dogs, and these would likely not have received a diagnosis of OA in routine clinical practice. Such variability creates significant uncertainty about the true rate of occurrence of OA in dogs.

In this study, the incidence of 24.9% represents the clinical diagnosis of OA at any age and by any criteria in dogs from a primary care population who died in 2019, with no fixed interval or duration of follow up. Diagnoses could be based on clinical impression, history and physical examination, radiographic interpretations, or other diagnostic procedures. Given the large size and broad geographic distribution of the study population, this should be reasonably representative of the occurrence of OA as routinely identified by general practice clinicians in companion dogs in the U.S.

Detection bias in retrospective cohort studies can influence both the apparent prevalence of a condition and the apparent impact of risk factors for the disease.(40) Owners of dogs in this population were offered various wellness plans, which consist of a prepaid packages of services that can reduce the cost of clinic visits and some diagnostic tests, including radiographs. Enrollment in such a wellness plan has previously been suggested to be a risk factor for detection bias,(37) and in this study it was strongly associated with OA diagnosis. Dogs with a wellness plan had far more clinic visits and were more likely to have radiographs than dogs not enrolled in such a plan (data not shown), likely leading to a higher rate of detection of OA. This factor was controlled for by stratification in the analysis of other putative risk factors.

Age was by far the strongest risk factor for OA diagnosis, consistent with the established understanding of OA as a disease of aging. This effect was consistent across breeds of different sizes and with different rates of OA occurrence (**Figure 2** and **Supplemental Table 2**). Diagnosis of OA in individual patients is more likely as time passes, both because it is an incurable condition and so will be present and available for diagnosis longer, and because it is progressive and so more likely to become clinically apparent as a dog ages.

In previous studies, sex has been inconsistently identified as a risk factor for OA.(6) In this study, males were at lower risk, though the size of this effect in the overall population was small. Within breeds, males were at lower risk in some breeds but not others, independent of body weight and BCS (**Figure 2** and **Supplemental Table 2**).

All types of OA were included in the case definition for this study, regardless of which joint was affected or whether a predisposing condition, such as joint dysplasia or cranial cruciate ligament rupture, was identified. Previous evaluations of sex as a risk factor for OA have focused more narrowly on particular joints, predisposing conditions, or breeds, and it is likely that the role of sex as a risk factor may vary among these.(4) The small overall risk difference between males and females suggests that diagnostic and preventative measures should be directed equally at dogs of both sexes.

Previous studies have shown that OA risk differs markedly between breeds.(6) Breed is a complex risk factor involving differences in genetic makeup, body size and conformation, and

likely also lifestyle variables influenced by owners, such as feeding practices and the type and intensity of activity. Because of the enormous phenotypic variability among dogs, evaluation of the role of body weight in OA risk can easily confound the effects of body size and breed with those of overweight.

In general, larger body size is often identified as a risk factor for OA in dogs. This pattern was confirmed in this study, with increased mature body weight positively associated with OA risk. When OA risk was compared among breeds, larger breeds had higher risk, consistent with previous findings **(Supplemental Figures 2** and **3** and **Supplemental Table 2**).

In an effort to disentangle the effects of body size and overweight to some extent, we examined the interaction between the percentage increase above mature body weight and the risk for OA. This analysis showed that weight gain after maturity, likely representing excess adipose mass, increases risk of OA. This effect is greater in larger dogs, possibly due to an exacerbation of the already elevated risk posed by larger body size, or because the absolute mechanical burden of weight gained after maturity is greater in larger dogs.

Ideally, body condition score should help to isolate overweight and obesity as a risk factor independent of mature body size, so it was expected that BCS would be a strong predictor of OA risk. In this study population, 40.1% of dogs were classed as overweight (BCS 6-7/9) and 4.1% as obese (BCS 8-9/9), and the proportion of overweight and obesity was higher in the dogs that developed OA (overweight= 50.8%, obese= 5.3%) than in those that did not (overweight= 36.7%, obese= 3.8%). These figures are broadly consistent with previous reports, though the estimated prevalence of overweight and obesity vary widely depending on the population, time period, assessment methods, and category definitions.(21,41–43)

While BCS was significantly correlated with OA risk, the size of this effect was very small. This relationship was stronger in smaller dogs, unlike the effect of weight gain after maturity. Overall, BCS was not a powerful predictor of OA diagnosis. A possible explanation for this unexpected result may be practical challenges in the implementation of BCS scoring. There are several scoring systems in use by veterinarians, and the validation data for these are limited, involving relatively small numbers of dogs, breeds, and clinicians.(44–47) Some studies have reported that BCS scoring correlates well with objective measures of body fat.(46) However, the strength of this correlation varies significantly between breeds. The consistency and reliability of BCS scoring among veterinarians scoring dogs of many different breeds and conformations in general practice is uncertain.

Various assessment tools for body condition were used at different times in evaluation of this population, and scores from a 3-point and a 5-point scale were mapped onto a 9-point scale for analysis. In principle, a system with more gradations should allow for a more accurate distinction between degrees of overweight among dogs and help to identify more clearly the relationship between BCS and clinical conditions such as OA. In practice, however, the distribution of BCS scores in this data set was clearly discontinuous, with the vast majority of dogs scored as 5/9 (45.4%) or 7/9 (35%). This suggests clinicians tended to lump dogs into broad "normal" and "overweight" categories, rather than utilizing BCS scoring as a more finely graded, continuous measure.

614

615   Though this was true across all sizes of dogs, there was greater use of the full range of
616 scores, particularly those below 5/9, in smaller dogs (**Supplemental Figure 4**). This suggests
617 clinicians may find it easier to distinguish gradations of body condition in smaller breeds. The
618 fact that BCS was a stronger predictor of OA in smaller dogs, among which BCS scores were
619 more granular, supports the possibility that the lumping of many dogs into either "normal" or
620 "overweight" obscured the overall relationship between BCS and OA.

621

622   Further evaluation of the reliability of extant BCS scoring systems in heterogenous
623 general practice populations, and the development and validation of alternative assessment tools
624 that obviate the limitations of BCS, would be useful in clarifying the role of overweight and
625 obesity as risk factors for disease.

626

627   Neuter status has been consistently identified as a risk for OA, with intact individuals at
628 lower risk than neutered dogs. There is also evidence that neutering before 12 months of age is
629 associated with an increased risk of several of the most important conditions predisposing to OA
630 (hip and elbow dysplasia and cranial cruciate ligament rupture), though this effect may only
631 appear in larger dogs (over approximately 43 lbs in one recent analysis).(18)

632

633   This study is consistent with previous findings that the risk of OA is increased following
634 desexing in most medium and large breed dogs (over 30 lbs) and in some smaller breeds. While
635 predisposing conditions were not evaluated, the impact of neutering on OA risk overall increased
636 with body size, and neutering was less frequently associated with OA risk in smaller breeds,
637 supporting the apparent greater significance of neutering as a risk factor in larger dogs.

638

639   Neutering is also an established risk factor for obesity,(21,22,37) and it is possible that
640 one way in which neutering increases OA risk is by increasing the propensity for overweight and
641 obesity. Because of challenges in the interpretation of BCS scores, it was difficult to compare the
642 occurrence of overweight and obesity between intact and neutered dogs. The effect of body
643 weight gain after maturity on OA risk was not different between intact and neutered dogs, so
644 overweight and obesity are clearly important risk factors in all dogs regardless of neuter status.
645 While increasing the incidence of overweight and obesity may be one mediator of the impact of
646 neutering on OA risk, this hypothesis could not be directly evaluated in this study.

647

648   In this study, age at neutering was inversely associated with OA risk in the total
649 population, indicating that risk decreased progressively with delayed neutering up to 2 years of
650 age. This effect was the same in dogs of different body sizes, which is not consistent with
651 previous reports suggesting earlier neutering (before 12 months of age) increased the risk of
652 predisposing conditions, such as hip and elbow dysplasia and cruciate ligament rupture, in larger
653 dogs more than smaller dogs.(18) In this large a cohort, the power to detect such a difference in
654 risk associated with size should be high, so these data suggest the OA risk associated with age at
655 neutering would apply to all dogs in similar, heterogenous primary care populations. Differences
656 between this study and others in the appearance of a size effect for this risk factor may be
657 explained by differences in detection strategies, case definitions, or study populations.

658

659 This study serves to confirm the importance of several key risk factors for OA in dogs,
660 including age, body weight, and neutering. Chronological age itself is not, of course, modifiable,
661 but the potential to delay the onset of age-associated health conditions, including OA, has been
662 demonstrated in dogs and numerous other species.(27,28) The most successful strategy for
663 achieving this in research animals, severe caloric restriction, is not practical in companion dogs.
664 Such a strategy requires precisely formulated diets and extensive monitoring to prevent
665 malnutrition, and it can actually reduce lifespan in some animals due to nutrition/gene
666 interactions.(48,49) Feeding is also a critical element of the human-animal bond, and asking dog
667 owners to drastically underfeed their canine companions is unlikely to be accepted by many.
668 However, caloric restriction research has done much to elucidate the general mechanisms of
669 aging, raising the possibility that pragmatic therapies to delay aging-associated diseases may be
670 developed.

672 Body weight is a function of both breed and body condition. Breed risks for specific
673 health conditions, such as OA, can potentially be modified in populations by selective breeding
674 and in individuals by nutritional interventions and, theoretically, the use of drugs targeting the
675 physiologic characteristics of specific breeds that increase disease risk.

677 Body condition can clearly be altered by nutrition and exercise. Despite the unexpectedly
678 small impact of BCS score on OA risk in this study, OA incidence was greater in overweight and
679 obese dogs than in dogs scored as normal weight. Weight gain after maturity, which likely
680 reflects accumulation of excess adipose, was also a significant risk factor for OA. These findings
681 support the role of obesity as a risk factor for OA and the importance of maintaining optimal
682 body condition in dogs through diet and exercise to minimize OA risk. These interventions are
683 particularly important in larger dogs, who are at greatest risk of obesity and most significantly
684 impacted by weight gain and other risk factors, such as neutering.

686 Neutering is an important modifiable risk factor for OA. Overall, gonadectomy appears to
687 increase the risk of OA, particularly in larger dogs. Earlier neutering adds to this effect in both
688 large and small dogs. The pathogenesis of OA, of course, is complex and incompletely
689 elucidated, and the role of neutering should be understood in this context, as one of many risk
690 interacting risk factors. Given this complexity, it is not likely that the decision whether or not to
691 neuter an individual dog will be the primary determinant of whether or not that individual
692 develops OA. However, recognizing that an association exists on a population level between
693 neutering and OA risk can help clinicians identify individuals who may be at elevated risk and
694 utilize more proactive surveillance to ensure early diagnosis and appropriate preventative and
695 therapeutic interventions.

697 Any potential increase in OA risk associated with neutering must also be considered in
698 the context of other risks and benefits associated with neutering on both an individual and
699 population level. Changes in neutering practices intended to mitigate one health risk may entail
700 unpredictable increases in other risks not yet identified, so judicious integration of such
701 information with the larger context and the circumstances and needs of individual patients is
702 critical.
703

Future research in such large, primary-care cohorts can further clarify the relationship between putative risk factors and common aging-associated diseases such as OA. This will support efforts to reduce the burden of these conditions on companion dogs and their caregivers by informing appropriate preventative intervention.

Limitations

As a retrospective cohort study, this analysis relied on electronic medical records, collected across thousands of clinics and veterinarians. While these data provide longitudinal insights into risk factors associated with incident diseases, the data themselves were not collected to test hypotheses surrounding risk factors for incident osteoarthritis. The study population (all dogs seen between 1998-2019 and dying in 2019) was large and expected to be representative of the patient population at Banfield during this period, but it may not be representative of the overall U.S. companion dog population.

Electronic health records rely on real-time recording of interactions between clinicians, clients, and patients. Information provided by clients, such as age, breed, and prior medical history, may be subject to misclassification or recall bias. Information provided by veterinarians, such as diagnosis of OA and scoring of BCS, may be subject to misclassification bias and may vary over time and between clinicians. For example, a diagnosis of OA could be based on clinical impression, history and physical examination, radiographic interpretations, or other factors, and no standardized diagnostic criteria were in place.

Overall incidence rates may differ from true population-level incidence, and should be interpreted with caution. Additionally, percentiles were used to summarize adult body weight and BCS across the follow-up window, which fails to capture duration of time over or underweight. Finally, age at desexing was only known for dogs being desexed at a Banfield Pet Hospital clinic, which does not account for desexing occurring outside of Banfield clinics.

Conflict of Interest

JG, BM, ZK are employed by Loyal, a biotechnology company developing drug therapies to extend lifespan and healthspan in dogs. JM and NS are employed by Banfield Pet Hospital.

Author Contributions

JG conducted the data analyses and wrote the Materials and Methods and the Results sections. BM wrote the Introduction and Discussion sections. All authors contributed to manuscript revisions and have read and approved the final manuscript.

Acknowledgements

743   veterinarians and clients of Banfield Pet Hospital for generating this invaluable information

744   resource.

745   **Contribution to the Field**

746   Osteoarthritis, also called degenerative joint disease, is the most common joint disorder in dogs.

747   It is an incurable, progressive condition that can cause significant pain and disability. Identifying

748   risk factors for the development of osteoarthritis can help veterinarians recognize individual dogs

749   at high risk and make appropriate efforts to diagnose and treat the condition as early as possible.

750   Identifying those risk factors that can be changed can help dog owners and veterinarians prevent

751   or mitigate the development of this condition in some dogs. This study analyzed a very large

752   body of data about companion dogs examined by veterinarians in many general practice

753   veterinary clinics throughout the United States. This analysis confirmed the importance of

754   several previously suspected risk factors for the development of osteoarthritis, including age and

755   body weight. The study also added to existing information about the relationship between the

756   risk of developing osteoarthritis and several factors, including body weight, desexing, and age at

757   desexing. This research will be useful both to clinicians treating canine patients and to other

758   researchers studying the factors that lead to the development of osteoarthritis in dogs.

759

760   **References**

761 1. O'Neill DG, James H, Brodbelt DC, Church DB, Pegram C. Prevalence of commonly diagnosed

762   disorders in UK dogs under primary veterinary care: results and applications. BMC Vet Res.

763   2021 Dec;17(1):1–14.

764 2. Robinson NJ, Dean RS, Cobb M, Brennan ML. Investigating common clinical presentations in

765   first opinion small animal consultations using direct observation. Vet Rec. 2015

766   May;176(18):463–463.

767 3. Wolf S, Selinger J, Ward MP, Santos-Smith P, Awad M, Fawcett A. Incidence of presenting

768   complaints and diagnoses in insured Australian dogs. Aust Vet J. 2020 Jul;98(7):326–32.

769 4. Anderson KL, O'Neill DG, Brodbelt DC, Church DB, Meeson RL, Sargan D, et al. Prevalence,

770   duration and risk factors for appendicular osteoarthritis in a UK dog population under primary

771   veterinary care. Sci Rep 2018 81. 2018 Apr;8(1):1–12.

772 5. Johnston SA. Osteoarthritis. Joint anatomy, physiology, and pathobiology. Vet Clin North Am

773   Small Anim Pract. 1997;27(4):699–723.

774 6. Anderson KL, Zulch H, O'Neill DG, Meeson RL, Collins LM. Risk Factors for Canine

775   Osteoarthritis and Its Predisposing Arthropathies: A Systematic Review. Front Vet Sci.

776   2020;7:220–220.

777 7. Belshaw Z, Dean R, Asher L. "You can be blind because of loving them so much": The impact

778   on owners in the United Kingdom of living with a dog with osteoarthritis. BMC Vet Res. 2020

779   Jun;16(1):1–10.

780 8. Pegram C, Gray C, Packer RMA, Richards Y, Church DB, Brodbelt DC, et al. Proportion and

781   risk factors for death by euthanasia in dogs in the UK. Sci Rep. 2021 Dec;11(1).

9. O'Neill DG, Church DB, McGreevy PD, Thomson PC, Brodbelt DC. Longevity and mortality of owned dogs in England. Vet J Lond Engl 1997. 2013 Dec;198(3):638–43.

10. Urfer SR, Kaeberlein M, Promislow DEL, Creevy KE. Lifespan of companion dogs seen in three independent primary care veterinary clinics in the United States. Canine Med Genet. 2020;7:7.

11. Bonnett BN, Egenvall A. Age patterns of disease and death in insured Swedish dogs, cats and horses. J Comp Pathol. 2010 Jan;142 Suppl 1:S33-38.

12. Clements DN, Carter SD, Innes JF, Ollier WER. Genetic basis of secondary osteoarthritis in dogs with joint dysplasia. Am J Vet Res. 2006 May;67(5):909–18.

13. Sanderson S. The epidemic of canine obesity and its role in osteoarthritis. Isr J Vet Med. 2012;67:195–202.

14. Shahid M, Manchi G, Slunsky P, Naseer O, Fatima A, Leo B, et al. A systemic review of existing serological possibilities to diagnose canine osteoarthritis with a particular focus on extracellular matrix proteoglycans and protein. Pol J Vet Sci. 2017 Mar;20(1):189–201.

15. Smith GK, Mayhew PD, Kapatkin AS, McKelvie PJ, Shofer FS, Gregor TP. Evaluation of risk factors for degenerative joint disease associated with hip dysplasia in German Shepherd Dogs, Golden Retrievers, Labrador Retrievers, and Rottweilers. J Am Vet Med Assoc. 2001 Dec;219(12):1719–24.

16. Torres de la Riva G, Hart BL, Farver TB, Oberbauer AM, Messam LLM, Willits N, et al. Neutering dogs: effects on joint disorders and cancers in golden retrievers. PloS One. 2013;8(2):e55937.

17. Hart BL, Hart LA, Thigpen AP, Willits NH. Long-term health effects of neutering dogs: comparison of Labrador Retrievers with Golden Retrievers. PLoS One. 2014 Jul;9(7):e102241–e102241.

18. Hart BL, Hart LA, Thigpen AP, Willits NH. Assisting Decision-Making on Age of Neutering for 35 Breeds of Dogs: Associated Joint Disorders, Cancers, and Urinary Incontinence. Front Vet Sci. 2020 Jul;7:388–388.

19. McKenzie B. Evaluating the benefits and risks of neutering dogs and cats. CABI Rev. 2010 Jan;2010:1–18.

20. Lefebvre SL, Yang M, Wang M, Elliott DA, Buff PR, Lund EM. Effect of age at gonadectomy on the probability of dogs becoming overweight. J Am Vet Med Assoc. 2013 Jul;243(2):236–43.

21. Lund EM, Armstrong PJ, Kirk CA, Klausner JS. Prevalence and risk factors for obesity in adult dogs from private US veterinary practices. Int J Appl Res Vet Med. 4(2):177–86.

22. Bjørnvad CR, Gloor S, Johansen SS, Sandøe P, Lund TB. Neutering increases the risk of obesity in male dogs but not in bitches — A cross-sectional study of dog- and owner-related risk factors for obesity in Danish companion dogs. Prev Vet Med. 2019 Oct;170:104730–104730.

23. Spain CV, Scarlett JM, Houpt KA. Long-term risks and benefits of early-age gonadectomy in dogs. J Am Vet Med Assoc. 2004 Feb 1;224(3):380–7.

24. Kutzler MA. Possible Relationship between Long-Term Adverse Health Effects of Gonad-Removing Surgical Sterilization and Luteinizing Hormone in Dogs. Anim Open Access J MDPI [Internet]. 2020 Apr;10(4). Available from: /pmc/articles/PMC7222805/

25. Grandi FC, Bhutani N. Epigenetic Therapies for Osteoarthritis. Trends Pharmacol Sci. 2020 Aug;41(8):557–69.

26. Shen J, Abu-Amer Y, O'Keefe RJ, McAlinden A. Inflammation and epigenetic regulation in osteoarthritis. https://doi.org/101080/0300820720161208655. 2016 Jan;58(1):49–63.

27. Kealy RD, Lawler DF, Ballam JM, Mantz SL, Biery DN, Greeley EH, et al. Effects of diet restriction on life span and age-related changes in dogs. J Am Vet Med Assoc. 2002 May 1;220(9):1315–20.

28. Kealy RD, Lawler DF, Ballam JM, Lust G, Smith GK, Biery DN, et al. Five-year longitudinal study on limited food consumption and development of osteoarthritis in coxofemoral joints of dogs. J Am Vet Med Assoc. 1997 Jan 15;210(2):222–5.

29. Huck JL, Biery DN, Lawler DF, Gregor TP, Runge JJ, Evans RH, et al. A Longitudinal Study of the Influence of Lifetime Food Restriction on Development of Osteoarthritis in the Canine Elbow. Vet Surg. 2009 Feb;38(2):192–8.

30. Runge JJ, Biery DN, Lawler DF, Gregor TP, Evans RH, Kealy RD, et al. The effects of lifetime food restriction on the development of osteoarthritis in the canine shoulder. Vet Surg VS. 2008 Jan;37(1):102–7.

31. Hazewinkel H, Goedegebuure SA, Poulos P, Wolvekamp W. Influences of chronic calcium excess on the skeletal development of growing Great Danes. J Am Anim Hosp Assoc. 1985;

32. Hedhammar A, Wu F, Krook L, Schryver H, Lahunta A de, Whalen J, et al. Overnutrition and skeletal disease. An experimental study in growing Great Dane dogs. Cornell Vet. 1974;

33. Manfredi S, Di Ianni F, Di Girolamo N, Canello S, Gnudi G, Guidetti G, et al. Effect of a commercially available fish-based dog food enriched with nutraceuticals on hip and elbow dysplasia in growing Labrador retrievers.

34. Cox DR. Regression Models and Life-Tables. J R Stat Soc Ser B Methodol. 1972;34(2):187–220.

35. Therneau TM, Grambsch PM. Modeling Survival Data: Extending the Cox Model [Internet]. New York, NY: Springer; 2000 [cited 2023 Jul 18]. (Dietz K, Gail M, Krickeberg K, Samet J, Tsiatis A, editors. Statistics for Biology and Health). Available from: http://link.springer.com/10.1007/978-1-4757-3294-8

36. Therneau TM, Grambsch PM. A Package for Survival Analysis in S, version 2.38. Model Surviv Data Extending Cox Model [Internet]. 2000; Available from: http://cran.r-project.org/package=survival

37. Benka VA, Scarlett JM, Sahrmann J, Rieke K, Briggs JR, Ruple A, et al. Age at gonadectomy, sex, and breed size affect risk of canine overweight and obese outcomes: a retrospective cohort study using data from United States primary care veterinary clinics. J Am Vet Med Assoc. 2023 May 19;1–10.

38. Wiles BM, Llewellyn-Zaidi AM, Evans KM, O'Neill DG, Lewis TW. Large-scale survey to estimate the prevalence of disorders for 192 Kennel Club registered breeds. Canine Genet Epidemiol. 2017;4:8.

39. Millis D, Tichenor MG, Hecht S, Hunt T. Prevalence of Osteoarthritis in Dogs Undergoing Routine Dental Prophylaxis. In: World Small Animal Veterinary Association World Congress Proceedings. Cape Town, South Africa; 2014.

40. Combelles L, Corbiere F, Calavas D, Bronner A, Hénaux V, Vergne T. Impact of imperfect disease detection on the identification of risk factors in veterinary epidemiology. Front Vet Sci. 2019;6(MAR):66–66.

41. Association for the Prevention of Pet Obesity. State of U.S. Pet Obesity 2022. 222AD.

42. Chiang CF, Villaverde C, Chang WC, Fascetti AJ, Larsen JA. Prevalence, Risk Factors, and Disease Associations of Overweight and Obesity in Dogs that Visited the Veterinary Medical Teaching Hospital at the University of California, Davis from January 2006 to December 2015. Top Companion Anim Med. 2022 May;48:100640–100640.

43. McGreevy PD, Thomson PC, Pride C, Fawcett A, Grassi T, Jones B. Prevalence of obesity in dogs examined by Australian veterinary practices and the risk factors involved. Vet Rec. 2005 May;156(22):695–702.

44. Laflamme D. Development and Validation of a Body Condition Score System for Dogs. Canine Pract. 1997;22(1):10–5.

45. Burkholder WJ. Use of body condition scores in clinical assessment of the provision of optimal nutrition. J Am Vet Med Assoc. 2000;217(5):650–4.

46. Mawby DI, Bartges JW, d'Avignon A, Laflamme DP, Moyers TD, Cottrell T. Comparison of Various Methods for Estimating Body Fat in Dogs. J Am Anim Hosp Assoc. 2004 Mar;40(2):109–14.

47. German AJ, Holden SL, Moxham GL, Holmes KL, Hackett RM, Rawlings JM. A Simple, Reliable Tool for Owners to Assess the Body Condition of Their Dog or Cat. J Nutr. 2006 Jul;136(7):2031S-2033S.

48. Lee MB, Hill CM, Bitto A, Kaeberlein M. Antiaging diets: Separating fact from fiction. Science. 2021 Nov 19;374(6570):eabe7365.

49. Nikolai S, Pallauf K, Huebbe P, Rimbach G. Energy restriction and potential energy restriction mimetics. Nutr Res Rev. 2015 Dec;28(2):100–20.