Master Thesis

Disease Burden of Dalmatians Compared to Crossbreds and Dogs of Unknown Breeds

Looking at the number of claims or visits to the veterinary clinic, the most commonly claimed for organ systems and survival time

Student:
Charlotte Vroomen
4266986

June 2020

Supervisor:
J.C.M. Vernooij
Department of Farm Animal Health
Faculty of Veterinary Medicine, Utrecht University

TABLE OF CONTENTS

Abstract	3
1. Introduction	4
2. Materials and Methods	6
2.1. Materials	6
2.2. Methods	7
3. Results	12
3.1. Frequency of records per observation time	14
3.2. Frequency of occurrence of organ systems	18
3.3. Survival time	19
4. Discussion	21
4.1. Frequency of records per observation time	21
4.2. Frequency of occurrence of organ systems	21
4.3. Survival time	22
4.4. Variables in datasets	23
4.5. Insurance data	24
4.6. Sex and neutering status	25
4.7. Data validity	25
5. Conclusion	27
Acknowledgement	28
References/ Bibliography	29
Appendix	32

ABSTRACT

OBJECTIVES: Disease burden of purebred dogs is an increasingly hot topic in veterinary medicine. Many breeds have been studied on this subject, however to this day little is known about the disease burden in Dalmatians. The aim of this study was to compare Dalmatians with a control group of mixed-breed dogs. All data was derived from three datasets: a veterinary practice software system and two different pet insurance companies.

METHODS: Breed health and disease burden were determined by comparing the frequency of visits to the veterinarian, frequency of expense claims to the insurance companies, determining which organ systems said claims were mostly attributed to by means of an organ code and the survival time respectively. A Quasi-Poisson regression model was used to compare the frequency of visits and claims per breed group, a Logistic regression model was used to compare the most commonly claimed for organ systems and a Kaplan-Meier graph and a multivariable Cox proportional hazard model was used to compare the survival time between the breed groups.

RESULTS: Compared to dogs of an unknown breed or mixed-breed, Dalmatians were found to have more visits (RR 1.4, 95% confidence interval: 1.1-1.8, p-value = 0.01) and claims (RR 1.2 (0.8-1.8, p-value = 0.3) and RR 9.4 (8.0-11.1, p-value <0.001) respectively for both insurance companies). All organ systems for which a significant association with breed was found, were in favour of mixed-breed dogs. Dalmatians had expense claims for all of these organ systems more often than mixed-breed dogs, with the lowest odds ratio (OR) for neurological conditions (OR 2.5, 95% CI 1.0-5.6) and the highest OR for pancreas (OR 11.6, (5.6-24)).

CLINICAL SIGNIFICANCE: The disease burden appears to be significantly higher for Dalmatians based on the frequency of visits or claims and the organ systems that were claimed for. However, the outcomes might be subjected to selection bias. It is therefore important to perform further research with more carefully selected and complete data.

1. INTRODUCTION

For thousands of years humans have been selecting dogs for the particular phenotypical and behavioural characteristics that fit our needs. In the course of time, this selection has resulted in a greater phenotypic diversity of dogs than any other mammal. Some dog breeds were even established through crossbreeding other dog breeds. However, many breed-lines have been deliberately genetically isolated in order to solely produce offsprings with the desired characteristics (Karlsson and Lindblad-Toh, 2008; Nielen et al., 2001). For example, between 1970 and 1990 approximately only 3-5% of registered dogs were used to produce the next generations of purebred dogs in the Netherlands (Ubbink et al., 1998). Unfortunately, this selective breeding has led to a decrease in gene pool and created population bottlenecks (Nielen et al., 2001; Syme, 2012), resulting in an increase of hereditary disorders in purebred dogs since pathogenic mutations may have accidentally been co-selected with the desired traits. The number of diseases that are recognized as being hereditary or having hereditary traits is nearly 700 (Donner et al., 2018). According to Ruvinsky and Sampson (2001) this number is still increasing with new disorders being discovered every year, a detailed and updated list can always be found at the "Online Mendelian Inheritance in Animals" (OMIA, accessed August 20, 2018). Many breeds are known to have more than 30 genetic disorders although the number of these disorders that are clinically relevant for every breed is around 4 - 8 (Ruvinsky and Sampson, 2001).

Very rightly, this increase in hereditary disorders concerns both veterinary professionals and the general public (Keijser et al., 2017). Many dog breeds, e.g. German Shepherds, French Bulldogs, Cavalier King Charles Spaniel and St. Bernard with breed-specific disorders have therefore already been studied intensively (Lingaas et al., 2003; Rusbridge and Knowler, 2004; Schlensker and Distl, 2016; Temwichitr et al., 2010). However, for dogs of the Dalmatian breed this is not yet the case. It is commonly known that Dalmatians suffers from unilateral or bilateral Canine Congenital Sensorineural Deafness (CCSD). In the USA the reported prevalence is 30%, but this is thought to be lower in Europe (Gough et al., 2018). Ruvinsky and Sampson (2001) state that 20% of Dalmatians is unilaterally and 5% is bilaterally deaf. They also found that it is twice as likely for unilaterally deaf dogs than normal dogs to produce deaf offsprings.

In contrast to CCSD, not as much is known about other possibly breed-related disorders in Dalmatians. Some books and articles list a few other disorders that are thought to be breed-related in Dalmatians, e.g. laryngeal paralysis and polyneuropathy, respiratory distress syndrome, panosteïtis, OCD in the shoulder, hyperuricosuria, urolithiasis and chronic hepatitis (Gough et al., 2018; Ostrander and Ruvinsky, 2012; Ruvinsky and Sampson, 2001; Trimble and Keeler, 1938). It is therefore important to find out more about these disorders and to assess how they might affect the disease burden of Dalmatians in order to know the right approach of managing these diseases and disorders in the Dalmatian population. As in other studies before (Keijser et al., 2019, 2017) it was chosen to use mixed-breed dogs and dogs of other breeds as the control group, because they are 'non-exposed' to being of the Dalmatian breed.

It is assumed that pet owners consult a veterinarian for diagnosis and treatment when their pet shows clear and prolonging discomfort. It is therefore proposed that visits to a veterinarian are quantifiable indicators that give an objective view of disease burden and reduced wellbeing due to breed-related disorders in Dalmatians (Keijser et al., 2017). As dogs in the Netherlands receive a high level of individual veterinary care, details about certain diseases and their possible connection with the dog breed are highly accessible and can therefore be easily studied (Ruvinsky and Sampson, 2001).

The aim of this comparative observational study is to gain an insight and a quantification of the disease burden of Dalmatians compared to mixed-breed dogs including dogs of an unknown breed. Similarly to Keijser et al. (2019), this insight into the disease burden was realised through an assessment of the survival time and frequency of visits for the Veterinary Practice Software System. For both insurance companies an insight into the disease burden was realized through an assessment of the survival time, the frequency of expense claims and the occurrence of codes for the organ systems that clinical signs were attributed to.

In this study, a Dalmatian is any dog that can be considered to belong to the breed based on phenotype, regardless whether the dog was registered at the kennel club or not. A mixed-breed dog is a dog not belonging to a specific breed, which comes from a mixed lineage. Dogs of unknown breeds can be either a purebred dog of a different breed or a mixed-breed, however in all cases are non-Dalmatian.

2. Materials and Methods

2.1. Materials

The study population for this observational study origins from three separate databases, of which one is a veterinary practice software system (VPSS) and two are Dutch pet insurance companies. The datasets were summarised and unnecessary data was removed. In all three datasets, the raw data was categorised in Dalmatians and 'mixed-breed dogs'. The mixed-breed group consists of true mixed-breed dogs (VPSS dataset) and of dogs of other, non-Dalmatian dog breeds (both insurance companies).

2.1.1. Veterinary practice software system

The information in this dataset origins from in total 20 veterinary clinics in the Netherlands. Dogs visited one of these clinics between January 2nd 2012 and December 12th 2017. This resulted in a study population of 324 Dalmatians, 3370 mixed-breed dogs and 12 crossings with Dalmatian (these dogs were later added to the mixed-breed group). As the breed label in this database was free text, the mixed-breed dogs were selected from the raw dataset using the following keyphrases: "ruising", "x", "X", "/"," - ", "ruisi", "-Kr", "--", " kr". For the same reason all true Dalmatian dogs were previously referred to with several different terms. Terms as: "Dalmatier", "Dalmatiër", "dalmatiers", "dalmatier", "Dalmatische Hond", "DalmatischeHond" and were all renamed "Dalmatian". Available information of each dog were patient demographic data (breed, sex, weight, birthdate, date of death, the patient key, first eight digits of the chip number) and information about the consultation (first and last known visit to the vet and the number of visits to the vet).

2.1.2. Insurance company 1

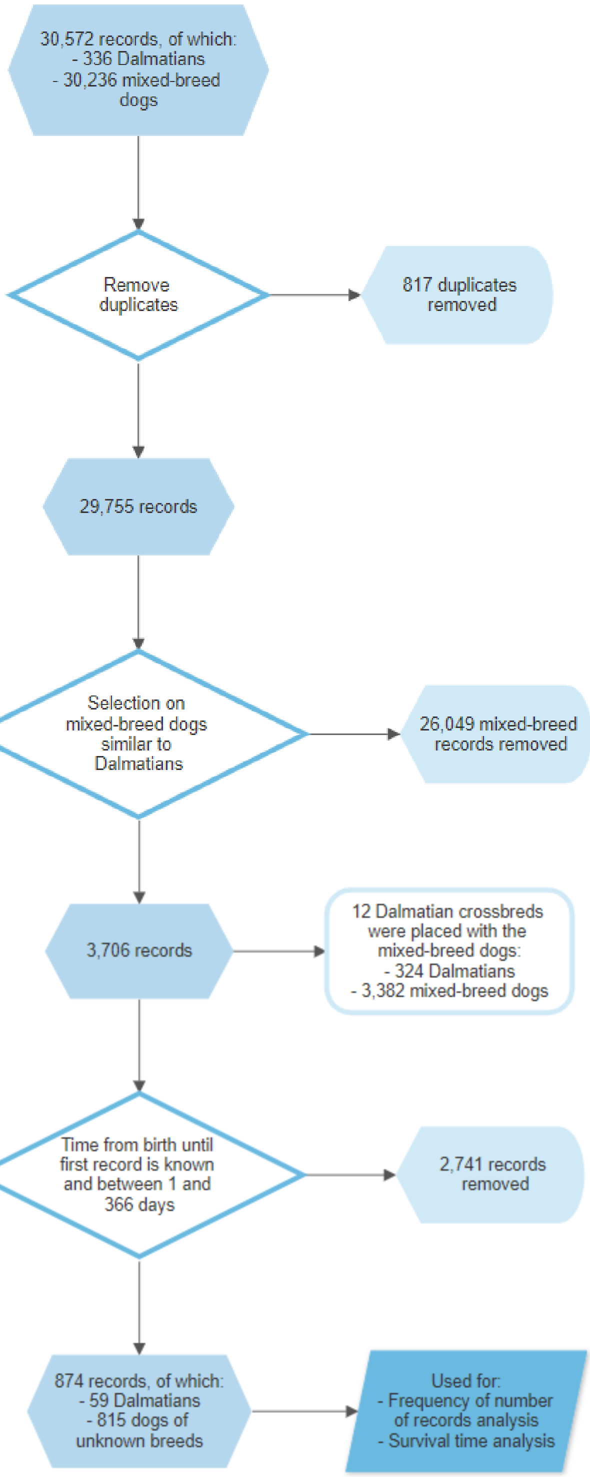
The study population of the insurance company 1 consists of 86 Dalmatians and 1513 mixed-breed dogs. The information origins from 594 individual veterinarians in the Netherlands after the dogs paid a visit to one of these veterinarians and made an expense claim between January 1st of 2010 and June 29th of 2016. Available data were patient demographic data (breed, sex, date of birth, the first three digits of the owners zip code, dog ID number and first six digits of the chip number) and information about the insurance and claim (starting date of the insurance, whether the insurance was ended because of death of the dog, date of visit to the veterinarian, organ system code, diagnosis and the ID number of the veterinarian).

2.1.3. Insurance company 2

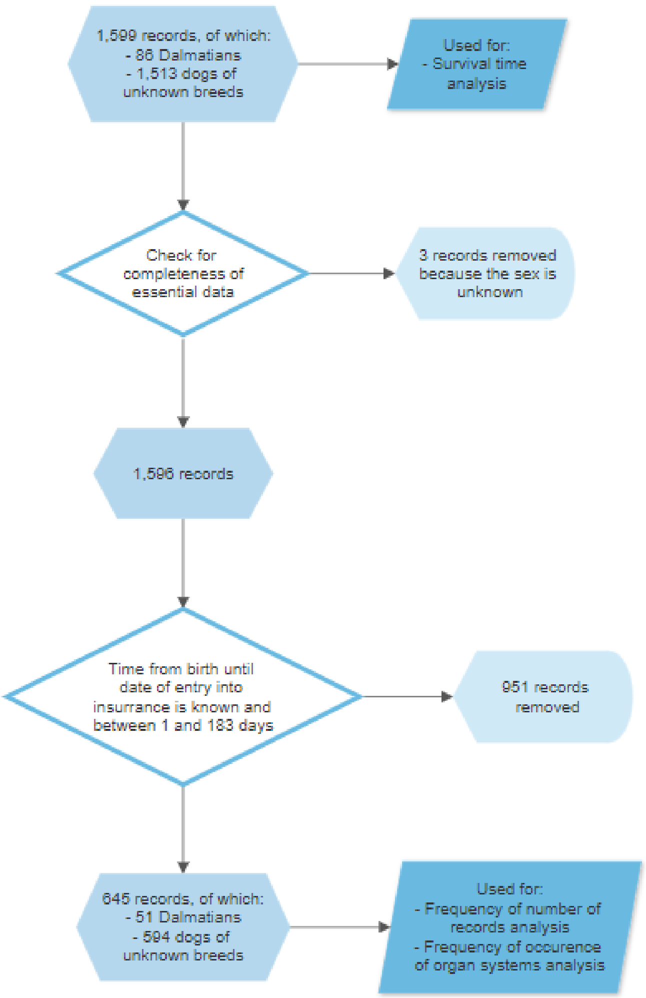
The study population for insurance company 2 includes 538 Dalmatians and 5561 mixed-breed dogs. The information origins from the Netherlands after the dogs registered to the insurance company or visited the vet between December 12th 1998 and December 31st 2016. The dataset of the second insurance company contains the following demographic data (breed, sex, birthdate, birthyear, date of death, animal identification number, whether or not the dog is in the Dutch Kennel Club, first three digits of the owners' zip code) and information about the expense claim (starting date of the insurance date of visit, the registered code of the affected organ).

2.2. Methods

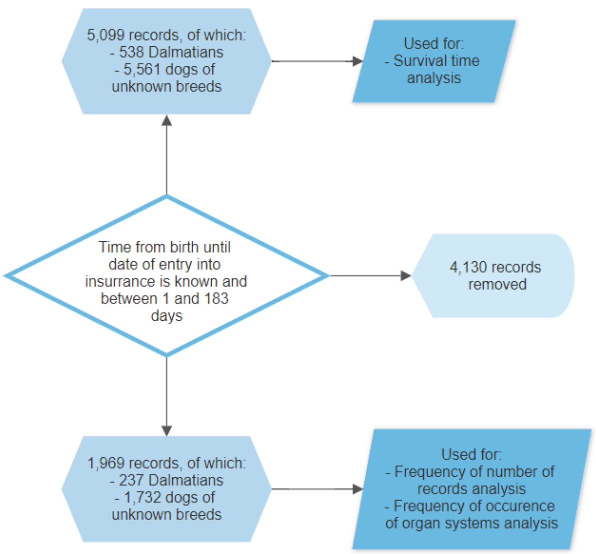
The selection procedure of the study populations was different for every dataset and is shown in Flow diagram 1, 2 and 3.



Flow diagram 1
Data cleaning and selection procedure for the database of the Veterinary Practice Software System



Flow diagram 2
Data cleaning and selection procedure for the database of insurance company 1



Flow diagram 3
Data cleaning and selection procedure for the database of insurance company 2

The data of all three datasets were analysed using R Statistical Software. Before starting the statistical analysis several variables were made or recoded.
By selecting the mixed-breed dogs in the original VPSS dataset based on the terms in the free text breed label, every mixed-breed dog was selected regardless of size. However, taking into consideration the possible correlation between dog size and the survival time (Adams et al., 2010; Michell, 1999) or predisposition for certain types of health problems, crossbreds from the VPSS dataset were selected to match the height and weight of a Dalmatian. Using the "Dog Breed Atlas" a list of dog breeds that are similar to Dalmatians was made. This list of breeds was later checked using the weight categories by Adams et al. (2010) and the outcome was found to be similar. Based on the corresponding number of individual dogs in the dataset that were a crossing with one of these selected breeds, a further selection of four breeds was made: Boxers, Collies, Retrievers and Malinois dogs (shown in Appendix Table 11). Crossbreds with Dalmatian or with at least one of the four breeds above were grouped together and named 'mixed-breed'. Non-matching crossings were then removed from the VPSS dataset. In the case of both insurance companies, the breed of the dogs was either Dalmatian or unknown (hereafter also named mixed-breed). This did not enable us to select dogs based on size.
For the analysis of the frequency of records per individual and the frequency of organ systems occurring per breed the variable "end of dataset" was added to the datasets as a censoring event. This was done in order to indicate the end of the study period and to make a statistical analysis of the frequency of records per observed year possible. For this date, the 31st of December of the year containing the absolute last record date from each dataset was taken and was the same for every individual dog that dataset that did not have a known date of death. Also, the time between birth and first record or starting date of the insurance had to be known and between 1 and 183 days for both insurance companies' databases and between 1 and 365 days for the VPSS database in order to have a relative certainty that the entire medical history was known. Also, in the case of the VPSS, an extra variable was created: number of records with at least 14 days in between. This was done because it was suspected that multiple following records within 14 days were check-ups for the same problem and not a visit to the clinic for a new health problem.
For the survival analysis birthyear and survival time (date of death respectively date of last record minus birthdate) variables were added to all datasets. Date of last record was chosen if the date of death was unknown, because it was definite that the dog was still alive at this point in time and no information is present after that date.
Simultaneously, the records of every database were checked for completeness of all relevant variables. Relevant variables were date of birth, date of death, sex, starting date of insurance, number of records, dates of the records time of observation and organ code, as they are all essential for performing the analyses. This check for completeness resulted in a further selection and thus a smaller study population (shown in Flow diagram 1, 2 and 3).

Table 1. An overview for every statistical analysis that was done per dataset.

Dataset	Statistical model: Quasi-Poisson Regression*	Multivariate logistic regression with a stepwise back approach**	Cox Proportional Hazard***
Veterinary Practice Software System	X		X
Insurance company 1	X	X	X
Insurance company 2	X	X	X

* This model was used to examine the frequency of records per observation time.

** This model was used to examine the frequency of occurrence of organ systems.

*** This model was used to examine the survival time.

2.2.1. Analysis of frequency of records per observation time

Hereafter, the number of "visits" in the VPSS dataset and the number of "expense claims" in the dataset of both insurance companies will all be named number of "records".

For the number of records a Pearson's Chi-square test was done at first to do an initial check on association between number of records and breed. Because the number of records per observation time are quantifiable, the most relevant variables (breed, sex and year of birth) were analysed using the Quasi-Poisson Regression model due to overdispersion (more variation in the outcome variable than expected). This gives the mean frequency of records per observation time and the corresponding risk ratio (RR). If an association for sex or year of birth wasn't found in the initial model, the variable was excluded in the final model. However, the purpose of this research is to investigate the difference between Dalmatians and dogs of a mixed or non-Dalmatian breed, therefore breed should always remain in the model even when the difference is not significant.

2.2.2. Frequency of occurrence of organ systems

This analysis was only possible for the dataset of both insurance companies, since there was no organ code in the large data dump of the VPSS. The most claimed organ systems per breed group were first analysed using a univariable Chi-square test. If that was not possible for a certain organ system, because one breed group did not contain any dogs with a claim for that organ system, a univariable Fisher's exact test was done. For every organ system, that was found to be associated with breed according to either one of these tests (p-value < 0.05), a multivariable logistic regression was performed. This multivariable logistic regression model examined if breed, sex and birthyear were associated with the prevalence of the specific organ system. Secondly a stepwise backward approach was used to remove non-significant variables from the model using the likelihood ratio test. The odds ratio (OR) was determined which showed the likelihood that a Dalmatian patient has a claim for the specific organ system compared to the likelihood for the same claim for a mixed-breed dog. In accordance with Keijser et al. (2017) an OR > 1.5 was considered an overrepresentation of Dalmatians compared to the other breed category.

2.2.3. Survival time

The Survival analysis, or Cox Proportional Hazard, uses the time until an event and was therefore used to analyse the survival time with death being the 'event'. First a Kaplan-Meier graph was drawn to create a general overview. Then a Cox Proportional Hazard analysis was done where the variable 'breed' was always kept in the analysis, the variables 'sex' and 'birthyear' were only used if they had a significant association with survival time. Lastly the assumption that the hazard is proportional was checked, the hazard was only found to be proportional for the VPSS dataset.

3. Results

Table 2. Demographics of the population of Dalmatians and mixed-breed dogs for the Veterinary Practice Software System dataset.

	Mixed-breed (n=3.169)			Dalmatian (n=308)		
Year of birth	Female (n=1.425)	Male (n=1.676)	Unknown (n=68)	Female (n=145)	Male (n=162)	Unknown (n=1)
1992 – 2002	125	160	4	27	36	
2003 – 2010	683	814	23	79	71	
2011 – 2017	617	702	41	39	55	1

Table 3. Demographics of the population of Dalmatians and mixed-breed dogs for the insurance company 1 dataset.

	Mixed-breed (n=1.510)		Dalmatian (n=86)	
Year of birth	Female (n=783)	Male (n=727)	Female (n=32)	Male (n=54)
1998 – 2006	81	71	2	5
2006 – 2011	473	462	14	25
2011 – 2016	229	194	16	24

Table 4. Demographics of the population of Dalmatians and mixed-breed dogs for the insurance company 2 dataset.

	Mixed-breed (n=5.535)			Dalmatian (n=536)		
Year of birth	Female (n=2.722)	Male (n=2.755)	Unknown (n=58)	Female (n=253)	Male (n=283)	Unknown (n=0)
1984 – 1996	489	560	7	10	16	
1997 – 2006	2232	2193	51	150	174	
2007 – 2016	1	2		93	93	

An insight in de demographics of the datasets can be seen in table 2, 3 and 4. Each show the distribution of the number of animals per breed, sex and birthyear period. The extended tables can be found in the appendix, table 12, 13 and 14.

Table 5 presents the total number and the proportion of Dalmatians and Mixed-Breed dogs that had various numbers of records during the observation time. The proportion of Dalmatians that had 2 or more records is larger than the proportion of mixed-breed dogs that had the same number of records. The highest number of records (with at least 14 days in between) was 67 records for one mixed-breed dog. No association was found between breed and number of records ($p = 0.97$).

Table 5. The exact number and the proportion of dogs categorised in cohorts of number of records (with at least 14 days in between) for Dalmatians and mixed-breed dogs for the Veterinary Practice Software System.

	Number of individuals (proportion)	
Number of records	Mixed-Breed (n=815)	Dalmatian (n=59)
1	230 (0.282)	9 (0.153)
2 – 5	286 (0.351)	24 (0.407)
6 – 25	274 (0.336)	23 (0.390)
26 – 50	23 (0.028)	3 (0.051)
51 – 100	2 (0.002)	0 (0.000)

In table 6 it is shown that the proportion of records for Dalmatians during the observation time is larger than the proportion of records for mixed-breed dogs in the 2 to 25 records categories. In the 26 to 50 records category the proportion of both breed groups was similar. There were no dogs of any breed that had more than 50 records. For insurance company 1 no association was found between breed and the number of records ($p = 0.054$)

Table 6. The exact number and the proportion of dogs for Dalmatians and mixed-breed dogs categorised in cohorts of number of records for insurance company 1.

	Number of individuals (proportion)	
Number of records	Mixed-breed (n=594)	Dalmatian (n=51)
0	171 (0.288)	10 (0.196)
1	72 (0.121)	4 (0.078)
2 – 5	203 (0.342)	24 (0.471)
6 – 25	136 (0.229)	12 (0.235)
26 – 50	12 (0.020)	1 (0.020)

In table 7 it is shown that the proportion of Dalmatians that had more than 6 records during the observation time is larger than the proportion of mixed-breed dogs that had the same number of records. There were no mixed-breed dogs that had more than 120 records, although there were 9 Dalmatians that had over 120 records with the highest number of records being 242. For insurance company 2 an association was found between breed and number of records, where Dalmatians were found to have significantly more records than mixed-breed dogs ($p < 0.001$).

Table 7. The exact number and the proportion of dogs for Dalmatians and mixed-breed dogs categorised in cohorts of number of records for insurance company 2.

	Number of individuals (proportion)	
Number of records	Mixed-breed (n=1732)	Dalmatian (n=237)
0	875 (0.505)	44 (0.186)
1	88 (0.051)	5 (0.021)
2 – 5	351 (0.203)	32 (0.135)
6 – 25	362 (0.209)	66 (0.278)
26 – 50	37 (0.021)	44 (0.186)
51 – 100	18 (0.010)	33 (0.139)
>100	1 (0.001)	13 (0.055)

3.1. FREQUENCY OF RECORDS PER OBSERVATION TIME

Hereafter, the 'number of records per observation year' will be named 'number of records'.

Figure 1 shows that mixed-breed dogs have a higher maximum number of records than Dalmatians in the VPSS dataset. Dalmatians in general have a higher median as well as a greater dispersion (shown as the height of the box) which means a greater interquartile range compared to mixed-breed dogs. Females seem to have a slightly higher median, although the absolute highest number of records are found in male group. Dogs of an unknown gender have the least number of records, however this group was only relatively small.

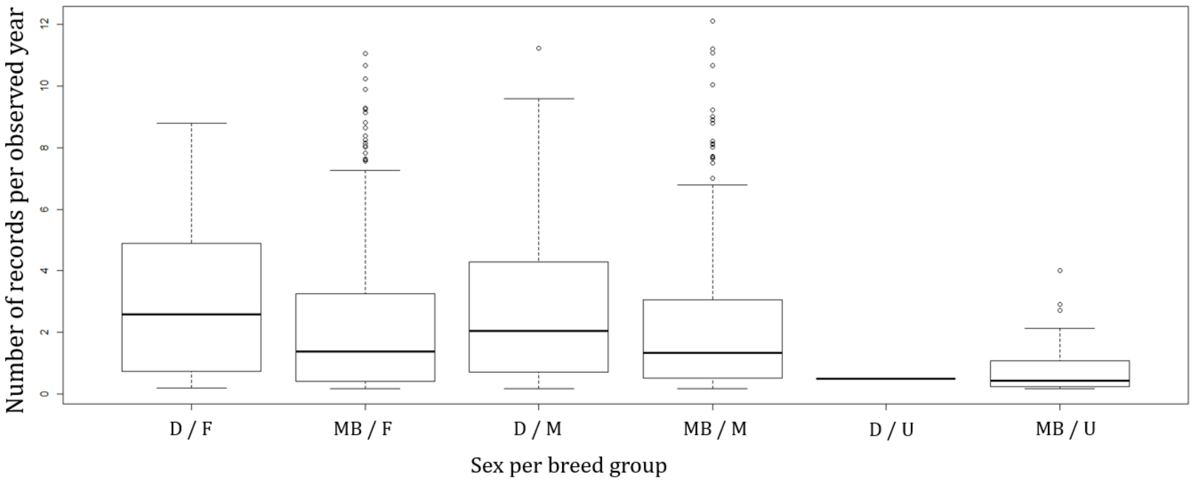


Figure 1. Number of records (with at least 14 days in between) shown for sex per breed for the Veterinary Practice Software System. Dalmatian: female (n=23), male (n=35), unknown sex (n=1); mixed-breed: female (n=366), male (n=425), unknown sex(n=24).
D = Dalmatian; MB = Mixed-breed; F = Female; M = Male; U = Unknown sex

Figure 2 shows that for every birthyear period Dalmatians have a higher median compared to mixed-breed dogs. It can also be seen, that the interquartile range was greater in the first two birthyear periods for Dalmatians compared to mixed-breed dogs. As well as a much higher number of records in the last birthyear period than the previous two birthyear periods for both breed groups.

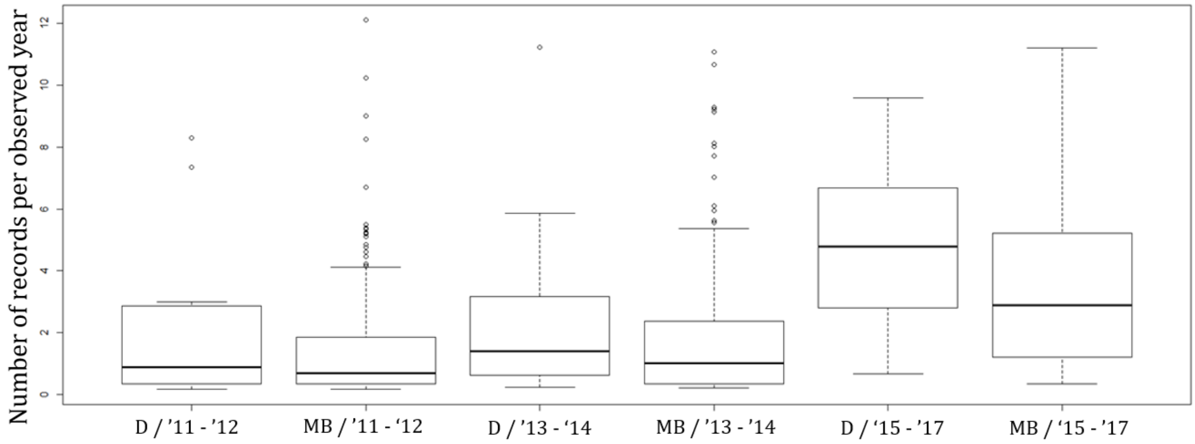


Figure 2. Number of records (with at least 14 days in between) shown for birthyear period (2011 – 2017) per breed for the Veterinary Practice Software System. Dalmatian: 2011 - 2012 (n=13), 2013 – 2014 (n=26), 2015 – 2017 (n=20); mixed-breed: 2011 – 2012 (n=280), 2013 – 2014 (n=272), 2015 – 2017 (n=263).
D = Dalmatian; MB = Mixed-Breed

Figure 3 gives the results for insurance company 1 and shows that Dalmatians have a slightly higher median and the boxplots are slightly raised compared to those of mixed-breed dogs indicating a slightly higher number of records for Dalmatians. Also, both boxplots of the mixed-breed group do not show a lower whisker which means that at least 25% of the dogs in this breed group have zero records per observed year. In the database of insurance company 1, the highest number of records can be found in the group of mixed-breed dogs as we can see by the high upper extremities. The sexes were found to be similar per breed, so there was no difference found between male and female dogs within the same breed group.

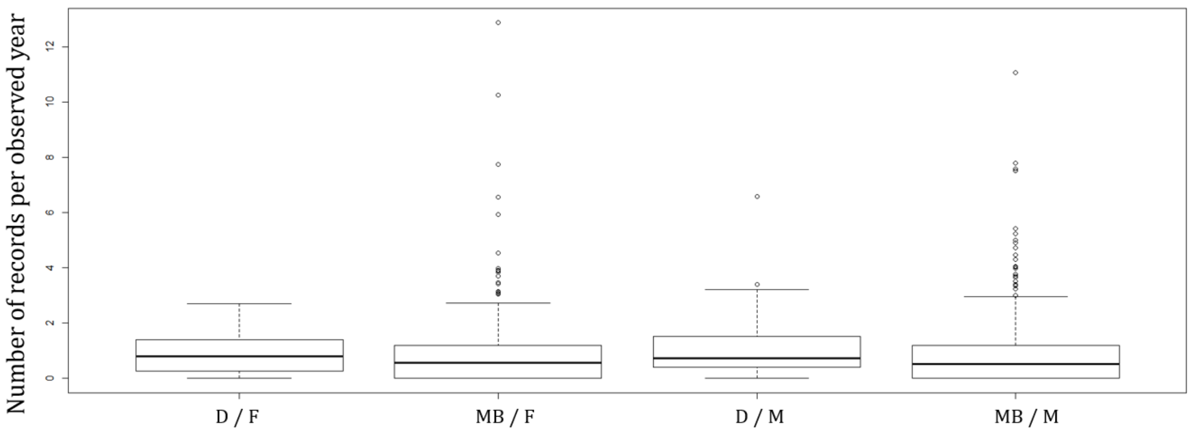


Figure 3. Number of records shown for sex per breed for insurance company 1. Dalmatian: female (n=22), male (n=29); mixed-breed: female (n=302), male (n=292).
D = Dalmatian; MB = Mixed-breed; F = Female; M = Male

In the dataset of insurance company 1, Dalmatians are also found to have a higher number of records compared to mixed-breed dogs. However, again the highest number of records can be found in the mixed-breed group. The difference between the two birth periods is not apparent, although the number of records seems to be slightly lower in the latter.

Figure 4. The number of records shown for birthyear period (2009 – 2016) per breed for insurance company 1. Dalmatian: 2009 - 2012 (n=33), 2013 – 2016 (n=18); mixed-breed: 2009 – 2012 (n=460), 2013 – 2016 (n=134).
D = Dalmatian; MB = Mixed-breed

Figure 5 shows that for the data of insurance company 2, Dalmatians clearly have more records than mixed-breed dogs. The highest median as well as the highest number of records in general can be found in this group. Female and male dogs have a similar number of records, so in this dataset no difference was found based on sex. Except for dogs of an unknown sex which have a considerably lower number of records, but this group of dogs was only very small.

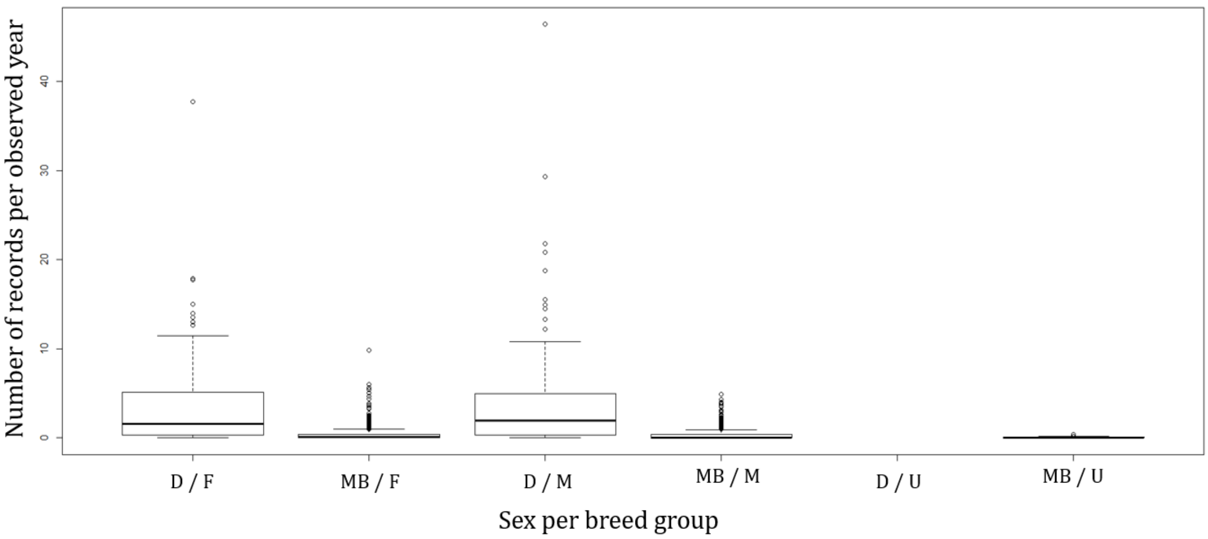


Figure 5. Number of records shown for sex per breed for insurance company 2.
Dalmatian: female (n=122), male (n=115), unknown sex (n=0); mixed-breed: female (n=870), male (n=851), unknown sex (n=11).
D = Dalmatian; MB = Mixed-breed; F = Female; M = Male; U = Unknown sex

From figure 6 it is very apparent that Dalmatians have a higher number of records compared to mixed-breed dogs, regardless of the birth period the dogs were born in. The number of records seems to increase for Dalmatians born in later years. Oddly enough, for mixed-breed dogs the number of records seems to decrease in the last birthyear cohort, however this group did only consist of 2 individual dogs.

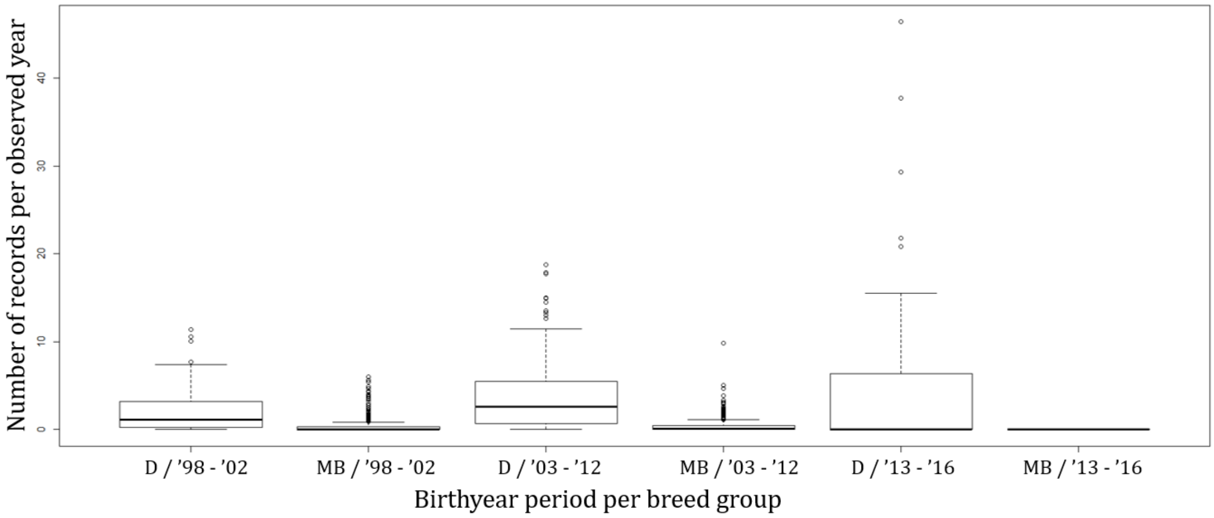


Figure 6. Number of records shown for every birthyear period (1998-2016) per breed for insurance company 2. Dalmatian: 1998 - 2002 (n=50), 2003 – 2012 (n=143), 2013 – 2016 (n=44); mixed-breed: 1998 – 2002 (n=900), 2003 – 2012 (n=830), 2013 – 2016 (n=2).
D = Dalmatian; MB = Mixed-breed

For the VPSS, there is a statistically significant difference in number of records between the two breed groups, the birthyear periods and the sexes (table 8). Dalmatians were found to have 40% more records per observed year than mixed-breed dogs. For the birthyear periods it was found that dogs born in later birthyear period, had more visits to the veterinarian per observed year. Male dogs were not found to differ in number of visits from females (although not significant), however dogs of an unknown sex were found to visit less than female.

For insurance company 1, neither breed nor sex or birth period were found to have a significant influence on the number of records (table 8). Although not significant, Dalmatians were found to visit 20% more.

For insurance company 2, both breed and birth period were found to be significantly influencing variables on the number of records (table 8). Dalmatians were found to have 9.4 times more records than mixed-breed dogs. Dogs born in 2003 – 2012 had 30% more records and dogs from birthyear cohort 2013 – 2016 had 2.5 times more records than dogs born in 1998 – 2002.

Table 8. Estimated risk ratios (RR) of the final* Quasi-Poisson model for the data of all datasets. Depicting the variables for every dataset that influence the number of records per observation time (in years).

Variable	**Category**	**RR**	**95% CI**		**P-value**
			Lower	*Upper*	
Veterinary Practice Software System					
Breed	Mixed-breed (Ref**) (n=815)	1			0.02
	Dalmatian (n=59)	1.4	1.1	1.8	0.01
Birthyear period	2011 – 2012 (Ref)	1			< 0.001
	2013 – 2014	1.2	1.0	1.4	0.04
	2015 – 2017	1.9	1.6	2.4	< 0.001
Sex	Female (Ref)	1			0.003
	Male	1.0	0.8	1.1	0.5
	Unknown	0.3	0.2	0.7	0.005
Insurance company 1					
Breed	Mixed-breed (Ref) (n=594)	1			0.3
	Dalmatian (n=51)	1.2	0.8	1.8	0.3
Insurance company 2					
Breed	Mixed-breed (Ref) (n=1.732)	1			< 0.001
	Dalmatian (n=237)	9.4	8.0	11.1	< 0.001
Birthyear period	1998 – 2002 (Ref)	1			< 0.001
	2003 – 2012	1.4	1.2	1.6	< 0.001
	2013 – 2016	2.5	1.4	4.0	< 0.001

95% CI = 95% Confidence Interval

* Variables in the initial model: breed, birthyear period and sex.

** Ref: reference category

3.2. Frequency of occurrence of organ systems

From the data of insurance company 1 it was found that Dalmatians are 2.6 times as likely to have expense claims (at least one) for joints (table 9). It was also found that sex and birthyear period are associated with at least one expense claim for joint, where male dogs are found to be twice as likely to have an expense claim for this organ system and dogs born between 2013 and 2016 were half as likely to have at least one claim for joints (appendix table 15). For all other organ systems, no association between breed group and having at least one claim was found in the insurance company 1 data.

In the data provided by insurance company 2 an association between breed and having at least one expense claim for an organ system was found for many organ systems, where Dalmatians were always more likely to have at least one claim than mixed-breed dogs (table 9). For some organ systems an additional association with either birthyear period or both birthyear period and sex was found. An association with both birthyear period and sex was found for the heart, pancreas, muscles and tendons and reproductive organs. For airways, gut, eyes and ears only birthyear period was additionally associated (appendix table 16).

Table 9. Descriptives and estimated odds ratios from the final model* for all organ systems for which, using the Chi-square test, breed was found to be a significant variable for having at least one expense claim concerning the specific organ system. Given are the estimated OR and 95% CI of Dalmatian (D) versus mixed-breed dogs (MB) for insurance company 1 and 2.

Organ system per dataset	**Proportion of cases D/MB**	**Adjusted OR (CI) of D vs MB**	**P-value**
Insurance company 1			
Joints	0.2 / 0.09	2.6 (1.2 – 5.3) **	0.02
Insurance company 2			
Denture	0.11 / 0.02	6.2 (3.6 – 10.4)	< 0.001
Heart	0.03 / 0.01	6.8 (2.3 – 19) **	< 0.001
Airways	0.41 / 0.13	6.6 (4.8 – 9.1) ***	< 0.001
Gut	0.42 / 0.13	6.5 (4.7 – 9.0) ***	< 0.001
Neurological conditions	0.03 / 0.01	2.5 (1.0 – 5.6)	0.04
Eyes	0.24 / 0.07	4.9 (3.4 – 7.1) ***	< 0.001
Ears	0.32 / 0.05	11.1 (7.6 – 16.2) ***	< 0.001
Pancreas	0.08 /0.01	11.6 (5.6 – 24) **	< 0.001
Muscles and tendons	0.33 / 0.16	3.7 (2.7 – 5.2) **	< 0.001
Reproductive organs	0.42 / 0.16	4.6 (3.4 – 6.4) **	< 0.001

* Variables in the initial model: breed, sex and birthyear.
** Adjusted for birthyear period and sex
*** Adjusted for birthyear period

3.3. Survival time

Until >3000 days of survival time, Dalmatians have a greater survival proportion than mixed-breed dogs in all datasets (figure 7). However, the mixed-breed dogs outlive the Dalmatians as the longest living individuals belong to the mixed-breed group for all datasets.

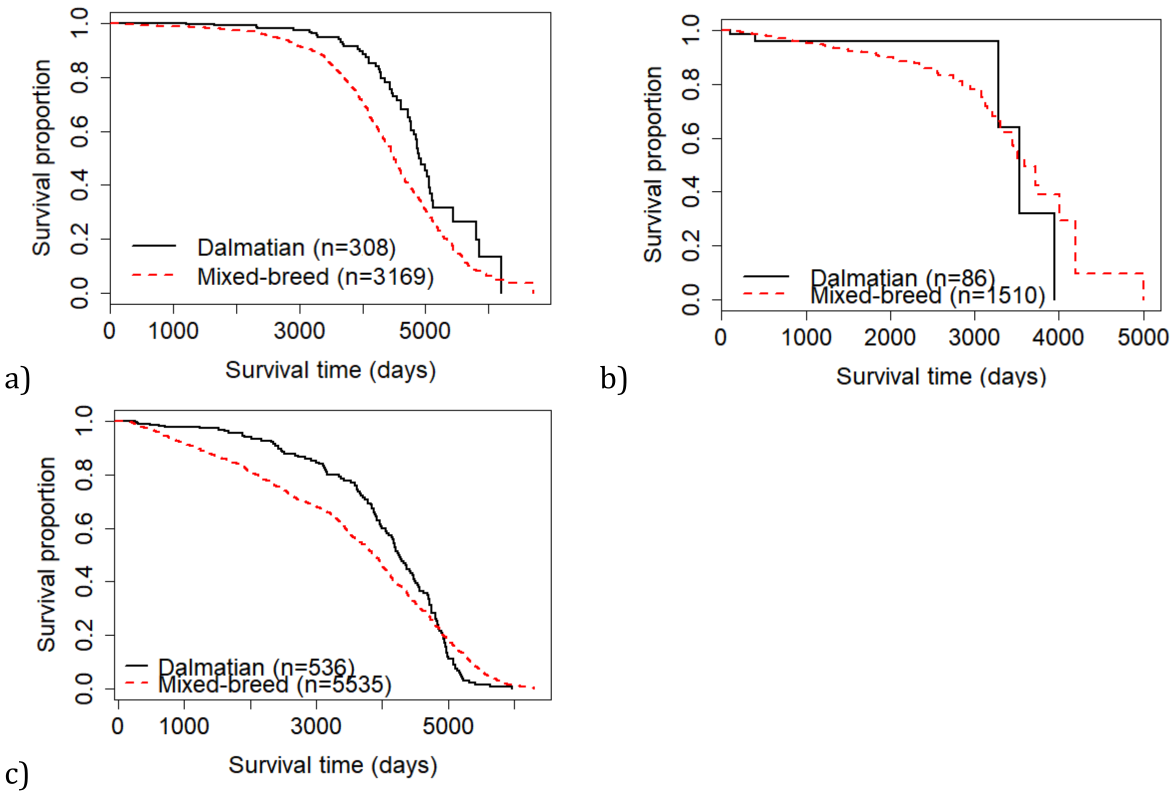


Figure 7. Kaplan Meier survival curves from birth date until death or censoring event per breed for (a) the Veterinary Practice Software System, (b) insurance company 1 and (c) insurance company 2.

In terms of the survival time of Dalmatian compared to mixed-breeds or dogs of an unknown breed the outcomes between the three datasets differed (table 10). According to the data from insurance company 1, although not significant, Dalmatians have a 20% higher risk of dying early. However, in the VPSS and insurance company 2 dataset it was found that Dalmatians actually have a lower risk of dying (40% and 70% respectively) compared to the risk to die of mixed-breed dogs. Survival time in the VPSS dataset was associated with breed, sex and birthyear period. Besides breed, survival time for insurance company 1 and 2 was only additionally associated with birthyear period.

Table 10. Descriptives and Hazard ratio for dying and 95% confidence interval (95% CI) in the final model* for the data from the Veterinary Practice Software System, insurance company 1 and insurance company 2.

Dataset	**n D/MB**	**Hazard ratio D vs. MB (95% CI)**	**P-value**
Veterinary Practice Software System	308/3,169	0.6 (0.5 – 0.9)**	0.002
Insurance company 1	86/1,510	1.2 (0.5 – 3.0)	0.68
Insurance company 2	536/5,535	0.3 (0.2 – 0.4)	< 0.001

* Variables in the initial model: breed, sex and birthyear.
** Adjusted for birthyear period and sex, the datasets of insurance company 1 and 2 is adjusted for birthyear period

4. Discussion

4.1. Frequency of records per observation time

In the VPSS, Dalmatians had 40% more visits to a veterinary practice per year than mixed-breed dogs. In insurance company 2 Dalmatians had 9.4 times more claims than mixed-breed dogs and although not significant, Dalmatians had 20% more claims than mixed-breeds in the insurance company 1 dataset. The higher number of records for Dalmatians could be explained by the idea that pure-bred dogs are often more affected by diseases than mixed-breed dogs. Mixed-breed dogs are commonly seen as the 'healthiest' dog breed (Karlsson and Lindblad-Toh, 2008; Keijser et al., 2017; Leroy, 2011), possibly resulting in the higher number of records for Dalmatians. However, for both insurance companies, Dalmatians were compared with dogs of 'unknown breeds'. The breed label was named 'unknown' when the breed label was either empty, missing or the breed of the dog was truly unknown. Since it is believed that a relatively higher percentage of purebred dogs is insured compared to mixed-breed dogs (Sánchez-Vizcaíno et al., 2017), it is likely that the group of dogs of which the breed is unknown partially consist of purebred dogs from other breeds. Therefore, it would be expected that the difference in number of records between Dalmatians and the dogs of unknown breeds is similar or smaller for both insurance companies than for the comparison made with true mixed-breed dogs for the VPSS. However, in insurance company 2 this is not the case. In fact, the difference is much larger than for the VPSS

For the VPSS and insurance company 2 it was additionally found, that dogs born in later birthyear periods have higher number of records. A possible explanation is that puppies usually visit the veterinarian more than average in the first year because of puppy check-ups and mandatory vaccinations. The younger dogs in the latter birthyear periods have had less time to compensate these relatively high number of records in their short observation time compared to the dogs in the earlier birthyear periods. This could also be the reason why Dalmatians were found to have a higher number of records for insurance company 2 than the mixed-breed dogs. Since there were only a few Dalmatians in the earlier birthyear periods and barely any mixed-breed dogs in the latter birthyear periods for insurance company 2 (as shown in table 4 and table 14). This could lead to unequal comparisons, as the great difference in number of claims per breed may in reality be based on unevenly divided dogs over the birthyear periods.
Sex was only found to be associated with number of visits for the VPSS. However, only dogs of an unknown gender had a significant difference in number of visits (70% less) compared to female dogs. There was no difference found between male and female dogs.

4.2. Frequency of occurrence of organ systems

From the data of insurance company 1 is has been found that Dalmatians were overrepresented in claims for joints. From literature it shows that OCD in the shoulder is common in Dalmatians (Nečas et al., 1999). However, in other articles it is also noted that Dalmatians are predisposed to develop laryngeal paralysis and poly-neuropathy, a neurological condition (Braund et al., 1994, 1989; Ganjei et al., 2016; Järvinen et al., 1995; Tarvin et al., 2016). Due to the smaller number of dogs for the Dalmatian breed compared to the mixed-breeds, it is possible that coincidentally there were no dogs with claims for this organ system in this database.

In de insurance company 2 database a breed association with Dalmatians was found for claims on account of denture, heart issues, airway problems, gut, neurological problems, eyes, ears, pancreatic problems, muscular and tendon disorders and also the reproductive organs. Heart, pancreas, muscles and tendons and reproductive organs were found to be associated with both birthyear period and sex. Airways, gut, neurological conditions, eyes and ears were found to be associated with only birthyear period additionally to breed. For every condition, dogs born in the latter birthyear period had less claims for the concerning organ system. An explanation for this finding could be that dogs born in earlier birthyear periods most likely had a longer observation time. Therefore, these dogs had a longer time span to develop health problems and have expense claims for an organ system as a result. Dalmatians were found to have 4.6 times more claims for reproductive organs than mixed-breed dogs. However, it should be noted that mixed-breed dogs are most likely less often used for breeding as true Dalmatians are. Therefore, Dalmatians could have more claims for reproductive organs as a direct result of the breeding (e.g. dystocia and caesarean section) or as a result of leaving the dogs intact (e.g. mamma carcinoma and testis cancers). Claims concerning reproductive organs were also found to be more common in females (60% more). However, the neutering status was not included in the dataset and therefore not in the analysis. It is not clear what the percentage of neutered versus intact dogs is for either breed or sex.

In the dataset of both insurance companies, for all organ systems, of which the number of expense claims were found to be associated with breed, Dalmatians had more claims. However, this does not automatically mean that all of these claims have a hereditary basis. It is very well possible that dogs visit the vet for diseases in certain organ systems, other than the ones they are predisposed for based on their breed. So, from our result it may seem as if Dalmatians are predisposed to conditions in certain organ systems when in reality they are not. However, we assumed that frequency of expense claims that are not based on a hereditary background concerning any organ system is the same for both Dalmatians and mixed-breed dogs. Therefore, it is still notable that Dalmatians have a higher OR for claims for many of these organ systems. This means that although there might not be a specific predisposition for an illness of these organ systems, possibly Dalmatians are a weaker breed in general than mixed-breed dogs. It is therefore of great importance that more specific research per organ system is done to study if Dalmatians are truly predisposed for illnesses in the organ systems we found in this study or that they possibly are a weaker breed leading to several different health problems in many organ systems. Also, it is important to keep in mind that having these claims does not mean that the health problem will be chronic. Many diseases and conditions can be easily treated leaving the dogs healed.

4.3. Survival time

In the survival time analysis for the VPSS dataset, it was found that mixed-breed dogs have a higher hazard ratio compared to Dalmatians and are therefore more at risk of dying early. Dogs born in the later birthyear periods were also found to be more at risk of dying early (appendix table 17). An explanation for this is that from all dogs that were born in earlier birthyear period, only the older ones were still alive at the start of the dataset. This means that all dogs that were born in the same birthyear period but had died before the start of the dataset, were not included in this analysis. These older dogs therefore falsely prolonged the survival time of this birthyear period. The exclusion of dogs born before the start of the dataset is not or less so the case for the middle and later birthyear period. This is shown in de Kaplan Meier survival curves (Appendix figure 8b, d and f), where it can be seen that the survival curves of the earlier birthyear period stay at 100% until almost 2000 days (± 5.5 years), whereas the other birthyear groups almost immediately start dropping. This was also the case for insurance companies 1 and 2 as the data selection procedure was different for this analysis (Flow diagram 2 and 3). However, it is expected that this phenomenon is the same for both Dalmatian and mixed-breed dogs and therefore it should not result in significant differences between the breeds. Also, male dogs were found to be more at risk of dying early than female dogs (Michell, 1999) and both were more at risk than dogs of an unknown sex, most likely because of the small number of dogs in this category. After checking the assumptions, the hazard was found to be proportional for this dataset. For insurance company 1 only birthyear period was found to be significantly associated with again the later birthyear period being more at risk of dying early (appendix table 18). Although breed was not found to be significantly associated with a risk for dying early, Dalmatians were found to be 20% more at risk. This model was not suitable for this analysis as the hazards were found not to be proportional. For insurance company 2 breed and birthyear period were significantly associated with Dalmatians being 70% less at risk and the later birthyear period again being more at risk (appendix table 19). The assumptions were checked, and the hazard was found not to be proportional for this dataset, therefore this model was not fit for this dataset. However, a long survival time does not always mean that the dog was in good health, as was found in previous studies (Keijser et al., 2017), and therefore is not by itself a good measure for disease burden.

4.4. Variables in datasets

For this cohort study we used existing databases that were not designed for these specific analytical purposes. Consequently, certain helpful and important variables were missing in all three datasets. For example, in both the insurance company 1 and the insurance company 2 databases, there was no information on the date of the first claim and therefore a survival analysis for the first expense claim could not be made for these two datasets. As it would have been interesting to look at the difference in time until the first record between the two breed group, to estimate the age of onset of a disease. In addition, there was no breed identification for the control group other than non-Dalmatian. It was assumed that there would be a relatively large proportion of other pure-bred dogs in these control groups, since an insurance population consists mainly of purebred dogs as found by (Sánchez-Vizcaíno et al., 2017). For the VPSS dataset it would have been useful to know what the reasons of the visits were. Therefore, it was not possible to analyse the most common reasons for visits per breed group. Also now, it was assumed that all visits within 14 days were most likely check-ups for the same problem (e.g. the removal of stitches from a surgery). Since we were only interested in new health problems, it was therefore decided to neglect these visits within 14 days of the previous visit. However, since no reason for the visits was given it could be that in some cases the second visit was for a new health problem, resulting in a higher number of visits. Although it was also assumed that this would be the same for both breed groups. For the VPSS a survival analysis could be done from birth until the first visit, however little information could be extracted from this outcome since nothing was known about the reason for the visit (expected is a mandatory puppy vaccination as a first visit). Bellumori et al. (2013) have studied the difference in mean age at first representation to a clinic with a disorder diagnosis per breed group (breed groups are purebred and mixed-breed) for every disorder. They found a large range in mean age of diagnosis, from the youngest age of diagnosis (for patent ductus arteriosus and ventricular septal defect) at 1.32 years to the oldest age of diagnosis that was found in their study (hyperadrenocorticism) at a mean age of 10.54 years. However, they concluded that out of 24 disorders, 13 had no significant difference in the occurrence in purebred and mixed-breed dogs. All three diagnoses above were also not found to be significantly different between the two breed groups. For the ten disorders they found to be more prevalent in purebred dogs, the OR ranged from 1.27 (for cataracts) to 3.45 (dilated cardiomyopathy), showing a greater risk for purebred dogs to have these conditions than for mixed-breed dogs which is similar to what was found in the present study.

4.5. Insurance data

Since two out of the three datasets were extracted from insurance data, it is difficult to say to which extend this has influenced the outcome of the study. First of all, it resulted in a non-random sample of the Dutch dog population as <10% of dogs in the Netherlands are insured (Keijser et al., 2019). The insured dogs might visit the veterinarian more often than non-insured dog, solely because they are insured and it will therefore be paid out by the insurance company. It is also possible that by using insurance data, there is an accidental selection for breeds that are common with health issues or specific dogs that have many problems concerning their health and are therefore insured. It was assumed that the proportion of purebred dogs was relatively high in the control groups of both insurance companies dataset compared to reality (Sánchez-Vizcaíno et al., 2017). Therefore, it is difficult to say if a true comparison with mixed-breed dogs was made for both insurance companies' datasets or that Dalmatian dogs were compared to a control group of both mixed-breed dogs and pure-bred dogs of other breeds. Another possibility is that there was an accidental selection for a certain type of owner, by only using insurance data. This was shown by Sánchez-Vizcaíno et al. (2017) who studied the demographics of companion animals to understand the distribution and determinants in animal disease in Great-Britain. They found that dogs in the veterinary-visiting population, owned by people living in the least-deprived areas of Great-Britain, were more likely to be purebred and insured. This might therefore also impact the clinical diseases that are observed within veterinary practices. Based on this study, there is an indication that the population structures of companion animals are associated with human and environmental factors (e.g. socioeconomic level) (Sánchez-Vizcaíno et al., 2017). It shows the importance of gaining more insight in this 'co-demographic' information to be able to rule out these possible co-founders and prevent a possible bias. Therefore, more information about the owner such as gender, age, if the owner owns more animals and how long the owner has been owning animals, the living environment and occupancy or predicted socioeconomic level related to the owners' address, would give a more complete view.

On the other hand, the VPSS dataset will also contain insured animals that we don´t know of. Possibly, many of the Dalmatians were insured whereas many of the mixed-breed dogs were not insured. If this is the case, the insured Dalmatians might visit the veterinarian more often than the non-insured crossbreds causing it to have an influence on the difference in number of records.

4.6. Sex and neutering status

For some diseases it is known that there is a sex predisposition. For example, it is known that uric acid bladder and kidney stones are very common in Dalmatians, especially in male Dalmatians (Safra et al., 2005). According to Safra et al. (2006), one in four male Dalmatians has clinical problems as a result of these uric acid stones. However, for many other diseases this predisposition for sex is not yet known. In this study an attempt was made to correct for the possible effect of sex, in order for it not to blur the effect breed has on the occurrence of the organ systems. However, neutering status was not corrected for in the present study and can affect the occurrence of certain diseases as well as survival time (Hoffman et al., 2018, 2013; Michell, 1999).

4.7. Data validity

There were many dogs that were excluded from the study because their birthdate was long before the first visit to a veterinarian or before entry into an insurance, so there is no knowledge about their health history. Ideally, the dogs were followed from the day of birth until the day of death and had complete information about breed, sex, neutering status, pedigree, birthdate, date of death, whether the dogs is insured or not, day of entry in the insurance, date of the visits or claims, at least of the first and last visit or claim, information about the reason of visit, the distribution across the country and information about the owner as mentioned above. Ideally we had known the cause of death for every dog as well, a previous study found that more than half of the pedigree Dalmatians in de United Kingdom die from old age and not from a specific, breed-dependant illness (Adams et al., 2010).

Not only would it have been better to have similar information in all three datasets, so the same analysis could have been done on a larger study population. But there are many more aspects that could have been studied to get a clearer view on the disease burden of Dalmatians. The study period for the dogs in the VPSS and insurance company 1 dataset is short (5 and 6 years respectively), only in the insurance company 2 dataset the study period was longer (18 years). Because of the short period of time that the dogs were studied in the VPSS and insurance company 1 dataset, there were mainly young dogs in both the case and the control group. As most dogs die at an older age than 5 or 6 years old, this made it difficult to study the possible difference in survival time between the breed groups for these datasets. And as mentioned above, because of missing variables in all three datasets no survival analysis could be done to study the age at which both groups will be presented with health issues for the first time. Perhaps it would also have been useful to see if both breed groups had a similar observation time to also take this into account as a variable.

Also, the diagnoses of disease might be subjected to bias since veterinarians are familiar with certain predispositions occurring in specific dog breeds. This might lead to an overrepresentation of claims for an organ system for Dalmatians as veterinarians possibly are attentive for specific organ systems, creating wrong proportions.

During the data cleaning procedure of this study many considerations and assumptions have been made that led to several decisions. One of the first decisions that was made, was to only continue with middle sized dogs similar in height and weight to Dalmatians. This decision was made because of the assumption that both survival time and the occurring illnesses were not only breed related, but also size related (Adams et al., 2010; Michell, 1999). It is generally thought that smaller dogs will grow older than bigger dogs. And since there was no information about the proportion of dog sizes in the VPSS dataset, it was decided to only use a few dog breeds that were found to be similar to Dalmatians and select those as the control group. However, it would have been better to solely select on similar bodyweight and not on breeds that generally have similar bodyweights as was done by Keijser et al. (2019). This gives a more heterogenous control group.
The selection on breeds similar in size and weight to Dalmatians in de VPSS dataset was done by using only one key phrase per breed, therefore it is possible that not all matching dogs were selected if the key phrase was not an exact match due to a spelling mistake in the database.

By creating a censoring-event similar for every dog, indicating the end of the study period to make statistical analysis possible, it was assumed that all dogs, of which no date of death was known, were still alive at that time. Meaning that the survival time would also be the same for both groups if they entered at similar times. In the veterinary practice it is not always noted when a dog died. Therefore, dogs that died before this censoring-event and were not noted in the VPSS database can lower the number of records. However, it was assumed that this would be similar for both breed groups. For insurance companies it was assumed that they are up to date with deaths of dogs.

By making all of the assumptions and selections as noted above, in the process of cleaning the dataset, it could have caused selection bias and it is difficult to say how truthful the remaining data still is. It is possible that all of the selection that was done together, eventually and accidentally sketch a situation that is different to reality.

5. Conclusion

Owners of Dalmatians visit a veterinary clinic and submit expense claims to insurance companies more often than owners of mixed-breed dogs. For all expense claims for organ systems (at least one) that were found to be significantly associated with breed, Dalmatians were more often affected than mixed-breed dogs. The occurrence of an expense claim for these organ systems ranged from an OR of 2.5 (neurological conditions, insurance company 2) and 2.6 (joints, insurance company 1) to 11.1 and 11.6 (ears and pancreas respectively, both insurance company 2). The most occurring organ systems differed between the two insurance companies, so no overlap could be found. Therefore, there was not one organ systems that could be named the absolute most occurring organ system. Lastly, Dalmatians were found to live longer than both mixed-breed dogs in general, irrespective of height and weight. This present study is a first step, however more complete data collection needs to be done to be able to study disease burden of Dalmatians in the future.

ACKNOWLEDGEMENT

I want to thank my supervisor Hans Vernooij for helping me extensively with data cleaning and selection, formulating the aims of this research, choosing the proper statistical models for every aim, writing the scripts for the statistical analysis, interpreting the results, helping to clearly and correctly formulate the results and for the multiple read-throughs and feedback moments. I especially want to thank him for the patience he has shown throughout the process of writing this report. I also want to thank Hans Vernooij and Mirjam Nielen for reading, assessing and grading this written report. Lastly, I want to thank the three companies that so kindly provided me with data from their datasets which were analysed in this research.

Adams, V.J., Evans, K.M., Sampson, J., Wood, J.L.N., 2010. Methods and mortality results of a health survey of purebred dogs in the UK. J. Small Anim. Pract. 51, 512–524. https://doi.org/10.1111/j.1748-5827.2010.00974.x

Bellumori, T.P., Famula, T.R., Bannasch, D.L., Belanger, J.M., Oberbauer, A.M., 2013. Prevalence of inherited disorders among mixed-breed and purebred dogs: 27,254 cases (1995-2010). J. Am. Vet. Med. Assoc. 242, 1549–1555. https://doi.org/10.2460/javma.242.11.1549

Braund, K.G., Shores, A., Cochrane, S., Forrester, D., Kwiecien, J.M., Steiss, J.E., 1994. Laryngeal paralysis-polyneuropathy complex in young Dalmatians. Am. J. Vet. Res. 55, 534–542.

Braund, K.G., Steinberg, H.S., Shores, A., Steiss, J.E., Mehta, J.R., Toivio-Kinnucan, M., Amling, K.A., 1989. Laryngeal paralysis in immature and mature dogs as one sign of a more diffuse polyneuropathy. J. Am. Vet. Med. Assoc. 194, 1735–1740.

Dog Breed Atlas [WWW Document], n.d. . Breed Comp. Tool. Accessed 16-07-2018. URL https://dogbreedatlas.com/

Donner, J., Anderson, H., Davison, S., Hughes, A.M., Bouirmane, J., Lindqvist, J., Lytle, K.M., Ganesan, B., Ottka, C., Ruotanen, P., Kaukonen, M., Forman, O.P., Fretwell, N., Cole, C.A., Lohi, H., 2018. Frequency and distribution of 152 genetic disease variants in over 100,000 mixed breed and purebred dogs. PLOS Genet. 14, e1007361. https://doi.org/10.1371/journal.pgen.1007361

Ganjei, J., Langenbach, A., Watrous, G., Hodgson, J., 2016. Comparison of bacterial cultures of the larynx between dogs with laryngeal paralysis and normal dogs. J. Small Anim. Pract. 57, 644–649. https://doi.org/10.1111/jsap.12586

Gough, A., Thomas, A., O'Neill, D., 2018. Breed Predispositions to Disease in Dogs and Cats. John Wiley & Sons.

Hoffman, J.M., Creevy, K.E., Promislow, D.E.L., 2013. Reproductive Capability Is Associated with Lifespan and Cause of Death in Companion Dogs. PLOS ONE 8, e61082. https://doi.org/10.1371/journal.pone.0061082

Hoffman, J.M., O'Neill, D.G., Creevy, K.E., Austad, S.N., 2018. Do Female Dogs Age Differently Than Male Dogs? J. Gerontol. Ser. A 73, 150–156. https://doi.org/10.1093/gerona/glx061

Järvinen, A.K., Saario, E., Andresen, E., Happonen, I., Saari, S., Rajamäki, M., 1995. Lung injury leading to respiratory distress syndrome in young Dalmatian dogs. J. Vet. Intern. Med. 9, 162–168.

Karlsson, E.K., Lindblad-Toh, K., 2008. Leader of the pack: gene mapping in dogs and other model organisms. Nat. Rev. Genet. 9, 713–725. https://doi.org/10.1038/nrg2382

Keijser, S.F.A., Meijndert, L.E., Fieten, H., Carrière, B.J., van Steenbeek, F.G., Leegwater, P.A.J., Rothuizen, J., Nielen, M., 2017. Disease burden in four populations of dog and cat breeds compared to mixed-breed dogs and European shorthair cats. Prev. Vet. Med. 140, 38–44. https://doi.org/10.1016/j.prevetmed.2017.02.016

Keijser, S.F.A., Vernooij, J.C.M., van Garderen, E., van Rooijen, P., Fieten, H., van Steenbeek, F.G., Hesselink, J.W., Nielen, M., 2019. Quantification of the health-status of the Dutch Labrador retriever population. Prev. Vet. Med. 171, 104764. https://doi.org/10.1016/j.prevetmed.2019.104764

Leroy, G., 2011. Genetic diversity, inbreeding and breeding practices in dogs: results from pedigree analyses. Vet. J. Lond. Engl. 1997 189, 177–182. https://doi.org/10.1016/j.tvjl.2011.06.016

Lingaas, F., Comstock, K.E., Kirkness, E.F., Sørensen, A., Aarskaug, T., Hitte, C., Nickerson, M.L., Moe, L., Schmidt, L.S., Thomas, R., Breen, M., Galibert, F., Zbar, B., Ostrander, E.A., 2003. A mutation in the canine BHD gene is associated with hereditary multifocal renal cystadenocarcinoma and nodular dermatofibrosis in the German Shepherd dog. Hum. Mol. Genet. 12, 3043–3053. https://doi.org/10.1093/hmg/ddg336

Michell, A.R., 1999. Longevity of British breeds of dog and its relationships with sex, size, cardiovascular variables and disease. Vet. Rec. 145, 625–629. https://doi.org/10.1136/vr.145.22.625

Nečas, A., Dvořák, M., Zatloukal, J., 1999. Incidence of osteochondrosis in dogs and its late diagnosis. Acta Vet. Brno 68, 131–139.

Nielen, A.L., van der Beek, S., Ubbink, G.J., Knol, B.W., 2001. Population parameters to compare dog breeds: differences between five Dutch purebred populations. Vet. Q. 23, 43–49. https://doi.org/10.1080/01652176.2001.9695075

Online Mendelian Inheritance in Animals, OMIA. Faculty of Veterinary Science, University of Sydney, Australia. Accessed 20-08-2018. Available: http://www.omia.org, 20180222

Ostrander, E.A., Ruvinsky, A. (ed), 2012. Genetics of the Dog. CABI.

Rusbridge, C., Knowler, S.P., 2004. Inheritance of Occipital Bone Hypoplasia (Chiari Type I Malformation) in Cavalier King Charles Spaniels. J. Vet. Intern. Med. 18, 673–678. https://doi.org/10.1111/j.1939-1676.2004.tb02605.x

Ruvinsky, A., Sampson, J., 2001. The genetics of the dog. Cabi Publishing.

Safra, N., Ling, G.V., Schaible, R.H., Bannasch, D.L., 2005. Exclusion of Urate Oxidase as a Candidate Gene for Hyperuricosuria in the Dalmatian Dog Using an Interbreed Backcross. J. Hered. 96, 750–754. https://doi.org/10.1093/jhered/esi078

Safra, N., Schaible, R.H., Bannasch, D.L., 2006. Linkage analysis with an interbreed backcross maps Dalmatian hyperuricosuria to CFA03. Mamm. Genome Off. J. Int. Mamm. Genome Soc. 17, 340–345. https://doi.org/10.1007/s00335-005-0137-5

Sánchez-Vizcaíno, F., Noble, P.-J.M., Jones, P.H., Menacere, T., Buchan, I., Reynolds, S., Dawson, S., Gaskell, R.M., Everitt, S., Radford, A.D., 2017. Demographics of dogs, cats, and rabbits attending veterinary practices in Great Britain as recorded in their electronic health records. BMC Vet. Res. 13, 218. https://doi.org/10.1186/s12917-017-1138-9

Schlensker, E., Distl, O., 2016. Heritability of hemivertebrae in the French bulldog using an animal threshold model. Vet. J. 207, 188–189. https://doi.org/10.1016/j.tvjl.2015.10.044

Syme, H.M., 2012. Stones in cats and dogs: What can be learnt from them? Arab J. Urol., Stones / Endurology 10, 230–239. https://doi.org/10.1016/j.aju.2012.06.006

Tarvin, K.M., Twedt, D.C., Monnet, E., 2016. Prospective Controlled Study of Gastroesophageal Reflux in Dogs with Naturally Occurring Laryngeal Paralysis. Vet. Surg. VS 45, 916–921. https://doi.org/10.1111/vsu.12539

Temwichitr, J., Leegwater, P.A.J., Hazewinkel, H.A.W., 2010. Fragmented coronoid process in the dog: A heritable disease. Vet. J. 185, 123–129. https://doi.org/10.1016/j.tvjl.2009.06.022

Trimble, H.C., Keeler, C.E., 1938. THE INHERITANCE OF “HIGH URIC ACID EXCRETION” IN DOGS. J. Hered. 29, 281–289. https://doi.org/10.1093/oxfordjournals.jhered.a104519

Ubbink, G.J., Broek, J. van de, Hazewinkel, H. a. W., Rothuizen, J., 1998. Risk estimates for dichotomous genetic disease traits based on a cohort study of relatedness in purebred dog populations. Vet. Rec. 142, 328–331. https://doi.org/10.1136/vr.142.13.328

Table 11. List of breeds that were found to be similar in size and weight to Dalmatians and the corresponding number of individual crossbreds of these breeds that were used as the mixed-breed group for the Veterinary Practice Software System database.

Dog breed	**Number of individual crossbred dogs selected**
Collies	332
Retrievers	513
Boxer	1885
Malinois dog	640
Dalmatian	324
Crossbreds with Dalmatian	12
Total	3706

For every breed only one key phrase was used, so different spellings were not selected.

Table 12. Number of individual dogs per breed, sex and birthyear for Veterinary Practice Software System (2012 – 2017).

	Mixed-breed (n=3.169)			**Dalmatian (n=308)**		
Birthyear	Female (n=1.425)	Male (n=1.676)	Unknown (n=68)	Female (n=145)	Male (n=162)	Unknown (n=1)
1995	3					
1996	5	3		2		
1997	8	2		1	1	
1998	12	10			2	
1999	10	13		5	6	
2000	28	23		7	10	
2001	24	35	3	7	8	
2002	35	74	1	5	9	
2003	64	61	1	9	3	
2004	61	66	2	14	7	
2005	73	85	2	14	10	
2006	79	99	2	7	11	
2007	89	121	1	14	15	
2008	105	108	5	4	10	
2009	104	122	7	9	7	
2010	108	152	3	8	8	
2011	133	145	8	8	7	
2012	133	152	12	12	9	
2013	107	145	7	2	12	1
2014	99	101	4	9	11	
2015	67	65	4	3	7	
2016	59	61	2	2	7	
2017	19	33	4	3	2	

Table 13. Number of individual dogs per breed, sex and birthyear for insurance company 1 (2010 – 2016).

	Mixed-breed (n=1.510)		Dalmatian (n=86)	
Birthyear	Female (n=783)	Male (n=727)	Female (n=32)	Male (n=54)
1998		1		
1999	1	2		
2000	1	1		
2001	2	1		1
2002	9	11		1
2003	13	8	1	
2004	9	17	1	
2005	18	15		1
2006	28	15		2
2007	31	26		2
2008	51	44	2	1
2009	82	95	1	5
2010	154	126	6	8
2011	155	171	5	9
2012	108	87	5	13
2013	44	47	4	3
2014	40	29	4	6
2015	33	27	3	
2016	4	4		2

Table 14. Number of individual dogs per breed, sex and birthyear for insurance company 2 (1998 – 2016).

	Mixed-breed (n=5.535)			**Dalmatian (n=536)**		
Birthyear	Female (n=2.722)	Male (n=2.755)	Unknown (n=58)	Female (n=253)	Male (n=283)	Unknown (n=0)
1984	1					
1986	2	2				
1987	3	6			1	
1988	11	12				
1989	23	18				
1990	21	36				
1991	44	46			1	
1992	54	67	1			
1993	52	71	1		3	
1994	86	89	3	1	4	
1995	80	93	1	4	2	
1996	112	120	1	5	5	
1997	117	128	3	6	6	
1998	187	173	8	15	10	
1999	241	253	6	10	17	
2000	307	279	4	13	19	
2001	322	325	3	20	24	
2002	326	316	10	25	26	
2003	259	241	4	14	20	
2004	273	260	4	16	28	
2005	164	169	7	21	14	
2006	36	49	2	10	10	
2007				9	18	
2008				13	15	
2009				8	7	
2010	1			15	15	
2011				16	6	
2012				9	5	
2013				4	3	
2014		2		6	5	
2015				3	5	
2016				10	14	

Table 15. The complete final* model for the variables that significantly influence the occurrence of organ systems for the data of insurance company 1.

Variable	**Category**	**Proportion**	**OR (95% CI)**	**P-value**
Joints				
Breed	Mixed-breed (Ref**)	0.09	1	0.02
	Dalmatian	0.20	2.6 (1.2 – 5.3)	0.02
Sex	Male (Ref)	0.13	1	0.02
	Female	0.07	0.5 (0.3 – 0.9)	0.03
Birthyear period	2009 – 2012 (Ref)	0.11	1	0.03
	2013 – 2016	0.06	0.5 (0.2 – 1.0)	0.048
Gut				
Breed	Mixed-breed (Ref)	0.35	1	0.03
	Dalmatian	0.49	2.0 (1.1 - 3.5)	0.02
Birthyear period	2009 – 2012 (Ref)	0.39	1	0.004
	2013 – 2016	0.27	0.6 (0.4 – 0.8)	0.005
Neurological conditions				
Breed	Mixed-breed (Ref)	0.06	1	0.02
	Dalmatian	0	***	***
Eyes				
Breed	Mixed-breed (Ref)	0.19	1	0.04
	Dalmatian	0.08	0.4 (0.1 – 1.0)	0.07
Sex	Male (Ref)		1	0.04
	Female		0.7 (0.4 – 1.0)	0.04
Birthyear period	2009 – 2012 (Ref)	0.22	1	0.006
	2013 – 2016	0.13	0.5 (0.3 – 0.8)	0.01

* Variables in the initial model: breed, sex and birthyear.

** Ref: referent category

*** There were no individual dogs for this category in this dataset therefore, the OR and p-value could not be defined.

Mixed-breed (n=594); Dalmatian (n=51)

Table 16. The complete final* model for the variables that significantly influence the occurrence of organ systems for data of insurance company 2.

Variable	Category	Proportion	OR (95% CI)	P-value
Denture				
Breed	Mixed-breed (Ref**)	0.02	1	< 0.001
	Dalmatian	0.11	6.2 (3.6 – 10.4)	< 0.001
Heart				
Breed	Mixed-breed (Ref)	0.01	1	< 0.001
	Dalmatian	0.03	6.8 (2.3 – 19)	< 0.001
Sex	Male (Ref)	0.01	1	0.05
	Female	0.00	0.3 (0.1 – 0.8)	0.03
	Unknown	0	***	***
Birthyear period	1998 – 2002 (Ref)	0.01	1	0.19
	2003 – 2012	0.01	1.0 (0.4 – 2.8)	1.0
	2013 – 2016	0.0	***	***
Airway				
Breed	Mixed-breed (Ref)	0.13	1	< 0.001
	Dalmatian	0.41	6.6 (4.8 – 9.1)	< 0.001
Birthyear period	1998 – 2002 (Ref)	0.16	1	< 0.001
	2003 – 2012	0.16	0.8 (0.6 – 1.0)	0.08
	2013 – 2016	0.13	0.2 (0.1 – 0.4)	< 0.001
Gut				
Breed	Mixed-breed (Ref)	0.13	1	< 0.001
	Dalmatian	0.42	6.5 (4.7 – 9.0)	< 0.001
Birthyear period	1998 – 2002 (Ref)	0.14	1	< 0.001
	2003 – 2012	0.18	1.0 (0.8 – 1.3)	0.8
	2013 – 2016	0.11	0.1 (0.1 – 0.3)	< 0.001
Neurological conditions				
Breed	Mixed-breed (Ref)	0.01	1	0.06
	Dalmatian	0.03	2.5 (1.0 – 5.6)	0.04
Eyes				
Breed	Mixed-breed (Ref)	0.07	1	< 0.001
	Dalmatian	0.24	4.9 (3.4 – 7.1)	< 0.001
Birthyear period	1998 – 2002 (Ref)	0.08	1	0.005
	2003 – 2012	0.10	1.0 (0.7 – 1.4)	1.0
	2013 – 2016	0.07	0.2 (0.0 – 0.6)	0.01
Ears				
Breed	Mixed-breed (Ref)	0.05	1	< 0.001
	Dalmatian	0.32	11.1 (7.6 – 16.2)	< 0.001
Birthyear period	1998 – 2002 (Ref)	0.08	1	0.02
	2003 – 2012	0.09	0.7 (0.5 – 1.1)	0.1
	2013 – 2016	0.17	0.3 (0.1 – 0.7)	0.01

Pancreas				
Breed	Mixed-breed (Ref)	0.01	1	< 0.001
	Dalmatian	0.08	11.6 (5.6 – 24)	< 0.001
Sex	Male (Ref)	0.01	1	0.01
	Female	0.03	3.1 (1.5 - 7.5)	0.001
	Unknown	0	***	***
Birthyear period	1998 – 2002 (Ref)	0.02	1	0.02
	2003 – 2012	0.02	0.8 (0.4 – 1.6)	0.5
	2013 – 2016	0	***	***
Muscles and tendons				
Breed	Mixed-breed (Ref)	0.16	1	< 0.001
	Dalmatian	0.33	3.7 (2.7 – 5.2)	< 0.001
Sex	Male (Ref)	0.15	1	0.01
	Female	0.21	1.4 (1.1 – 1.8)	0.005
	Unknown	0.09	0.7 (0.04 – 3.6)	0.7
Birthyear period	1998 – 2002 (Ref)	0.21	1	< 0.001
	2003 – 2012	0.16	0.6 (0.5 – 0.8)	< 0.001
	2013 – 2016	0.09	0.1 (0.03 – 3.0)	< 0.001
Reproductive organs				
Breed	Mixed-breed (Ref)	0.16	1	< 0.001
	Dalmatian	0.42	4.6 (3.4 – 6.4)	< 0.001
Sex	Male (Ref)	0.16	1	< 0.001
	Female	0.23	1.6 (1.2 – 2.0)	< 0.001
	Unknown	0	***	***
Birthyear period	1998 – 2002 (Ref)	0.16	1	< 0.001
	2003 – 2012	0.23	1.3 (1.0 – 1.6)	0.04
	2013 – 2016	0.09	0.1 (0.04 – 0.3)	< 0.001

* Variables in the initial model: breed, sex and birthyear.

** Ref: referent category

*** There were no individual dogs for this category in this dataset therefore, the OR and p-value could not be defined.

Mixed-breed (n=1.732); Dalmatian (n=237)

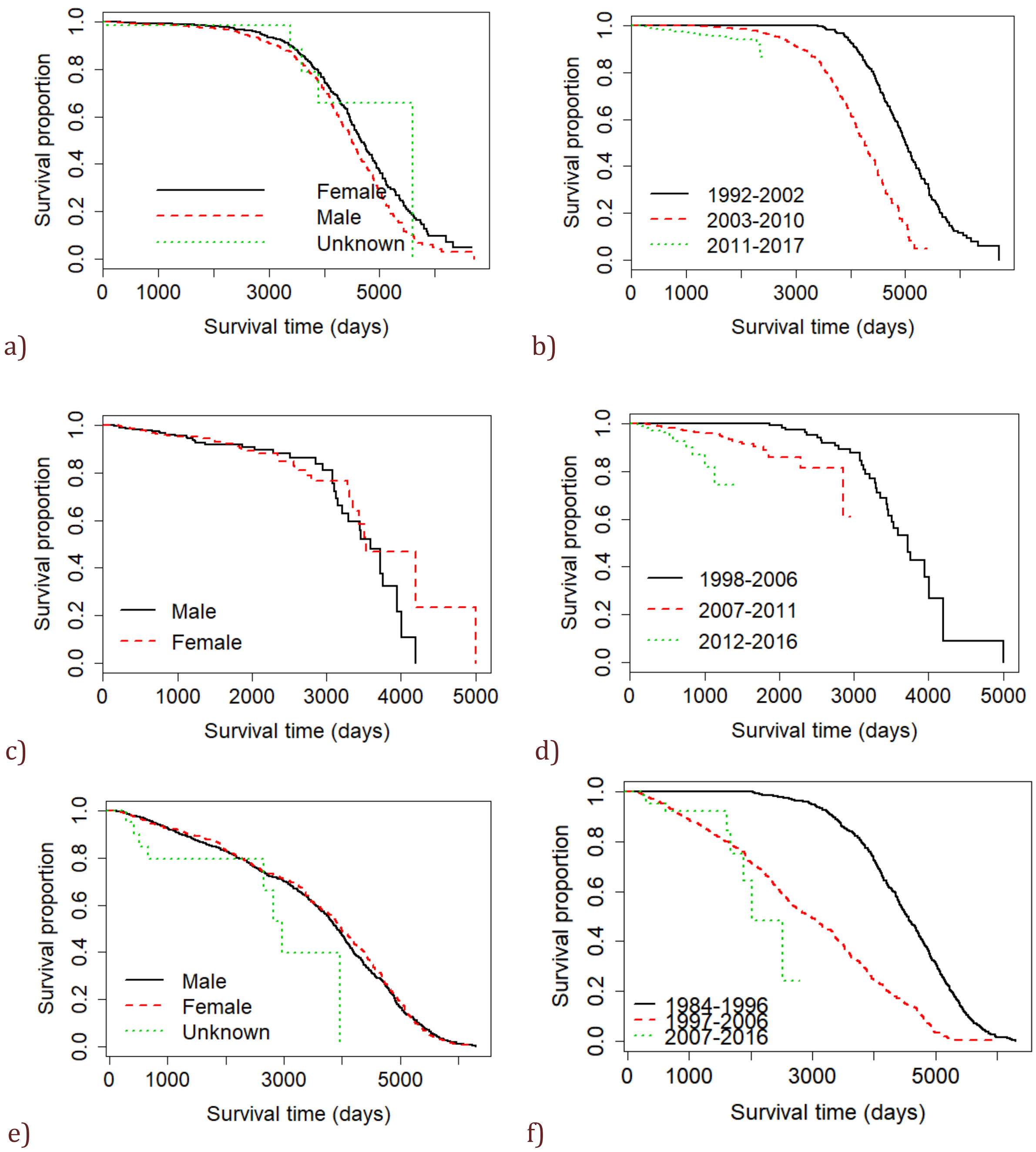


Figure 8. Kaplan Meier survival curves from birth date until death or censoring event per sex and birthyear period for the Veterinary Practice Software System (a and b respectively), insurance company 1 (c and d respectively) and insurance company 2 (e and f respectively).

Table 17. Hazard ratio and 95% confidence interval for dying in the final model* for the data from the Veterinary Practice Software System.

Variable	**Category**	**Hazard ratio**	**95% CI**		**P-value**
			Lower	*Upper*	
Breed	Mixed-breed (Ref**) (n=3.169)	1			0.001
	Dalmatians (n=308)	0.6	0.5	0.9	0.002
Birth period	1992 – 2002 (Ref)	1			< 0.001
	2003 – 2010	3.4	2.8	4.2	< 0.001
	2011 – 2017	17.9	10.5	30.6	< 0.001
Sex	Female (Ref)	1			0.003
	Male	1.3	1.1	1.6	0.008
	Unknown	0.9	0.4	2.2	0.8

* Variables in the initial cox proportional hazards model: breed, sex and birthyear.
** Ref: Reference category

Table 18. Hazard ratio and 95% confidence interval for dying in the final model* for the data from insurance company 1

Variable	**Category**	**Hazard ratio**	**95% CI**		**P-value**
			Lower	*Upper*	
Breed	Mixed-breed (Ref**) (n=1.510)	1			0.7
	Dalmatians (n=86)	1.2	0.5	3.0	0.68
Birth period	1998 – 2006 (Ref)	1			< 0.001
	2007 – 2011	4.7	2.0	10.8	< 0.001
	2012 – 2016	18.5	6.5	52.2	< 0.001

* Variables in the initial model: breed, sex and birthyear.
** Ref: Reference category

Table 19. Hazard ratio for dying and 95% confidence interval in the final model* for the data from insurance company 2

Variable	**Category**	**Hazard ratio**	**95% CI**		**P-value**
			Lower	*Upper*	
Breed	Mixed-breed (Ref**) (n=5.535)	1			< 0.001
	Dalmatians (n=536)	0.3	0.2	0.4	< 0.001
Birth period	1984 – 1996 (Ref)	1			< 0.001
	1997 – 2006	5.9	5.0	6.9	< 0.001
	2007 – 2016	23.0	11.2	47.2	< 0.001

* Variables in the initial model: breed, sex and birthyear.
** Ref: Reference category