

1 **Dog Size and Patterns of Disease History Across the Canine Age Spectrum: Results**
2 **from the Dog Aging Project**

3

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47 **Abstract**

48 Age in dogs is associated with the risk of many diseases, and canine size is a major factor in that risk.
49 However, the size effect is not as simple as the age effect. While small size dogs tend to live longer,
50 some diseases are more prevalent among small dogs. Utilizing owner-reported data on disease history
51 from a substantial number of companion dogs, we investigate how body size, as measured by weight,
52 associates with the prevalence of a reported condition and its pattern across age for various disease
53 categories. We found significant positive associations between weight and prevalence of skin,
54 bone/orthopedic, gastrointestinal, ear/nose/throat, cancer/tumor, brain/neurologic, endocrine, and
55 infectious diseases. Similarly, weight was negatively associated with the prevalence of eye, cardiac,
56 liver/pancreas, and respiratory disease categories. Kidney/urinary disease prevalence did not vary by
57 weight. We also found that the association between age and disease prevalence varied by dog size for
58 many conditions including eye, cardiac, orthopedic, ear/nose/throat, and cancer. Controlling for sex,
59 purebred/mixed breed, and geographic region made little difference in all disease categories we
60 studied. Our results align with the reduced lifespan in larger dogs for most of the disease categories but
61 suggest potential avenues for further examination.
62

63 **Introduction**

64 Age is the single greatest predictor of disease risk for most causes of mortality in both human and dog
65 populations (1–3). However, unlike in humans, for many dog diseases, body size is a comparably
66 important predictor of risk (1,4,5). Companion dogs show considerable variation in longevity across size
67 classes (6–8). Between species of mammals, larger ones tend to live longer than smaller ones, while
68 within species, smaller individuals tend to live longer than larger individuals (9). Accordingly, dogs from
69 larger size classes tend to have a shorter lifespan. Additionally, different size classes of dogs tend to
70 manifest with different diseases, and ultimately to die from different causes. For instance, larger breed
71 dogs more often die of musculoskeletal and gastrointestinal causes whereas smaller dogs die more
72 frequently of endocrine causes (1,2).

73 Jin et al (10) studied a multimorbidity index (e.g. a count of the number of conditions a dog has
74 experienced) and found that although the index increased steadily with age, the size of the dog had no
75 significant effect on the index. This suggests that over time, dogs in larger size classes are not
76 accumulating *more* conditions, but rather *different* conditions. An understanding of which conditions
77 manifest differently across age and size could inform our understanding of size-related longevity
78 differences. The Dog Aging Project (DAP) provides a unique opportunity to address these issues in a
79 large community-based population of companion dogs. Specifically, we use data from the “DAP Pack”, a
80 collection of over 25,000 survey respondents from across the US.

81

82 **Methods**

83 The Dog Aging Project (DAP) was launched in Fall 2019 (11). Dog owners self-selected and could enroll
84 one dog per household. Enrollment consisted of completing a web-based Health and Life Experience
85 Survey (HLES) that elicited from the dog owner information on a wide array of topics. The curated 2020

86 release of the HLES data contained 27,541 survey records collected on or before December 31st, 2020.
87 The survey consisted of ten sections including dog demographics, environment, health status, and
88 owner demographics. In the health status section, dog owners were asked if their dogs have acquired
89 and been diagnosed with various medical conditions, organized by organ system or pathophysiologic
90 process category. We focused on thirteen disease categories of interest within which conditions were
91 reported in 500 or more dogs. Categories that were considered include skin disorders, infectious or
92 parasitic disease, orthopedic, GI, ocular, ear/nose/throat, kidney/urinary, cancer, cardiac, neurologic,
93 liver/pancreas, respiratory, and endocrine disorders.

94 We presented the frequency and proportion of owner-reported disease history by age categories in
95 Table 1, and by weight categories in Table 2. Disease categories are listed in descending order of overall
96 frequency. Owners were asked to answer the year and month the dog was born if known or to provide
97 an estimated age. Based on this calculated age, we categorized them into puppies (<1 year), adolescents
98 (1 to <3 years), young adults (3 to <7 years), older adults (7 to <11 years), or seniors (11+ years). Owners
99 were asked to report the dog's exact weight in pounds, to the best of their knowledge. We converted
100 the unit of weight from pounds to kilograms and classified them into five size groups: <10 kg, 10 to <20
101 kg, 20 to <30 kg, 30 to <40kg, or 40+ kg.

102 To understand the trend of disease history across age and size, we modeled lifetime prevalence of each
103 disease category in three ways: 1) as a function of age and weight, 2) as a function of age, weight, and
104 the age by weight interaction, and 3) as a function of age, weight, and their interaction, and adjusted for
105 the dog's sex, purebred/mixed breed, and census division. We used continuous age and weight and they
106 were standardized by subtracting their means and dividing by their standard deviations. Dog's sex was
107 classified into four levels, neutered/intact male, or spayed/intact female, using both responses to the
108 sex of the dog and whether the dog has been spayed or neutered. For census division, we used the
109 reported state of address where the dog resides and divided them into the nine census divisions that are
110 adopted by the United States Census Bureau (12).

111 Poisson regression with robust standard error estimates (13) was used to estimate prevalence ratios
112 (PR) and construct 95% confidence intervals (CI) of the PRs. The Wald tests were to test whether lifetime
113 prevalence increased with age, and whether the size of the dog influenced either the prevalence of a
114 reported condition in the disease category or its pattern across age. Based on the estimated PRs with
115 increasing weight from the unadjusted model without the interaction term, we separated the result
116 tables and figures into two sections: one for disease categories more common in larger dogs and the
117 other for disease categories less or equally common in larger dogs. In addition, we graphically illustrated
118 the predicted prevalence of each disease category as a function of continuous age for each size class.
119 These estimates were predicted using Poisson regression models fit with continuous age, categorical
120 size, and the interaction of those two as predictors. Though fitted models included dogs aged 15+ years,
121 we produced predictions for age from 0 to 15 as dogs older than 15 were very rare. Given the large
122 sample size of the study and continuous nature of the exposures we used $p < 0.01$ to denote statistical
123 significance. For interactions with $p < 0.01$ we also visually inspected the figures for qualitative evidence
124 of important interaction.

125 All statistical analyses were performed in R 4.1.2 (14). The Dog Aging Project is an open data project.
126 These data are available to the general public at dogagingproject.org/open_data_access (15).

127 **Results**

128 There were 27,541 dog owners that completed the Health and Life Experience Survey and are included
129 in this report. The dogs ranged in age from puppies to very senior dogs, with a median age of 7 years
130 (IQR 4 to 11). The dogs were equally distributed by sex (50% male) and purebred versus mixed breed
131 status (49% purebred). The respondents were distributed across the US, with the following percentages
132 according to census divisions in decreasing order of representation: Pacific 24%, South Atlantic 18%,
133 East North Central 15%, Mountain 10%, Mid-Atlantic 9%, West South Central 8%, New England 6%, West
134 North Central 6%, East South Central 3%. The dogs most commonly resided in suburban locations (62%),
135 with 17% residing in urban locations and 21% in rural locations. We now provide results for each disease
136 category individually, with the categories that were positively associated with dog size discussed first,
137 followed by those that were either negatively or not associated with dog size.

138 *Skin Conditions*

139 A total of 7915 (28.7%) dog owners reported that their dogs had a history of conditions within the skin
140 disease category (Table 1). The most commonly reported specific skin problems were seasonal allergies
141 (n=1878) followed by pruritus (n=1164) and sebaceous cysts (n=943) (Supplementary Table 1). The
142 proportion of dogs with a reported history of skin conditions increased steadily with age, ranging from
143 7% in puppies to 37% in senior dogs (Table 1). History of skin disease was reported less for smaller vs.
144 larger dogs, ranging from 26% in dogs <10kg to 33% in dogs over 40kg (Table 2). In the Poisson
145 regression model with the main effects of age and weight, each SD increment of age (4 years) was
146 associated with a 29% greater relative prevalence of a reported history of skin conditions (PR 1.29, 95%
147 CI 1.27-1.31, p<0.001). Prevalence also increased with the owner-reported weight of the dog, with each
148 SD increment (13 lbs) associated with 12% higher relative prevalence of skin condition history (PR 1.12,
149 95% CI 1.10-1.14, p<0.001). There was no significant interaction between age and weight, which was in
150 alignment with the results in Figure 1 that older dogs were reported to have skin conditions more often
151 by a similar relative margin across different size classes. In Figure 1 we illustrate these patterns using a
152 categorical representation of dog size. We see strongly increasing trends over age that are similar across
153 size classes. Toy dogs have the lowest rates across age, and a history of skin conditions is reported
154 progressively more often for each successively larger size category regardless of age at the time of the
155 survey. Adjustment for sex, breed and geographic region did not have any notable impact on the
156 associations, and this was true for all disease categories we studied.

157 *Orthopedic Conditions*

158 A total of 5287 (19.2%) dog owners reported that their dogs had a history of conditions within the
159 orthopedic disease category (Table 1). The three most commonly reported specific orthopedic problems
160 were osteoarthritis (n=1777) followed by cruciate ligament rupture (n=982) and patellar luxation

161 (n=693) (Supplementary Table 1). Unsurprisingly, the proportion of dogs reported to have a history of
162 orthopedic conditions increased sharply with age (from 1% in puppies to 39% in the oldest dog group,
163 Table 1) and slightly with size (from 19% in the <10kg dogs to 23% in the dogs over 40kg, Table 2). On
164 average, the prevalence of a reported history of orthopedic conditions doubled with every SD increment
165 in age (PR 2.00, 95% CI 1.95-2.04, p<0.001), but as indicated by the interaction term, the prevalence
166 across age increased much more sharply as the size of the dog increased. This is illustrated in Figure 1,
167 where for puppies and adolescents (<3 years) there is very little difference in prevalence by size class,
168 but for older adult to senior (7+ years) the larger dogs have a much greater prevalence of a history of
169 orthopedic conditions.

170 *Gastrointestinal (GI) Conditions*

171 A total of 3914 (14.2%) dog owners reported that their dogs had a history of conditions within the GI
172 disease category (Table 1). The most commonly reported specific GI conditions were chronic or
173 recurrent diarrhea (n=786) followed by anal sac impaction (n=720) and foreign body ingestion or
174 blockage (n=685) (Supplementary Table 1). The reported proportion of dogs with a history of GI
175 conditions increased with age (from 7% in puppies to 18% among senior dogs) but only slightly with size
176 (14% in dogs <10kg to 16% in dogs over 40kg). Each SD increment in dog age was associated with a 22%
177 higher relative prevalence (PR 1.22, 95% CI 1.19-1.26, p<0.001), while each SD increment in dog weight
178 was associated with 4% greater relative prevalence (PR 1.04, 95% CI 1.01-1.07, p=0.01). In Figure 1 we
179 see that all size groups increase steadily with age. Dogs <30kg are all similar, dogs between 30-40kg
180 have somewhat higher prevalence, and dogs over 40kg have notably higher prevalence across all ages.

181 *Ear, Nose, and Throat (ENT) Conditions*

182 A total of 3569 (13%) dog owners reported that their dogs had a history of conditions within the ENT
183 disease category (Table 1). The three most commonly reported specific ENT conditions were chronic or
184 recurrent ear infections (n=1998) followed by hearing loss (n=653) and acquired deafness (n=405)
185 (Supplementary Table 1). Reported history of ENT conditions increased from 3% among puppies to 25%
186 among senior dogs. Trends across size were slight, ranging from 13% in the smallest dogs (<10kg) to 16%
187 in the largest dogs (>=40kg). Controlling for the weight of the dog, on average the relative prevalence of
188 ENT conditions was 74% higher for each SD increment in age (PR 1.76, 95% CI 1.70-1.82, p<0.001).
189 However, there was a significant interaction between size and weight. Specifically, for larger dogs the
190 trend across age was flatter. Puppies to young adults (<7 years) had higher prevalence of ENT history for
191 larger dogs, but for seniors (11+ years), small dogs (<20 kg) had caught up to the largest dogs. This is
192 illustrated in Figure 1.

193 *Cancer/Tumors*

194 A total of 1751 (6.4%) dog owners reported that their dogs had a history of conditions within the
195 cancer/tumor category (Table 1). The most commonly reported specific cancer sites were skin of
196 trunk/body/head (n=502) followed by muscle or other soft tissue (n=376) and skin of limb/foot (n=254).
197 The most commonly known types of cancer were mast cell tumor (n=349) and lipoma (n=217). However,

198 many owners were unsure of types of cancer (n=499) (Supplementary Table 1). The proportion of dogs
199 for whom a history of cancer was reported increased sharply with age, ranging from <1% in puppies and
200 adolescent dogs, 2% in young adult dogs, 8% in older adult dogs, and 15% in senior dogs. Prevalence by
201 size ranged from 4% in dogs <10kg, to between 6-8% among dogs over 10kg. The increasing pattern
202 across age was much more pronounced in larger dogs. For dogs of the same size, each SD increment in
203 dog age was associated with a two-and-a-half-fold increase in the prevalence of cancer history (PR 2.56,
204 95% CI 2.45-2.67, p<0.001). For each additional SD increment in size, the age trend increased by 7%. In
205 Figure 1 we see this illustrated graphically, where for puppies and adolescents (<3 years), prevalence is
206 low for all sizes, but for seniors (11+ years) the prevalence has risen rapidly, especially for dogs over
207 30kg.

208 *Neurologic Conditions*

209 A total of 1324 (4.8%) dog owners reported that their dogs had a history of conditions within the
210 neurologic disease category (Table 1). The three most commonly reported specific neurologic conditions
211 were seizures (n=606) followed by dementia/senility (n=153) and vestibular disease (n=147)
212 (Supplementary Table 1). The proportion of dogs with a history of neurologic conditions increased from
213 <1% in puppies and adolescent dogs to 12% in senior dogs. On average there was no apparent trend
214 across sizes, though the largest dogs had a much steeper increasing pattern across age than dogs <40kg.
215 Before older adulthood the prevalence of neurologic conditions was low, and similar across size classes.
216 In older adult and senior dogs the prevalence increased in a similar way for dogs <40kg, and more
217 steeply for dogs over 40kg.

218 *Endocrine Conditions*

219 A total of 913 (3.3%) dog owners reported that their dogs had a history of conditions within the
220 endocrine disease category (Table 1). The three most commonly reported specific endocrine conditions
221 were hypothyroidism (n=520), followed by Cushing's disease (n=175) and diabetes mellitus (n=83)
222 (Supplementary Table 1). The prevalence of a reported history of endocrine conditions was <1% through
223 young adulthood, 4% for older adult dogs, and 8% for senior dogs. On average there was not a strong
224 size pattern with prevalence ranging between 3-4%. However, controlling for age the influence of size
225 on prevalence was apparent (PR 1.27, 95% CI 1.19, 1.35, p<0.001). The increasing pattern of endocrine
226 condition history across age was similar for all size classes. These patterns are illustrated in Figure 1,
227 where the prevalence of reported history of endocrine conditions increases over time at a similar rate
228 for each size class, but the larger the dog the higher the estimated prevalence curve.

229 *Infectious Diseases*

230 A total of 7339 (26.6%) dog owners reported that their dogs had a history of conditions within the
231 infectious disease category (Table 1). The three most commonly reported specific infectious conditions
232 were *Giardia* (n=1958) followed by *Bordetella* and/or parainfluenza (kennel cough) (n=1277) and
233 tapeworms (n=816) (Supplementary Table 1). The proportion of dogs with a reported history of
234 infectious diseases followed a unique pattern relative to all other conditions studied. The prevalence

235 among puppies was 25%, and this did not increase across other age groups ranging between 25-28%
236 with no particular trend. The smallest dogs <10kg had the lowest reported history of infectious diseases
237 at 19%, but all other size classes were similar to each other, with 27-30% prevalence. These patterns are
238 most clearly illustrated in Figure 1, where the pattern across age groups is flat, and the curve for the
239 smallest dogs is lowest.

240 *Ocular Conditions*

241 A total of 3625 (13.2%) dog owners reported that their dogs had a history of conditions within the ocular
242 disease category (Table 1). The three most commonly reported specific ocular conditions were adult-
243 onset cataracts (n=1114) followed by conjunctivitis (n=759) and corneal ulcers (n=321) (Supplementary
244 Table 1). A reported history of ocular conditions increased steadily with age group, from 5% in puppies
245 to 28% among senior dogs. In contrast, the proportion with a positive history was lower among larger
246 dogs, ranging from 17% in the smallest dogs to just 10% in the dogs over 40kg. This was reflected in the
247 models where the significant interaction between age and weight is seen as a steeper slope in smaller
248 dogs. Graphically we can see in Figure 2 that below adulthood the size categories have roughly the same
249 prevalence but then the smaller dogs increase much more quickly in reported history of ocular
250 conditions.

251 *Kidney or Urinary Conditions*

252 A total of 2122 (7.7%) dog owners reported that their dogs had a history of conditions within the kidney
253 or urinary disease category (Table 1). The three most commonly reported specific kidney or urinary
254 conditions were chronic or recurrent urinary tract infection (n=813) followed by urinary incontinence
255 (n=636) and urinary crystals or stones in bladder or urethra (n=423) (Supplementary Table 1). The
256 proportion of dogs with reported history of kidney or urinary conditions increased steadily with age,
257 from 2% in puppies to 15% in senior dogs. Across size categories differences were not dramatic, but the
258 prevalence was highest in the smallest dogs at 9% in dogs <10kg and lowest in largest dogs at 6% in dogs
259 >=40kg. Differences between size classes were most apparent in older adults and seniors, as evidenced
260 by the significant age by weight interaction, and the graphical representation in Figure 2.

261 *Cardiac conditions*

262 A total of 1567 (5.7%) dog owners reported that their dogs had a history of conditions within the cardiac
263 disease category (Table 1). The three most commonly reported specific cardiac conditions were murmur
264 (n=1156) followed by valve disease (n=139) and congestive heart failure (n=137) (Supplementary Table
265 1). The proportion of dogs with a reported history of cardiac conditions exhibited strong trends across
266 both age and dog size. Among puppies and adolescents the proportion was <1%, increasing to 14%
267 among senior dogs. Dog weight was inversely associated, with dogs <10kg reporting an 11% prevalence
268 of a history of cardiac conditions, declining to only 2% among the largest dogs over 40kg. These trends
269 were highly significant, with each SD increment in age associated with over a doubling of prevalence (PR
270 2.19, 95% CI 2.1-2.29, p<0.001), and each SD increment in size reducing prevalence by a third (PR 0.67,
271 95% CI 0.63-0.71, p<0.001). Additionally, we observed a significant interaction where the prevalence

272 was not only higher for smaller dogs but was associated with a significantly steeper increase in
273 prevalence across age groups.

274 *Liver or Pancreas Conditions*

275 A total of 970 (3.5%) dog-owners reported that their dogs had a history of conditions within the liver or
276 pancreas disease category (Table 1). The three most commonly reported specific liver or pancreas
277 conditions were pancreatitis (n=587) followed by chronic inflammatory liver disease (n=86) and exocrine
278 pancreatic insufficiency (n=35) (Supplementary Table 1). A reported history of liver or pancreas
279 conditions was more common among older dogs ranging from <1% in puppies and adolescent dogs to
280 8% in senior dogs. In contrast the proportion was lower among larger dogs, ranging from 6% in the
281 smallest size category down to 2% among larger dogs. Each SD increment in age more than doubled the
282 prevalence of a reported history of liver/pancreas conditions (PR 2.12, 95% CI 2.00 to 2.24, p<0.001),
283 while each SD increment in size reduced the prevalence by approximately one quarter (PR 0.75, 95% CI
284 0.69-0.81, p<0.001). The smallest dog category (<10kg) in particular had a notably higher prevalence of
285 liver condition history.

286 *Respiratory Conditions*

287 A total of 950 (3.4%) dog owners reported that their dogs had a history of conditions within the
288 respiratory disease category (Table 1). The three most commonly reported specific respiratory
289 conditions were chronic or recurrent cough (n=236) followed by tracheal collapse (n=169) and
290 pneumonia (n=163) (Supplementary Table 1). The proportion of dogs with a reported history of
291 respiratory conditions went up with increased age, from <1% in puppies to 8% in senior dogs. The
292 proportion decreased with increasing size, from 6% in the smallest dogs to 3% in the largest dogs. For
293 every 1 SD increment in age the prevalence of a reported history of respiratory conditions doubled (PR
294 2.01, 95% CI 1.89-2.14, p<0.001), while for every 1 SD increment in weight the relative prevalence was
295 20% lower (PR 0.80, 95% CI 0.74-0.87, p<0.001). These patterns are illustrated in the final panel of Figure
296 2.

297

298 **Discussion**

299 We are interested in identifying potential patterns of disease contributing to decreased average lifespan
300 with increasing size in pet dogs. As found in other retrospective studies of the domestic dog (1,10,16–
301 20), we found that owner-reported diagnoses (grouped by organ system or pathophysiologic process)
302 disproportionately affect dogs of different sizes. Some conditions were reported less commonly for
303 larger dogs and as such are unlikely to be an important contributor to their shorter lifespan. These
304 included ocular, cardiac, liver/pancreas, and respiratory conditions. The proportion reporting a history
305 of urinary conditions did not vary by weight. Many conditions were reported more commonly with
306 increasing weight category, including skin, orthopedic, gastrointestinal, ear/nose/throat, cancer,
307 neurologic, and endocrine conditions. The infectious disease category showed a distinct pattern that the
308 smallest dogs (<10kg) had much lower prevalence than the other categories and there were no

309 increasing patterns across age. With the exception of infectious diseases, the proportion of dogs with a
310 reported history of each disease category increased with increasing age group as expected. Effects of
311 size included differences in relative prevalence of reporting a history of disease as well as variable
312 patterns of increase in prevalence across age categories.

313 Higher growth rates in larger dogs have been implicated in increased oxidative damage during early life
314 that may predispose to certain diseases such as skin diseases, orthopedic conditions, cancer, and cardiac
315 disorders (21). Skin is a common site for evidence of oxidative damage; increased production of free
316 radicals including reactive oxygen species (ROS) can overwhelm the body's mechanisms for reducing
317 their damaging effects and manifest as skin lesions and other pathology (22). In mouse models,
318 increased oxidative stress induced by exposure to diisodecyl phthalate (DIDP) exacerbated symptoms of
319 allergic dermatitis (23). A retrospective study of 721 dogs by Dreschel (24) measuring associations
320 between behavioral health and physical health found that dogs with severe fear and separation anxiety
321 disorders had both significantly higher prevalence and severity of skin diseases as well as significantly
322 shorter lifespan (24). The author suggests that these associations may be due to physiological stress
323 responses in dogs with behavioral disorders and resulting changes in hormone regulation, immunity,
324 and disease risk.

325 Faster growth rates and larger body size have also been associated with increased risk for orthopedic
326 diseases (6). Growth patterns in larger dog breeds involve rapid weight gain throughout the period of
327 skeletal development and maturity, which has been linked to increased risk of developmental
328 musculoskeletal and orthopedic diseases including hip dysplasia, osteoarthritis, and osteochondrosis
329 (6,25,26). These conditions have been implicated in reducing longevity in Labrador Retrievers (27). In
330 our cohort, osteoarthritis (OA), was spread similarly among dogs with body weight greater than ten
331 kilograms in our cohort, the morbidity associated with OA may vary. Orthopedic pain from any of these
332 diagnoses can significantly reduce quality of life (27). Poor QOL has been identified as one of the most
333 influential factors for owners choosing to euthanize their dogs and thereby shorten their lifespan to
334 prevent pain and distress (28). Most medications commonly used to alleviate pain from OA are dosed by
335 weight and are thus more likely to be cost-prohibitive for owners with larger dogs; such factors may also
336 lead to differential effects of OA by size on QOL and decisions about euthanasia. Additionally, mobility
337 problems due to orthopedic disease are more easily accommodated in dogs of smaller size, as owners
338 are more likely to be capable of lifting or carrying smaller dogs and/or assisting their movement with
339 slings, harnesses, and other devices.

340 Across all body sizes, several retrospective studies of large cohorts of companion dogs in North America
341 and Europe have consistently found that cancer (1,17,19,20,28,29) is one the most common causes of
342 mortality in pet dogs. Multiple studies that have considered body size in relation to causes of morbidity
343 and mortality have reported that cancer diagnoses are more common in larger dogs than smaller dogs
344 (1,30–32). Several theories about the contributing factors to reduced longevity in larger dogs are
345 consistent with increased risk of cancer in larger dogs including correlations between increased serum
346 IGF-1 levels in larger dogs and downstream effects on growth, oxidative damage, and cancer risk
347 (6,30,33,34). Artificial selection to produce the extreme variation in growth rates between breeds has
348 resulted in wide variation in serum IGF-1 levels before and after skeletal maturity. For example, Great
349 Danes gained weight at 17 times the rate of miniature poodles in a study following the first 21 weeks of

350 life (35). Correspondingly higher levels of mean basal IGF-1 detected in the plasma of Great Danes
351 compared to miniature poodles from age 13 weeks to 27 weeks in a related study suggested that Great
352 Danes may enter a period of physiologic gigantism postnatally (36). Plasma levels of IGF-1 remain higher
353 in larger breed dogs compared to smaller breed dogs past maturity, and this inverse correlation
354 between IGF-1 levels and longevity is consistent with patterns found in many other species (6).

355 Studies investigating the relationship between average breed growth rates and prevalence of life-
356 limiting disorders linked to oxidative damage have revealed correlations between breed size and risk of
357 developing cardiac pathology. Increased risk of cardiac disease and associated mortality has been
358 reported at both extremes of the body size spectrum in dogs, though the prevalence of specific cardiac
359 pathophysiologies varies widely from small dogs to giant breed dogs (1,19,20). Artificial selection for
360 extreme size (both small and giant) may have contributed to the distribution of cardiac disease risk in
361 dogs, as many genes associated with body size in dogs also contribute to cardiac development and
362 structure (37). Telomere length in peripheral blood mononuclear cells was positively correlated with
363 lifespan and inversely correlated with risk of mortality due to cardiac disease in a study of 15 breeds of
364 dog, with the shortest age-adjusted telomere length in the Great Dane (38). In our cohort, reported
365 prevalence of cardiac disease increases more rapidly with age in smaller dogs. Contribution of cardiac
366 disease to mortality risk in our cohort is unknown.

367 Reported prevalence of diagnoses in the gastrointestinal category was more common as size increased
368 in our cohort. The most commonly reported diagnoses in this category (chronic or recurrent diarrhea,
369 anal sac impactions, foreign body ingestion or blockage, and food or medicine allergies) can vary widely
370 in severity, and therefore potential effects on longevity are difficult to predict. Increased risk of
371 mortality due to gastrointestinal disease with increasing body size has been reported by Fleming et al.
372 (1).

373 In our cohort, larger dogs were also more likely to have diagnoses in the neurological category. Of these
374 diagnoses "seizures (including epilepsy)" was the most commonly reported specific condition, and was
375 distributed fairly evenly across body sizes. Fleming, et al. (1) found that larger dogs were relatively
376 spared from death due to neurological diseases. Our results are not inconsistent with this finding, as
377 many dogs with seizures do not die as a direct result of their neurological disease; the majority of dogs
378 with epilepsy (the most common cause of recurrent seizures in dogs) can be treated successfully with
379 conventional drugs (39) and, similarly, the majority of companion dogs with epilepsy die of a cause not
380 directly related to epilepsy (40). Additionally, neurological diseases associated with greater mortality risk
381 compared to epilepsy are more common in smaller dogs (e.g., intervertebral disc disease), and tend to
382 present later in life than epilepsy, such that neurological disease in smaller dogs would be less frequent
383 in our cohort than in cohorts examined retrospectively for causes of mortality.

384 Previously, Fleming et al. (1) reported that larger breeds are spared from death by endocrine disease. In
385 our cohort, the reported prevalence of a diagnosis in the endocrine category was more likely in larger
386 dogs. This contrast between reported mortality versus prevalence may be driven almost entirely by the
387 most commonly reported specific endocrine disorder, hypothyroidism. Hypothyroidism was more
388 prevalent in larger dogs, and this diagnosis alone was responsible for most of the trend by size for the
389 endocrine category. While untreated hypothyroidism can cause significant morbidity and even
390 mortality, it is relatively easy and inexpensive to treat in dogs (41,42). In contrast, Cushing's disease and

391 diabetes mellitus, two frequently diagnosed diseases that are more prevalent in smaller dogs in our
392 cohort, carry greater mortality risk and financial burden for the owner (43–46). It is noteworthy that
393 Fleming et al. (1) used data from dogs seen in referral institutions while the dogs in our study were
394 recruited directly from the community. It is therefore likely that referral bias (47) could also explain the
395 difference in these results, as treatment of hypothyroidism is usually straightforward and does not
396 require referral (48).

397 For the ENT category, the most commonly reported diagnosis, ear infection, was drastically skewed
398 toward larger dogs. Ear infections in dogs are commonly associated with allergic skin disease and food
399 allergies and thus increased prevalence in larger dogs would be consistent with the aforementioned
400 theories about increased oxidative damage and skin manifestations. While ear infections can sometimes
401 be easily treated, chronic/recurrent ear infections are also common and can drastically affect quality of
402 life (49–52). Recurrent ear infections can be expensive to monitor and treat, with surgery to remove the
403 entire ear canal(s) as the only curative option for some dogs. Because significant financial resources may
404 be necessary to avoid negative impacts on quality of life due to ear infections, cost may be a factor
405 guiding euthanasia decisions and thus lifespan (52,53). The next most frequent diagnoses in the ENT
406 category were hearing loss and deafness, which both have frequencies skewed toward smaller dogs. In
407 general, pet dogs do not receive treatment for hearing loss or deafness, nor do they receive adaptive
408 devices such as hearing aids and thus financial limitations of the owner do not tend to change the
409 prognosis for the patient with chronic ear infections. Hearing loss is typically not associated with pain,
410 and dogs are often capable of maintaining a good quality of life despite partial or complete deafness.

411 Our study has several strengths and limitations that should be noted. Strengths include the large sample
412 size of this study, which allows us to estimate patterns accurately across the whole age and size
413 spectrum. Additionally, we have a very diverse sample of dogs distributed across the entire United
414 States. Since the sample is not veterinary-hospital or clinic-based it may be more representative of the
415 general population of dogs. Conversely, while our observations can suggest which conditions manifest
416 differently across age and size, they do not prove any causal relationships due to the cross-sectional
417 nature of the analysis. Over time, longitudinal data will be collected on these dogs, and we will be able
418 to examine disease incidence. In addition, recall bias may occur when owners fill out the survey. It is
419 possible that owners may not remember past events at all or incorrectly at the time of the survey.
420 Future studies will compare HLES data to Veterinary Electronic Medical Records data to measure the
421 accuracy of owner's reported diagnoses and confirm the trends seen in HLES. Prevalence of a history of
422 conditions was expected to go up regardless of an increasing age-specific prevalence because it was
423 calculated in a cumulative way. Finally, the sample is not random but self-selected so that data are
424 subject to self-selection bias. Owners who are more exposed to this survey and who tend to participate
425 in surveys are more likely to nominate their dogs and complete the survey, possibly leading to a biased
426 sample. The Dog Aging Project endeavors to create a representative sample of the companion canine
427 population. However, computer access is a necessary condition for survey completion, as well as the
428 ability to complete the surveys in English.

429 In this study we have quantified the reported prevalence of a history of conditions within several
430 different disease categories as a function of dog age and size, with and without adjustment for sex,
431 geographic location, and pure versus mixed breed status. These results provide insights into the disease

432 categories that may contribute to reduced lifespan in larger dogs and suggest multiple further avenues
433 for further exploration. More focused efforts to look at individual conditions within categories may yield
434 additional insights. Within and across categories, the co-occurrence of different disease subtypes may
435 also be an important factor to evaluate. Of course, as prospective data become available the
436 longitudinal associations of these conditions with subsequent morbidity and mortality will be evaluated.

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Table 1: Proportion with Disease History by Age

Disease	Puppy (<1yr)	Adolescent (1 to <3yr)	Young Adult (3 to <7yr)	Older Adult (7 to <11yr)	Senior (>=11yr)	Overall
	N=591	N=4622	N=8249	N=7666	N=6413	N=27541
Skin	40 (7%)	796 (17%)	2181 (26%)	2556 (33%)	2342 (37%)	7915 (29%)
Infection/Parasites	147 (25%)	1269 (27%)	2291 (28%)	2009 (26%)	1623 (25%)	7339 (27%)
Bone/Orthopedic	7 (1%)	239 (5%)	849 (10%)	1699 (22%)	2493 (39%)	5287 (19%)
Gastrointestinal	39 (7%)	488 (11%)	1059 (13%)	1158 (15%)	1170 (18%)	3914 (14%)
Eye	31 (5%)	283 (6%)	586 (7%)	906 (12%)	1819 (28%)	3625 (13%)
Ear/Nose/Throat	19 (3%)	302 (7%)	745 (9%)	916 (12%)	1587 (25%)	3569 (13%)
Kidney/Urinary	14 (2%)	153 (3%)	406 (5%)	591 (8%)	957 (15%)	2121 (8%)
Cancer/Tumors	1 (<1%)	21 (<1%)	177 (2%)	586 (8%)	966 (15%)	1751 (6%)
Cardiac	3 (<1%)	45 (<1%)	167 (2%)	440 (6%)	912 (14%)	1567 (6%)
Brain/Neurologic	2 (<1%)	25 (<1%)	188 (2%)	359 (5%)	750 (12%)	1324 (5%)
Liver/Pancreas	2 (<1%)	24 (<1%)	125 (2%)	277 (4%)	542 (8%)	970 (4%)
Respiratory	4 (<1%)	53 (1%)	132 (2%)	242 (3%)	519 (8%)	950 (3%)
Endocrine	0 (<1%)	8 (<1%)	77 (<1%)	310 (4%)	518 (8%)	913 (3%)

Table 2: Proportion with Disease History by Weight Category

Disease	<10kg	10 to <20kg	20 to <30kg	30 to <40kg	>=40kg	Overall
	N=6207	N=5613	N=8219	N=5167	N=2335	N=27541
Skin	1628 (26%)	1531 (27%)	2369 (29%)	1621 (31%)	766 (33%)	7915 (29%)
Infection/Parasites	1186 (19%)	1593 (28%)	2441 (30%)	1478 (29%)	641 (27%)	7339 (27%)
Bone/Orthopedic	1187 (19%)	931 (17%)	1461 (18%)	1181 (23%)	527 (23%)	5287 (19%)
Gastrointestinal	892 (14%)	786 (14%)	1119 (14%)	749 (14%)	368 (16%)	3914 (14%)
Eye	1079 (17%)	800 (14%)	934 (11%)	571 (11%)	241 (10%)	3625 (13%)
Ear/Nose/Throat	827 (13%)	713 (13%)	915 (11%)	752 (15%)	362 (16%)	3569 (13%)
Kidney/Urinary	530 (9%)	452 (8%)	639 (8%)	369 (7%)	131 (6%)	2121 (8%)
Cancer/Tumors	273 (4%)	327 (6%)	565 (7%)	428 (8%)	158 (7%)	1751 (6%)
Cardiac	671 (11%)	362 (6%)	301 (4%)	177 (3%)	56 (2%)	1567 (6%)
Brain/Neurologic	362 (6%)	278 (5%)	346 (4%)	235 (5%)	103 (4%)	1324 (5%)
Liver/Pancreas	393 (6%)	209 (4%)	195 (2%)	130 (3%)	43 (2%)	970 (4%)
Respiratory	385 (6%)	169 (3%)	207 (3%)	124 (2%)	65 (3%)	950 (3%)
Endocrine	194 (3%)	190 (3%)	264 (3%)	176 (3%)	89 (4%)	913 (3%)

Table 3: Association of Age and Weight with Lifetime Prevalence (Part 1: Conditions More Common in Larger Dogs)

Condition	Characteristic	Model 1 ^a			Model 2 ^b			Model 3 ^c		
		PR	95% CI	p-value	PR	95% CI	p-value	PR	95% CI	p-value
Skin	Age	1.29	(1.27, 1.31)	<0.001	1.29	(1.27, 1.31)	<0.001	1.27	(1.25, 1.3)	<0.001
	Weight	1.12	(1.1, 1.14)	<0.001	1.12	(1.1, 1.14)	<0.001	1.13	(1.11, 1.15)	<0.001
	Age * Weight	-	-	-	0.98	(0.96, 1)	0.02	0.98	(0.96, 0.99)	<0.01
Bone/Orthopedic	Age	2	(1.95, 2.04)	<0.001	2	(1.96, 2.05)	<0.001	1.98	(1.93, 2.03)	<0.001
	Weight	1.22	(1.19, 1.25)	<0.001	1.17	(1.13, 1.2)	<0.001	1.17	(1.13, 1.2)	<0.001
	Age * Weight	-	-	-	1.08	(1.05, 1.11)	<0.001	1.08	(1.05, 1.11)	<0.001
Gastrointestinal	Age	1.22	(1.19, 1.26)	<0.001	1.22	(1.19, 1.26)	<0.001	1.21	(1.18, 1.25)	<0.001
	Weight	1.04	(1.01, 1.07)	0.01	1.04	(1.01, 1.07)	0.01	1.03	(1, 1.06)	0.06
	Age * Weight	-	-	-	0.98	(0.96, 1.01)	0.24	0.99	(0.96, 1.02)	0.42
Ear/Nose/Throat	Age	1.76	(1.7, 1.82)	<0.001	1.74	(1.68, 1.79)	<0.001	1.73	(1.68, 1.79)	<0.001
	Weight	1.16	(1.12, 1.19)	<0.001	1.21	(1.17, 1.24)	<0.001	1.19	(1.16, 1.23)	<0.001
	Age * Weight	-	-	-	0.89	(0.87, 0.92)	<0.001	0.9	(0.87, 0.92)	<0.001
Cancer/Tumors	Age	2.56	(2.45, 2.67)	<0.001	2.54	(2.43, 2.66)	<0.001	2.52	(2.41, 2.64)	<0.001
	Weight	1.4	(1.35, 1.45)	<0.001	1.33	(1.27, 1.39)	<0.001	1.35	(1.28, 1.41)	<0.001
	Age * Weight	-	-	-	1.07	(1.03, 1.11)	<0.001	1.07	(1.02, 1.11)	<0.01
Brain/Neurologic	Age	2.46	(2.33, 2.59)	<0.001	2.48	(2.35, 2.62)	<0.001	2.49	(2.35, 2.63)	<0.001
	Weight	1.08	(1.02, 1.15)	<0.01	1.04	(0.97, 1.12)	0.3	1.01	(0.94, 1.09)	0.7
	Age * Weight	-	-	-	1.06	(1, 1.12)	0.05	1.07	(1.02, 1.13)	0.01
Endocrine	Age	2.6	(2.46, 2.75)	<0.001	2.6	(2.46, 2.75)	<0.001	2.59	(2.45, 2.74)	<0.001
	Weight	1.27	(1.19, 1.35)	<0.001	1.26	(1.18, 1.35)	<0.001	1.24	(1.16, 1.33)	<0.001
	Age * Weight	-	-	-	1.01	(0.96, 1.06)	0.74	1.02	(0.97, 1.07)	0.52
Infection/Parasites	Age	0.97	(0.95, 0.99)	<0.01	0.97	(0.96, 0.99)	0.01	0.96	(0.94, 0.98)	<0.001
	Weight	1.09	(1.07, 1.11)	<0.001	1.1	(1.08, 1.12)	<0.001	1.11	(1.09, 1.13)	<0.001
	Age * Weight	-	-	-	1.04	(1.02, 1.06)	<0.001	1.04	(1.02, 1.06)	<0.001

Note:

Age (years) and Weight (kg) are standardized by subtracting their means 7, 23 and dividing by their standard deviations 4, 13.

^a A model with the main effects of age and weight.

^b A model with the main effects of age, weight, and the interaction.

^c A model with the main effects of variables in Model 2 plus adjusted for sex, purebred/mixed breed, and geographic region.

Table 4: Association of Age and Weight with Lifetime Prevalence (Part 2: Conditions Less or Equally Common in Larger Dogs)

Condition	Characteristic	Model 1 ^a			Model 2 ^b			Model 3 ^c		
		PR	95% CI	p-value	PR	95% CI	p-value	PR	95% CI	p-value
Eye	Age	1.86	(1.81, 1.92)	<0.001	1.8	(1.74, 1.86)	<0.001	1.81	(1.75, 1.87)	<0.001
	Weight	0.93	(0.9, 0.96)	<0.001	0.98	(0.94, 1.02)	0.27	0.96	(0.93, 1)	0.05
	Age * Weight	-	-	-	0.89	(0.87, 0.92)	<0.001	0.91	(0.88, 0.94)	<0.001
Kidney/Urinary	Age	1.76	(1.69, 1.83)	<0.001	1.75	(1.68, 1.82)	<0.001	1.72	(1.65, 1.79)	<0.001
	Weight	1.01	(0.97, 1.05)	0.77	1.02	(0.98, 1.07)	0.32	1.07	(1.02, 1.12)	<0.01
	Age * Weight	-	-	-	0.96	(0.93, 1)	0.06	0.94	(0.91, 0.98)	<0.01
Cardiac	Age	2.19	(2.1, 2.29)	<0.001	2.1	(1.98, 2.21)	<0.001	2.11	(2, 2.23)	<0.001
	Weight	0.67	(0.63, 0.71)	<0.001	0.71	(0.66, 0.77)	<0.001	0.7	(0.65, 0.75)	<0.001
	Age * Weight	-	-	-	0.92	(0.87, 0.97)	<0.01	0.93	(0.88, 0.99)	0.02
Liver/Pancreas	Age	2.12	(2, 2.24)	<0.001	2.12	(1.99, 2.26)	<0.001	2.12	(1.98, 2.26)	<0.001
	Weight	0.75	(0.69, 0.81)	<0.001	0.75	(0.68, 0.82)	<0.001	0.75	(0.68, 0.82)	<0.001
	Age * Weight	-	-	-	1.01	(0.94, 1.08)	0.85	1.02	(0.95, 1.09)	0.67
Respiratory	Age	2.01	(1.89, 2.14)	<0.001	2.04	(1.9, 2.2)	<0.001	2.06	(1.91, 2.21)	<0.001
	Weight	0.8	(0.74, 0.87)	<0.001	0.78	(0.71, 0.86)	<0.001	0.76	(0.69, 0.84)	<0.001
	Age * Weight	-	-	-	1.04	(0.96, 1.13)	0.32	1.06	(0.98, 1.15)	0.13

Note:

Age (years) and Weight (kg) are standardized by subtracting their means 7, 23 and dividing by their standard deviations 4, 13.

^a A model with the main effects of age and weight.

^b A model with the main effects of age, weight, and the interaction.

^c A model with the main effects of variables in Model 2 plus adjusted for sex, purebred/mixed breed, and geographic region.

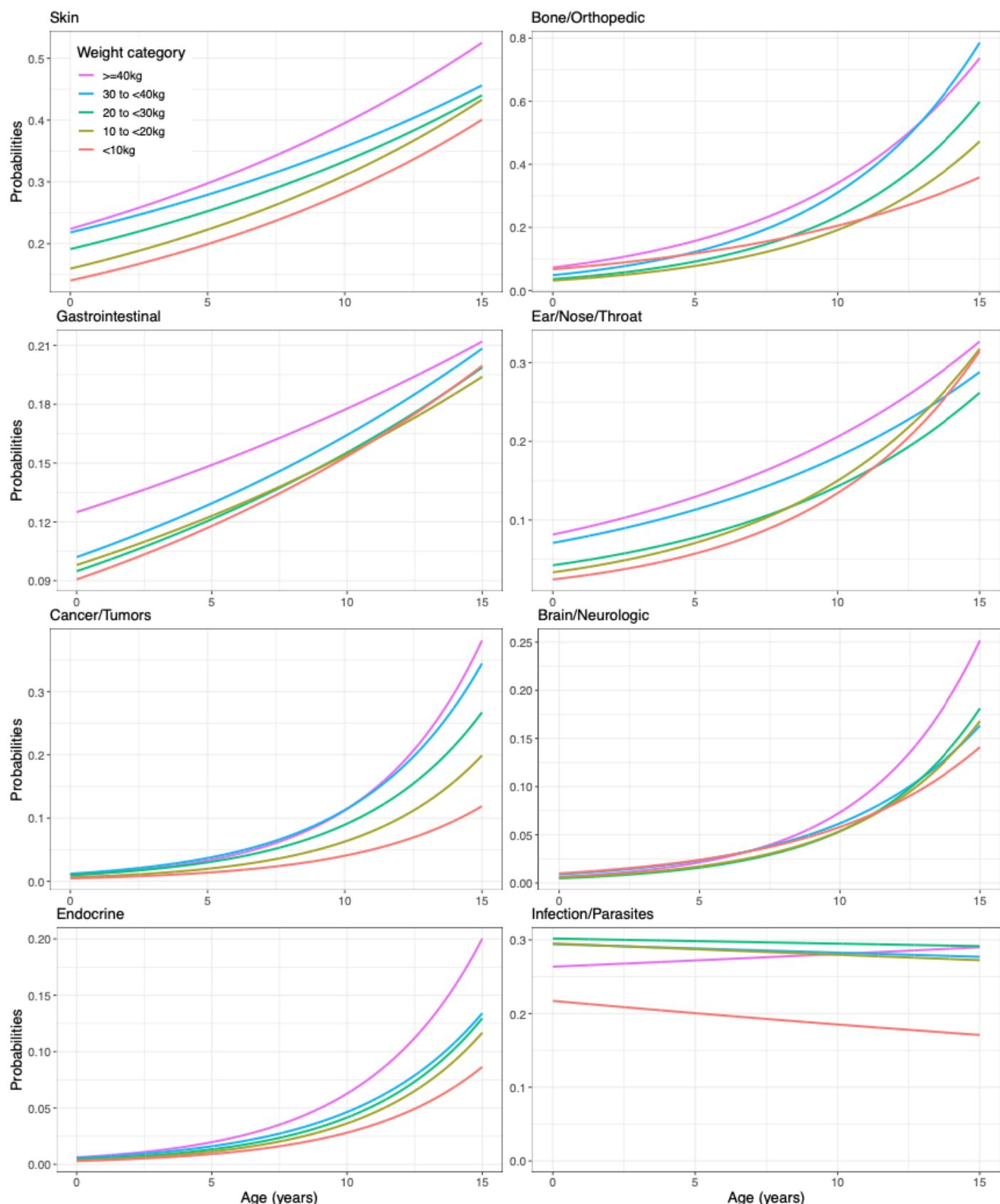


Figure 1: Results from Model 2 with Continuous Age by Weight Category (Part 1: Conditions More Common in Larger Dogs)

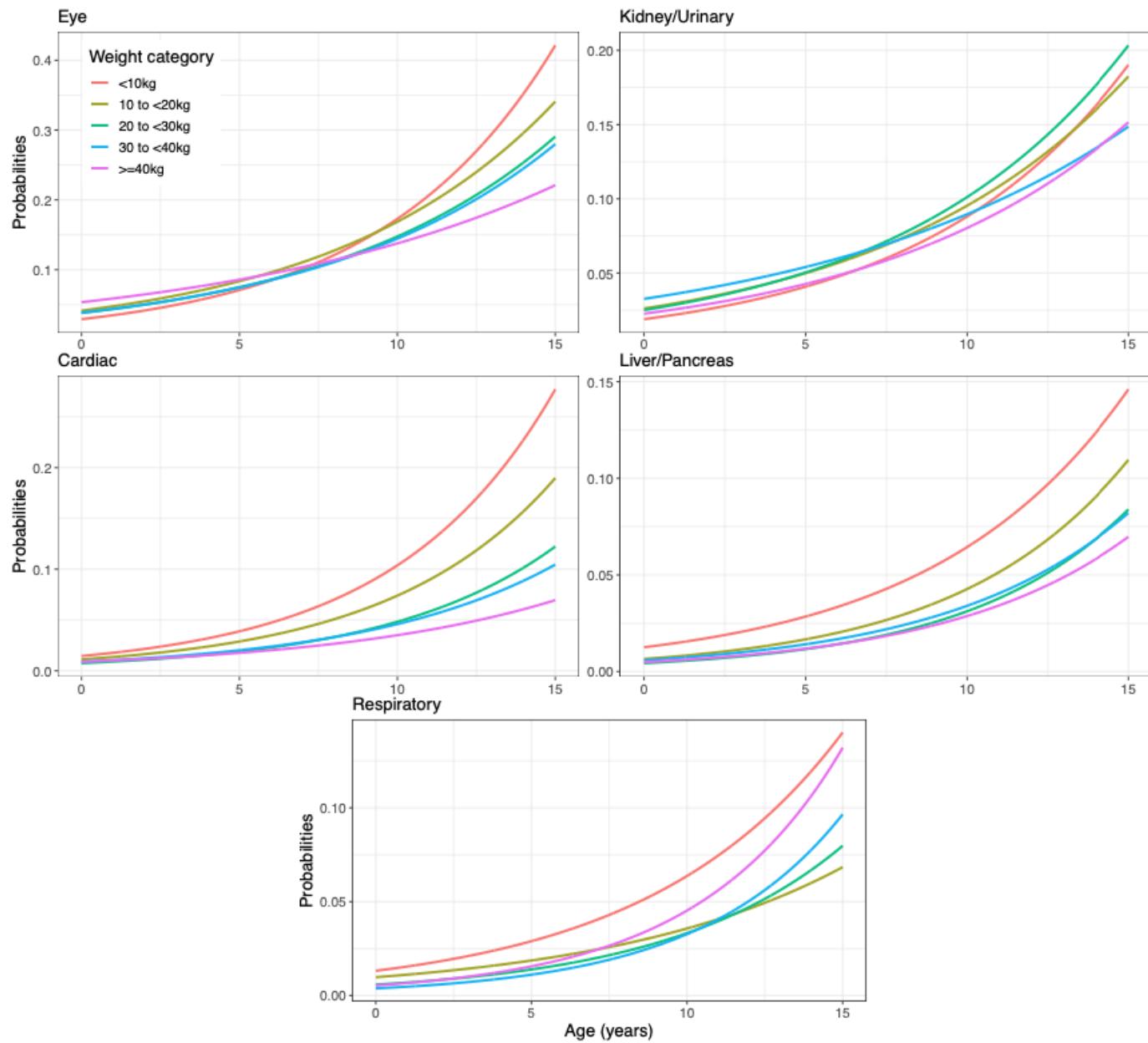


Figure 2: Results from Model 2 with Continuous Age by Weight Category (Part 2: Conditions Less or Equally Common in Larger Dogs)

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