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# **Genetic analysis of lifespan in Irish wolfhounds**

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EMABG

# EUROPEAN MASTER IN ANIMAL BREEDING AND GENETICS

*Genetic analysis of lifespan in Irish wolfhounds*

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### 2.1 Abstract

Irish Wolfhounds are an ancient and large dog breed. Their lifespan is an average of 7 years only, which is associated with their size. The genetics behind the short lifespan and the combination with different known diseases in this breed is poorly understood. We used data from the Irish wolfhound database (IWDB) on 118095 Irish wolfhounds of which 10122 have a known longevity and with 6057 of these having a known cause of death (COD) and 10144 a known sire and dam. Longevity and COD were analysed separately and together using sex, birthyear, country of origin and inbreeding coefficient in the model, to estimate heritabilities, maternal effects, genetic variances and breeding values. Genetic and residual correlations between longevity and COD were estimated as well. Both longevity (0.27) and COD (0.04-0.16) were moderately heritable. Longevity had a standard deviation of 482 days while the standard deviation of COD ranged from 0.05 to 0.19. However, most COD did not have a genetic or residual correlation to longevity that was significantly different from zero, they are mostly independent traits. Only heart disease, infections and accident/injury/poison/surgery complications were negatively significantly correlated to longevity and old age/weak rear was positively significantly correlated to longevity. These results show that there is a large potential to breed for longevity and against disease occurrence in Irish wolfhounds.

### 3.1 Introduction

Dog species exhibit a wide range of morphologies, behaviors and diseases. Consequently, variation in mortality and longevity between breeds is not unexpected. Shorter longevity in and of itself does not have to be a welfare issue if the life was healthy and the process of dying was not prolonged or with great pain. Similarly, longer longevity does not automatically mean an improved quality of life. For example, if a dog is subjected to long distressing periods of decline leading to death or euthanasia. However, if shorter longevity is accompanied by a high occurrence of a particular disease, this may reveal serious welfare concerns. A study on dog breeds registered with the UK Kennel Club found that the most commonly reported causes of death are old age (13.8%), cancer (8.7%) and heart failure (4.9%) (Lewis et al, 2018). There is a wide variation in overall median longevity, in the prevalence of causes of death among breeds and in the median longevity across causes of death. The same study showed that nine causes of death were identified as tending to result in death at an earlier age, among those causes were the diseases cardiomyopathy, bone and brain tumors, lymphoma, bloat and epilepsy (Lewis et al, 2018). Six causes of death were identified as tending to result in death at an older age, among these causes were arthritis, old age, stroke and liver failure (Lewis et al, 2018). Also, a variation in the rate of death for specific diseases between males and females has been shown (Egenvall et al, 2005). Multiple studies show an inverse correlation between body size and longevity (Lewis et al, 2018; Adams et al, 2010). Larger breeds tend to have a shorter lifespan than smaller breeds because larger breeds tend to age more quickly (Kraus et al, 2013).

Larger breeds spent relatively more energy to reach adult size than small breeds. Thereby they would have relatively less energy left for health maintenance (Fan et al, 2016). Giant and large breed dogs are also at an increased risk of osteosarcoma (bone cancer), while smaller breeds have a decreased risk (Breur et al, 2001). So size has an important influence on longevity and disease risk in dog breeds.

The Irish wolfhound (IW) is an ancient breed, it has written records going back to before Christian times. This breed originated in Ireland, it is the dog of many (Celtic) legends and mythology and is now known as the national dog of Ireland (Starbuck, 2021; IWCOI, 2018). Historically this breed was used for hunting wolves and other large game. These hunts were often long, solitary and based on the dog's ability to visualize its surroundings, as it is a sighthound. Unlike scent dogs who rely on scent instead of sight (Flaim, 2020). This breed came close to extinction in the 18<sup>th</sup> and 19<sup>th</sup> century. The exact number left across Ireland is unknown, but there were enough possible descendants to revive the breed. This resurrection started around 1863 and many outcrosses were made, to Scottish deerhounds, Great Danes, borzoi, one mastiff and one mysterious "Tibetan dog", who some believe to be a Kyi Apso (Flaim, 2020; Flatberg, IWDB; NIWC, 2020). This established the type for the natural successor of the Irish Wolfhound. Around 1940 the last known outcross was done, but the records of those bloodlines are now lost. The last known founder, Sile Deirin of Coolafin, was registered in 1931 with 'pedigree, breeder and date of birth unknown'. After its resurrection, the breed has been through three bottlenecks, during World War I, World War II and the 1960s (Flatberg, IWDB).

During WW I very few of the existing animals survived. The breed was mainly based in the UK at this point and the breeding of pets was prohibited during the war. After the war, the breed had its first major international expansion. Litters were bred across Europe and Asia, mainly from the remaining UK dogs. WW II saw another significant drop in breeding all over Europe, outside the USA very few litters were bred, leading to small breeding stock in Europe after the war. The popularity of the breed exploded after 1960. From only 26 litters born worldwide in 1960 to 673 litters born only 15 years later. This in and of itself created another bottleneck because the breeding population was very small before the explosion in popularity. Worldwide the population peaked at 26.000 dogs in 1997 and the current registered population is estimated at 19.000 dogs worldwide. Irish wolfhounds are bred on all continents, except Antarctica. The USA and Germany are the countries with the largest populations and an estimated 500 litters are born worldwide every year. Currently, for most dogs, their most recent founder can be traced to 16-20 generations back in time, and for most of them, lineage can be traced back to the earliest founders about 70 generations ago (Flatberg, IWDB).

The Irish wolfhound is a rough-coated dog known as the largest and tallest of all galloping breeds. Not to be confused as the heaviest since their built is more like the greyhound. Their minimum size is defined by the American Kennel Club (AKC) as 81 cm for mature males and 76 cm for mature females, it is not unusual to see females meet the minimum heights of the males. Irish Wolfhounds weigh in general 45-55 kg. Both these standards are defined differently in Ireland and England by The Kennel Club (KC). The litter size of Irish wolfhounds ranges from 4 to 8 puppies. Lifespan expectancy is relatively short, like for many large breeds, between 6 and 10 years with 7 being the average. When afflicted with a disease at a young age, owners may have to part with their beloved hounds even earlier than this, to prevent suffering for the animal (Simpson, 2016; Urfer et al, 2007; Flatberg, IWDB). The Irish Wolfhound is generally not a very popular breed population-wise, because it is expensive to breed, keep and it is a special interest breed (Flatberg, IWDB). But many people have kept Irish wolfhounds for a long time and are especially fond of the breed. Mainly due to its very close bond to its owner, as they are extremely faithful dogs and have a gentle nature. They have other specific characteristics like independence, intelligence, tolerance, sensitivity, gracefulness, patience and forgiveness (Foreman; IWC; IWCAb). These characteristics make them very popular for specific people, which is seen all over the world. These people are often very passionate about preserving the breed, as many countries have their own Irish Wolfhound Breed organizations. Ireland (IWOIC), The United Kingdom (IWC), The Netherlands (NIWC), America (AKC and IWCAb) and Norway

(IUN) among others. As Irish wolfhound populations in different countries are genetically similar, it was assumed that specific loci found to be genetically associated with a disease in one population would also be found in another. However, this was found to be untrue for dilated cardiomyopathy, different populations have different loci genetic associated with this disease (Simpson et al, 2016).

The leading causes of death for Irish Wolfhounds are dilated cardiomyopathy and bone cancer (Urfer et al, 2007), which are also the most reported causes of death for dog breeds in general, besides old age (Lewis et al, 2018). A study from the US found that between 1966 and 1986 34% of Irish Wolfhounds died from cancer, of which 61% died from osteosarcoma (Bernardi, 2021). Osteosarcoma can be assumed to have a hereditary component (Urfer et al, 2007; Karlsson et al, 2013). Often when these dogs are diagnosed with osteosarcoma, they are euthanized because of the poor quality of life they would otherwise have (Simpson, 2016). It has been shown that castrating males gives a higher risk for bone cancer in dogs (Urfer et al, 2007; Corp-Minamiji, 2013). For other breeds, it was often found that osteosarcoma is more prevalent in males than females, but this was not true for Irish wolfhounds (Bernardi, 2021). An average of 15% of Irish wolfhounds dies from cardiovascular diseases, with cardiomyopathy in some form being the most common heart disease (Bernardi, 2021). Several forms of cardiomyopathy have been shown to have a heritable component, with heritability estimates ranging from 39% to 64% (Urfer et al, 2007; Simpson et al, 2016). Dilated cardiomyopathy (DCM) is a well-researched type of cardiomyopathy and has been shown to cause early death in Irish wolfhounds (Vollmar et al). DCM has an occurrence rate of 10-20% and the genes involved in canine DCM are dissimilar to the over 50 genes involved in human DCM (Simpson et al, 2016; Philipp et al, 2012). The mixed monogenic polygenic model inheritance model is thought to include a sex-dependent allele effect for DCM (Distl et al, 2007; Simpson et al, 2016; Philipp et al, 2012; Wang et al, 2012). DCM usually has a period of subclinical symptoms with no or only slight welfare problems. On average Irish wolfhounds show clinical signs of DCM at 4 years old. One symptom often seen is fluid build-up in the pleural cavity, causing compression of the lungs and difficult breathing. This is seen as an extreme welfare problem and Irish wolfhounds are often euthanized to prevent this from happening. But since the disease is usually not detected until very late, affected dogs could have been used for breeding, which will extend the problem to later generations (UFAW, 2011). Another disease that is common in Irish Wolfhounds is bloat and/or gastric torsion, with an occurrence of 12% (Bernardi, 2021). It is thought that gastric torsion may partially be explained by the inheritance of body shape or temperament. Many other diseases have been reported for this breed, like hereditary intrahepatic portosystemic shunt (occurs in 2.1% to 3.4% of all puppies). Arthritis (Urfer et al, 2007). Pneumonia, for which a heritable base is assumed in IW. Greenwell & Brain found an occurrence rate of 36% for aspiration pneumonia (Simpson et al, 2016; Greenwell & Brain, 2014; Clercx et al, 2003; Leisewitz et al, 1997). Lastly epilepsy, with an estimated heritability of 87% (Casal et al, 2006). Many of these diseases can cause lifelong struggle for the animal due to the welfare problems they cause and often owners euthanize their dog due to low quality of life.

The accumulation of DNA damage through fast cell proliferation during growth is thought to be the reason large dogs have a decreased lifespan compared to smaller dogs. This damage results in an earlier onset of aging and degenerative diseases, including the earlier onset or higher incidence of some cancers. However, deaths due to other hereditary diseases and hereditary cancers are independent of this. Osteosarcoma was not listed as a cause of death in the first lifespan study performed for Irish wolfhounds, while there is a very high incidence of this found now (Urfer et al, 2007). This seems to indicate that this disease has a heritable base. However, osteosarcoma may not influence the lifespan of these animals. Another study showed that excluding animals who died from cancer, cardiovascular disease or gastric torsion did not increase the average lifespan of the animals. But this study did remark that excluding these animals, over 60%, would likely change the distribution of diseases. This means that the reduction of these genetic diseases in the population does not mean fewer dogs are born; it just means their deaths are due to other causes. Even though

there are studies done on the lifespan of Irish Wolfhound, many of these studies have right-censored data. This means that not all animals in the sample have died yet and this would cause low lifespan estimates. Also, many of these studies have a relatively small sample size and often these samples were taken in specific places (Urfer et al, 2007).

The objective of this paper is to evaluate the potential of selecting for a longer and healthier life for the Irish wolfhound breed, using a large sample size and a wide distribution around the world. This objective will be reached by answering the following questions:

- Is there genetic variation in longevity?
- Is there a significant difference in longevity between different Causes of Death (COD)?
- What is the 'residual' genetic variation for longevity when correcting for COD?
- Is a specific COD heritable and is there genetic variation for COD?
- Is there a genetic and/or residual correlation between different COD and longevity?

#### 4.1 Material and methods

For this thesis, I will make use of data from the Irish wolfhound database (IWDB). They have an estimated 98% of all Irish wolfhounds ever registered in this database. The following datasets were received: The complete and public IWDB dataset and The private Irish Wolfhound Longevity Study dataset (which includes pedigree data, mortality information and health data). The pedigree consists of 167132 dogs, from 1859 to 2020, with 11558 dogs having longevity records and of these 11558, 11550 have a known sire and dam. A little over 6000 animals in the pedigree do not have ancestry information, but these animals are not considered founders if they are born after 1945. This is because the last known founder was registered in 1931 and the last known outcross was made in 1940 (Flatberg, IWDB). Unfortunately, for many animals without parentage information, the date of birth is not known. Only 10 animals have a date of birth before 1946 and no parentage information. Even without a known date of birth more founders, besides these 10, can be identified. It is known that many founders were not Irish wolfhounds and that after 1940 no more outcrosses were made. All animals in the pedigree with a known breed other than Irish wolfhound, which includes 524 animals, are therefore founders. This means there are 534 known founders for this breed.

There might be certain biases in this database, the first is a veteran bias for the mortality information. This is because mortality information collection started in 2012 with veterans (dogs that reached 8 years of age). This was reinforced due to the fact people are more willing to share information about a dog that lived a long life, instead of a short one. From 2016 on mortality information on all Irish Wolfhounds is collected. To possibly correct for this bias the model will be tested with and without the animals born between the start of 2012 and the end of 2015, which is 8.5% of total longevity records.

When collection on all animals started in 2016 this included information on deceased dogs, by looking back and collecting information from books, magazines, kennel club databases and other data sources. This might cause the second bias; all this information is collected from older records and for the earlier years 1859-1978 less than a hundred longevity records per year exist. To possibly correct for this bias the model will be tested with and without these records. These records form 8.1% of total longevity records.

The last bias is from the later years, as animals born in recent years have not yet had the chance to die. To possibly correct for this bias the model will be run without animals born after 2013, which is 4.3% of all longevity records. This point was decided on the fact that animals born in 2013 will have the chance to reach the average age of 7, but every animal born after 2013 has not had this chance.

Bias tests were done by comparing the estimated breeding values (EBV), variances, heritability, maternal effect and inbreeding effect on longevity for four year groups. To be able to compare the possible biases the first group excludes all years with possible bias, this group then consists of the

years 1979-2011, and the other three groups include 1 possible bias each. The three groups then include the years 1859-2011, 1979-2013 and 1979-2020 respectively. It was decided to test the 2012-2016 bias until the end of 2013, to prevent overlap with the 2013-2020 group. The dataset used for running further models includes the years 1979-2013. For the interpretation of this dataset R 4.0.3 (R Core Team, 2020) and ASReml 4.1 (Gilmour et al, 2015) will be used.

For the reduced dataset used in modelling to prevent possible bias there are 118095 dogs in total, of which 10122 have longevity records and of these 10122, 10114 have a known sire and dam. Figure 1 shows the number of sires and dams that have a specific number of offspring, with known longevity. Because of the large spread in the number of sires/dams the data is separated into two graphs. Where A includes the number of offspring for which more than 40 sires are responsible for this number and B includes the number of offspring for which less than 40 sires are responsible for this number. There are 6057 animals with a record for cause of death along with longevity records in the modelling dataset. There are 133 different categories for cause of death which are divided into 12 main categories (COD) as defined by the IWDB. For example, COD A includes causes of death 1, 2, 3, 59, 67, 90 and 113 which represent DCM, heart attack, unspecified heart disease, circulatory system failure, congestive heart failure, other heart disease and aneurysm respectively. One COD (NULL) was added as some of the 133 causes of death are not included in the 12 COD as defined by the IWDB. So, all these causes of death were included in COD NULL. To prevent exclusion of longevity records because a cause of death is not included in the 12 original COD as defined by the IWDB.



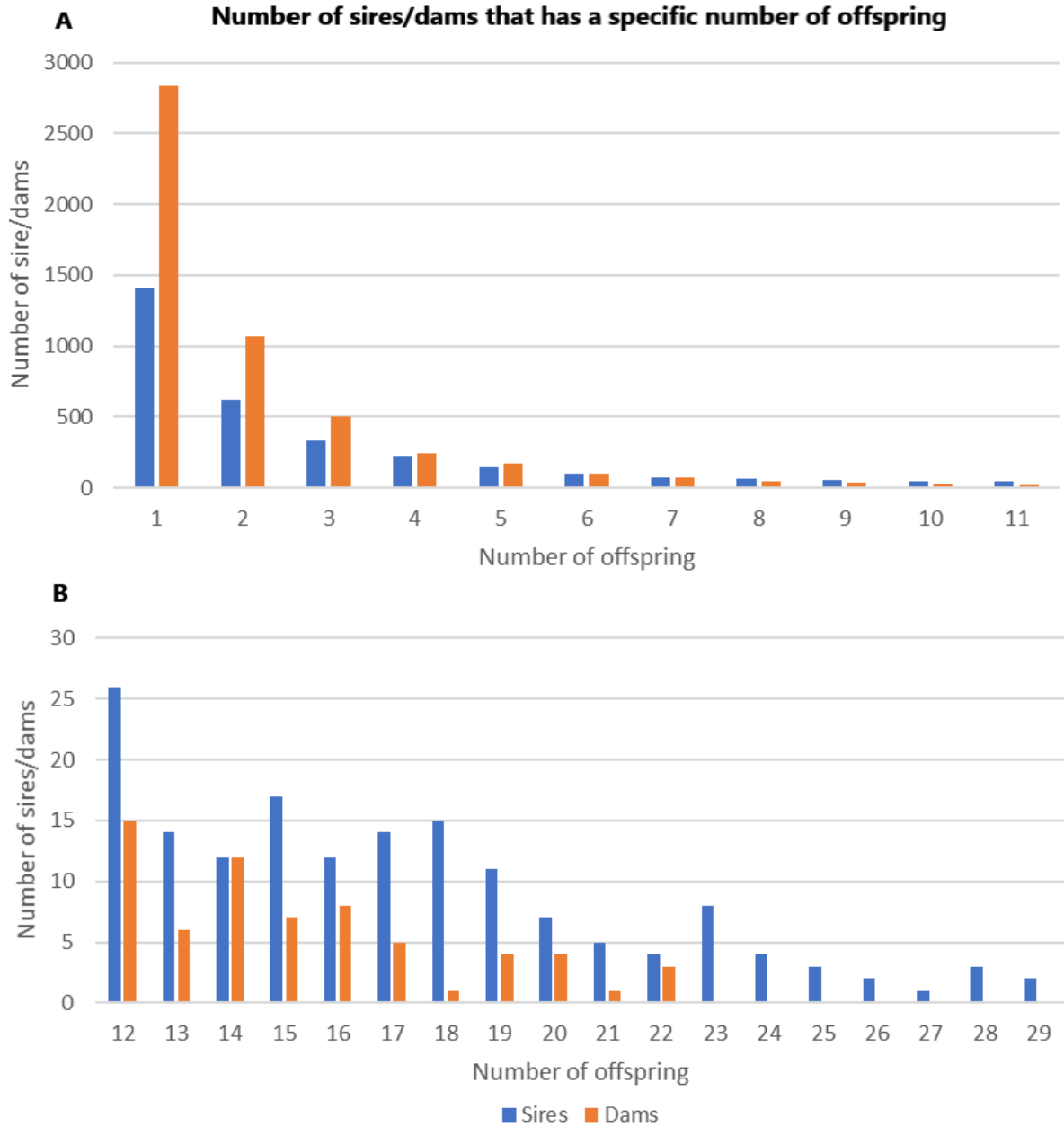


Figure 1: Number of sires and dams that have a specific number of offspring. The graph is divided into A, more than 40 sires responsible for the number of offspring, and B, less than 40 sires responsible for the number of offspring. After 29 offspring the other numbers of offspring are omitted from the graph, as this is the last number of offspring where more than 1 sire is responsible for the number of offspring. After this 1 sire each is responsible for 30, 33, 34, 35, 39, 43, 46, 51, 52 and 56 offspring.

The first model will be used for the estimation of genetic variance of longevity along with the heritability and maternal effect. These estimated variance components are then used to predict EBV for longevity for all animals. This model is used for bias testing, the estimations of heritability, maternal effect, genetic variance and EBV for all three bias year groups are compared to the year group without bias.

$$L_{ijklkm} = \mu + S_i + B_j + C_l + \beta F_{ijklkm} + a_k + d_m + e_{ijklkm} \quad (1)$$

L = Longevity;  $\mu$  = general mean; S = fixed sex effect ( $i = 1$  or  $2$ ); B = fixed birthyear effect ( $j = 1979$  till  $2013$ ); C = fixed country of origin effect ( $l = 1$  till  $18$ ); F = inbreeding coefficient calculated from the pedigree, with regression coefficient  $\beta$  giving the regression of longevity on F. Further in the model  $a_k$  is the random additive genetic effect of the  $k^{\text{th}}$  animal with breeding values assumed to be  $\sim N(0,$

$A\sigma_a^2$ ),  $d_m$  is a random effect of the  $m^{\text{th}}$  dam, with dam effects assumed to be  $\sim N(0, I\sigma_m^2)$  and  $e_{ijklkm}$  is the residual term with residuals assumed to be  $\sim N(0, I\sigma_e^2)$ . In which  $A$  is the additive genetic relationship matrix,  $\sigma_a^2$  is the additive genetic variance,  $I$  is an identity matrix,  $\sigma_m^2$  is the maternal variance, and  $\sigma_e^2$  is the residual variance. For an overview of the minimum, maximum and mean and its standard deviations (sd) of longevity, sex, birth year and inbreeding coefficient for the modelling dataset see table 2. For an overview of country of origin for the modelling dataset see table 3.

Table 2: Overview of variables in the models. The minimum, maximum and the mean  $\pm$  sd are given for the animals with known longevity in the modelling dataset. For an overview of Country of Origin see table 3.

Variable	Min	Max	Mean
Longevity (days)	0	5479	2648 $\pm$ 925
Sex <sup>1</sup>	1	2	1.5 $\pm$ 0.5
Birthyear (year)	1979	2013	2001 $\pm$ 8.8
Inbreeding coefficient	0	0.69	0.36 $\pm$ 0.05

<sup>1</sup> Males are denoted with 1 and females with 2.

Table 3: Overview for the variable country of origin. The frequency of records is given, for the animals with known longevity in the modelling dataset, along with the minimum, maximum and mean  $\pm$  sd of longevity for these records in days. The countries are given as two-letter ISO codes.

Country	Frequency	Min (days)	Max (days)	Mean (days)
AT	0.02	71	5113	2923 $\pm$ 1072
AU	0.03	306	4508	2786 $\pm$ 842
BE	0.03	177	4671	2642 $\pm$ 935
CA	0.03	333	4579	2745 $\pm$ 893
Combi <sup>1</sup>	0.05	46	5479	2772 $\pm$ 967
CZ	0.13	0	4870	2384 $\pm$ 958
DE	0.14	59	5050	2736 $\pm$ 897
DK	0.03	54	4471	2473 $\pm$ 905
FI	0.09	61	4799	2381 $\pm$ 877
FR	0.02	799	4774	3115 $\pm$ 835
GB	0.12	4	4748	2743 $\pm$ 867
HU	0.01	99	4856	2806 $\pm$ 886
IE	0.03	548	4969	3179 $\pm$ 773
NL	0.03	327	4408	2629 $\pm$ 832
NO	0.05	97	4748	2331 $\pm$ 958
PL	0.01	104	4388	2532 $\pm$ 977
SE	0.05	52	4564	2543 $\pm$ 901
US	0.13	93	5113	2784 $\pm$ 878

<sup>1</sup> Combi consists of 21 countries that each had a total number of animals included below 100, these were gathered in one combination variable.

The second model will be used for the estimation of the genetic variance of longevity when correcting for a specific COD. The heritability, maternal effect and COD effect will also be estimated.

$$L_{ijklkmo} = \mu + S_i + B_j + C_l + \beta F_{ijklkmo} + D_o + a_k + d_m + e_{ijklkmo} \quad (2)$$

The third model is used for the estimation of the genetic variance of a specific COD, along with the heritability and maternal effect. These estimated variance components are then used to predict EBV for all COD for all animals

$$D_o = \mu + S_i + B_j + C_l + \beta F_{ijklkmo} + L_{ijklkmo} + a_k + d_m + e_{ijklkmo} \quad (3)$$

For both models L = Longevity and D = 1 for the COD analyzed and all other COD D = 0. Both models were run for each of the 12 CODs separately. For both models, no effects were estimated for COD NULL, as this COD does not have a clear categorization. But this COD was included in the model runs for the other COD, with D = 0, as it is known these animals did not die from one of the other 12 COD. All animals without a known COD were not included in these models, as it is not known whether these animals died from one of the COD or not.

Heritability's and maternal effects for models 1, 2 and 3 were calculated as:

$$h^2 = \frac{\sigma_a^2}{\sigma_p^2} \quad \text{and} \quad m^2 = \frac{\sigma_m^2}{\sigma_p^2}$$

For which the phenotypic variance was calculated as:  $\sigma_p^2 = \sigma_a^2 + \sigma_m^2 + \sigma_e^2$  where  $\sigma_a^2$  is the additive genetic variance,  $\sigma_m^2$  is the maternal variance and  $\sigma_e^2$  is the residual variance.

The fourth model is a bivariate model for longevity and COD fitting the following two models which are like models 1 and 3.

$$L_{ijklm} = \mu + S_i + B_j + C_l + \beta F_{ijklm} + a_k + e_{ijklm} \quad \text{and} \quad D_o = \mu + S_i + B_j + C_l + \beta F_{ijklmo} + a_k + e_{ijklmo}$$

The dam effect was excluded from the bivariate model and the other variables have the same descriptions as given above. The dam effect was excluded from this model due to convergence issues and small effect sizes observed in the univariate models. For model 4 longevity was rescaled, divided by 1000, to prevent large differences in variances between longevity and COD, as COD showed a much smaller variance in the univariate analysis than longevity.

Heritability for model 4 was calculated as:

$$h^2 = \frac{\sigma_a^2}{\sigma_p^2}$$

For which the phenotypic variance was calculated as:  $\sigma_p^2 = \sigma_a^2 + \sigma_e^2$  where  $\sigma_a^2$  is the additive genetic variance and  $\sigma_e^2$  is the residual variance.

Using the estimated breeding values (EBV) calculated for longevity and COD from models 1 and 3, the selection differential (S) will be calculated for the EBV of longevity and COD, using the following formula.

$$S = \mu_s - \mu_p$$

Where  $\mu_s$  = the mean EBV of the selected parents and  $\mu_p$  = the mean EBV of the candidate population. The correlated response of the EBV of longevity when selecting against COD will also be calculated. Selection differential is usually calculated with the phenotypic means of the trait. Since both COD and longevity are traits only measured after death, an indication of the response to selection will be given by using the EBV.

The candidate population will consist of animals that would be available for breeding in 2021. By including only animals who are assumed to be alive, have no longevity records, and who are born between the start of 2015 and the end of 2019. Hereby, at the start of 2021, animals are at least 1 year old and a maximum of 6 years old. This was decided as the IWCA kennel club suggests breeding females at a maximum of six years old (IWCAc). No restriction was given for males so they were given the same age restriction as females. Generally, in dog breeds males can breed from 6 to 12 months of age and females from 12 to 18 months of age, on average animals can breed from 1 year old. The selected parents will consist of the top or bottom 10% of the candidate population, based on the EBV of the trait considered. The top 10% for longevity and COD I, as you would like an increase in these

traits and the bottom 10% for all other COD as you would like to decrease the frequency of these traits. In both the candidate and selected population there is an almost equal number of males and females.

## 5.1 Results

The dataset used for modelling includes the years 1979-2013 this is based on the similarity of the 1979-2013 group to the 1979-2011 group as seen from the values given in table 4 and by looking at the changes in estimated breeding values (EBV) for longevity when comparing groups as seen in figure 2. The figure shows the EBV from the three bias year groups against the EBV from the 1979-2011 group. This is to see what the effect of including these years is on the EBV. Looking at figure 2A many of the EBV from the years 1859-2011 are lower compared to those of the years 1979-2011, causing the spike downwards. Meaning the EBV from the year group 1859-2011 are very different from the EBV from the year group 1979-2011. Looking at figures 2B and C both the year groups 1979-2013 and 1979-2020 are more comparable to the EBV from 1979-2011 than the 1859-2011 year group was. But the EBV from the years 1979-2020 causes a larger spread than the EBV from the years 1979-2013. So, the EBV from the years 1979-2013 are more comparable to the EBV from the 1979-2011 group than those of the 1979-2020 group.

*Table 4: Variances, heritabilities, maternal effects and inbreeding coefficient effects on longevity (given as the effect on longevity in days from a 1% increase in inbreeding) for the four different groups looked at for possible bias effects. The estimates shown are  $\pm$  the SE. All variances and standard error (SE) of variances shown have been divided by 1000 for easier interpretation, for the original values multiply both with 1000.*

	<b>1979-2011</b>	<b>1859-2011</b>	<b>1979-2013</b>	<b>1979-2020</b>
$\sigma_a^2$	253 $\pm$ 29	297 $\pm$ 29	233 $\pm$ 26	217 $\pm$ 25
$h^2$	0.29 $\pm$ 0.03	0.33 $\pm$ 0.03	0.27 $\pm$ 0.03	0.26 $\pm$ 0.03
$m^2$	0.04 $\pm$ 0.01	0.04 $\pm$ 0.01	0.04 $\pm$ 0.01	0.05 $\pm$ 0.01
$\sigma_m^2$	34 $\pm$ 9	33 $\pm$ 9	35 $\pm$ 8	40 $\pm$ 8
$\sigma_r^2$	583 $\pm$ 15	576 $\pm$ 15	578 $\pm$ 14	572 $\pm$ 14
$\sigma_p^2$	870 $\pm$ 20	906 $\pm$ 20	846 $\pm$ 18	828 $\pm$ 17
<b>F (days)</b>	-10 $\pm$ 2.7	-8.1 $\pm$ 2.5	-9.6 $\pm$ 2.6	-8.4 $\pm$ 2.5

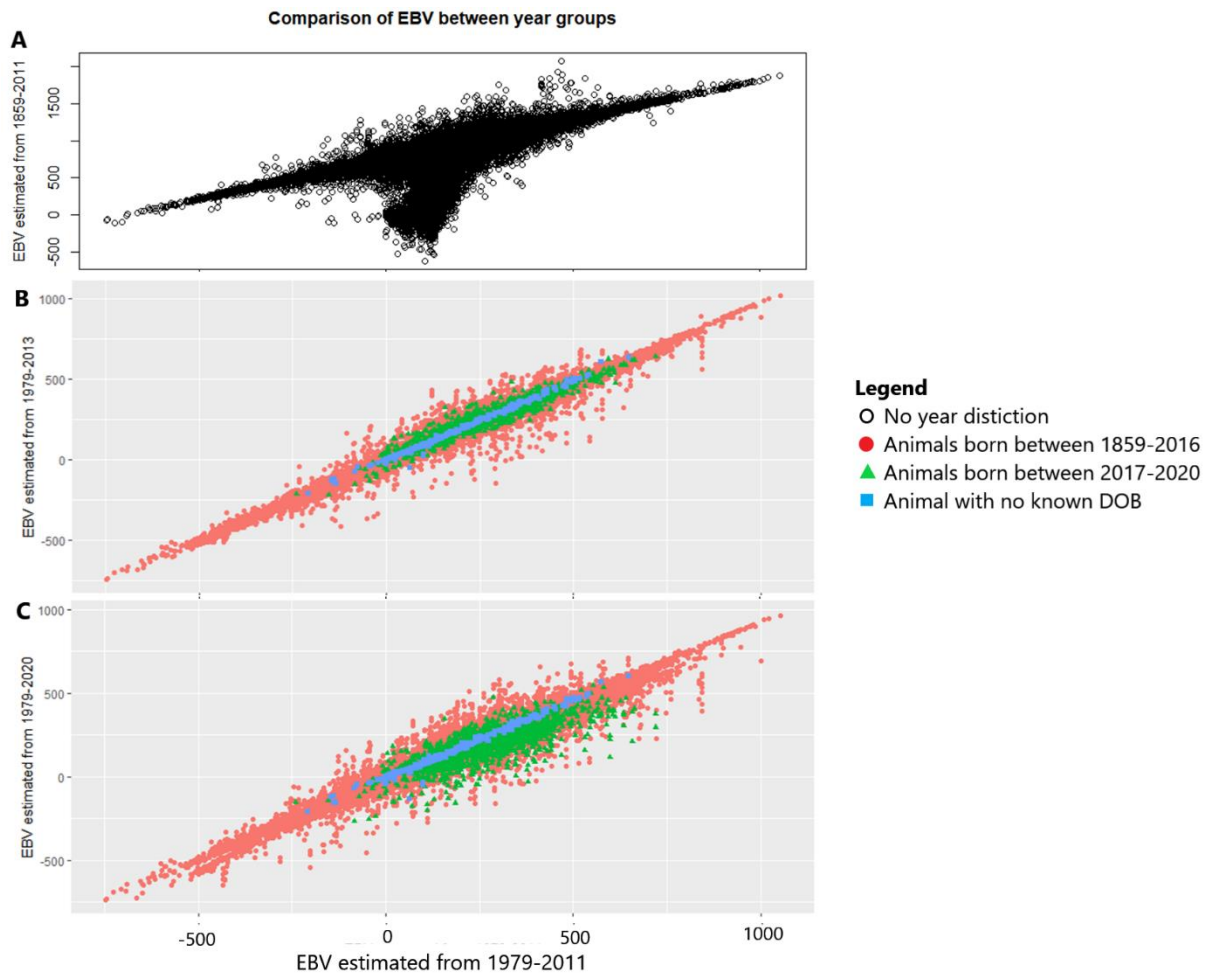


Figure 2: Comparisons of EBV between different years groups. All plots have the same X-axis as seen in plot C. A shows the EBV when using data from the years 1979-2011 on the x-axis against the EBV when using data from the years 1859-2011 on the y-axis. B shows the EBV when using data from the years 1979-2011 on the x-axis against the EBV when using data from the years 1979-2013 on the y-axis. C shows the EBV when using data from the years 1979-2011 on the x-axis against the EBV when using data from the years 1979-2020 on the y-axis.

For the distribution of longevity for the modelling dataset see figures 3 and 4, a close to normal distribution of longevity is shown. Table 5 gives an overview of the COD categories, it can be seen that more than half of all animals die from cancer or heart related diseases and that the most common COD after that is old age/weak rear. The mean phenotypic longevity calculated for all animals in the complete dataset was 2601 days (7.13 years) with a standard deviation of 974 days. The dataset used for modelling had phenotypic mean longevity of 2648 days (7.26 years) with a standard deviation of 925 days. The averages found for longevity in this study are in line with earlier average ages found for Irish wolfhounds (Simpson, 2016; Urfer et al, 2007). It was found that of the animals in the modelling dataset with known longevity 18% were 5 years or younger, 57.7% were 7 years or older and 27.6% were 9 years or older.

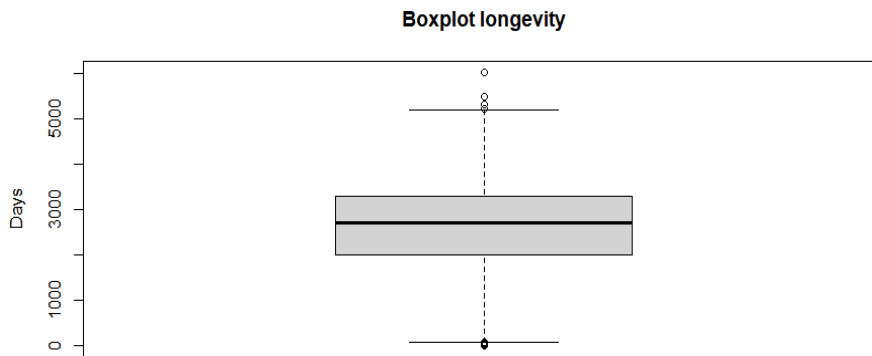


Figure 3: Boxplot of longevity data for the modelling dataset.

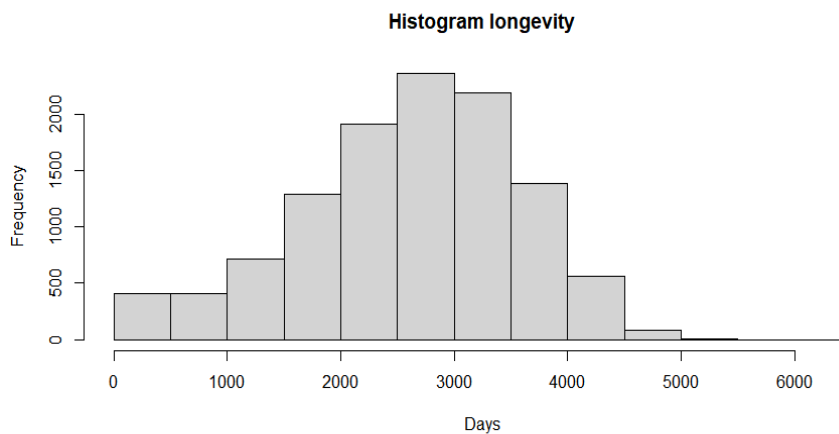


Figure 4: Histogram of longevity data for the modelling dataset.

Table 5: The division of COD categories with the explanation of each category as defined by the IWDB (except NULL). Includes the frequency of the occurrence of a COD, for all animals with known longevity in the modelling dataset, and the mean and standard deviation of longevity for each COD in days. There is also a category H (Whelping complications) defined by the IWDB, but in the division of causes of death over the COD whelping complications falls under COD J. Seeing that only 48 animals would have fallen under category H when separated and the division between whelping and surgical complications was not always clear, no separate COD H was included for these analyses.

<b>COD</b>	<b>Explanation of COD category</b>	<b>Frequency</b>	<b>Mean (days)</b>	<b>SD (days)</b>
A	Heart disease	0.18	2459	804
B	Cancer	0.34	2503	709
C	Bloat/Gastric Torsion/Gastrointestinal disease	0.09	2292	876
D	Pneumonia/respiratory disease	0.07	2241	975
E	Kidney disease	0.03	2385	910
F	Liver disease	0.009	1151	1071
G	Infections	0.04	2005	1025
I	Old age/Weak rear	0.11	3534	643
J	Accident/Injury/Poison/Surgery complications	0.08	1645	1006
K	Epilepsy	0.01	1798	979
L	Musculoskeletal disorder	0.03	2213	1131
M	Autoimmune and Bleeder disease	0.01	1963	902
NULL	Cause of death known but not a part of the 12 COD as defined by the IWDB	0.03	2010	931
	All animals with known cause of death	1.00	2648	925

The first model showed a heritability of 0.27 and a maternal component of 0.04 for longevity. A genetic standard deviation of 482 days was also found for longevity. In table 4 it is also seen that according to model 1 a 1% increase in inbreeding would cause a decrease in longevity of 9.6 days. The mean EBV for the candidate population described above, animals born between the start of 2015 and the end of 2019 who are assumed to be alive, is +244. The mean EBV for the selected population, the top 10% of these candidates based on their EBV for longevity, is +496, a difference of +252. So, the offspring of these top 10% animals are expected to live 252 days longer than the average longevity of the candidate population, dogs born between 2015 and 2019.

The second model showed a lower heritability ( $0.25 \pm 0.03$ ) for longevity, indicating that COD describes a small part of the genetic variance in longevity, and only longevity corrected for COD J had a maternal effect that was significantly different from zero ( $0.03 \pm 0.01$ ). Table 6 gives the COD effects on longevity, along with their genetic variance and inbreeding effect on longevity, for every COD separately. Genetic variance of longevity is comparable for all COD, except for COD I and J, which show a lower genetic variance. This model also showed that when correcting for COD in the model, except for COD I, the negative inbreeding effect on longevity seems to become stronger.

Table 6: Model 2 estimates. The COD effects on longevity, inbreeding effects on longevity (given as the effect on longevity in days from a 1% increase in inbreeding) and the genetic variance of longevity.  $h^2_{\text{Longevity}} = 0.25 \pm 0.03$  for all COD. Only COD J had a small maternal effect that significantly differed from zero with  $0.03 \pm 0.01$ . All estimates are  $\pm$  SE. Genetic variance and its SE have been divided by 1000 for easier interpretation, for the original values multiply both with 1000. COD effect estimates significantly different from zero are in bold.

COD	COD effect (days)	$\sigma^2_g$	F (days)
A	56 $\pm$ 30	210 $\pm$ 32	-12.2 $\pm$ 3.4
B	41 $\pm$ 24	208 $\pm$ 32	-12.2 $\pm$ 3.3
C	<b>-101 <math>\pm</math> 40</b>	205 $\pm$ 32	-12.4 $\pm$ 3.3
D	-81 $\pm$ 44	208 $\pm$ 32	-12.1 $\pm$ 3.3
E	15 $\pm$ 64	209 $\pm$ 32	-12.3 $\pm$ 3.3
F	<b>-1063 <math>\pm</math> 119</b>	205 $\pm$ 31	-12.0 $\pm$ 3.3
G	<b>-373 <math>\pm</math> 56</b>	209 $\pm$ 32	-11.9 $\pm$ 3.3
I	<b>1048 <math>\pm</math> 34</b>	152 $\pm$ 26	-10.2 $\pm$ 3.1
J	<b>-778 <math>\pm</math> 40</b>	194 $\pm$ 30	-12.4 $\pm$ 3.3
K	<b>-629 <math>\pm</math> 115</b>	208 $\pm$ 32	-12.5 $\pm$ 3.3
L	-56 $\pm$ 64	209 $\pm$ 32	-12.3 $\pm$ 3.3
M	<b>-472 <math>\pm</math> 108</b>	209 $\pm$ 32	-12.1 $\pm$ 3.3

As seen in table 7 most COD have a heritability estimate significantly different from zero, derived from model 3, but they are relatively small. All COD with a heritability significantly different from zero also have genetic variance significantly different from zero. But genetic variance is also relatively small for all COD. For COD E, G and M not all effects could be estimated or were estimated at zero. Most COD do not have a maternal effect significantly different from zero, except for COD J, K and L, these are also relatively low.

Table 7: Heritabilities, maternal effects and genetic variances for model 3. All estimates are  $\pm$  the SE and estimates significantly different from zero are in bold.

COD	$h^2$	$m^2$	$\sigma^2_g$
A	<b>0.16 <math>\pm</math> 0.03</b>	0.02 $\pm$ 0.01	<b>0.023 <math>\pm</math> 0.005</b>
B	<b>0.16 <math>\pm</math> 0.03</b>	0.02 $\pm$ 0.01	<b>0.037 <math>\pm</math> 0.008</b>
C	<b>0.06 <math>\pm</math> 0.02</b>	0.001 $\pm$ 0.01	<b>0.004 <math>\pm</math> 0.002</b>
D	<b>0.1 <math>\pm</math> 0.03</b>	0.009 $\pm$ 0.01	<b>0.007 <math>\pm</math> 0.002</b>
E	0.00 $\pm$ 0.00	0.02 $\pm$ 0.01	0.00 $\pm$ 0.00

F	0.02 ± 0.02	0.02 ± 0.01	0.0002 ± 0.0002
G	<b>0.04 ± 0.02</b>	0.00 ± 0.00	<b>0.002 ± 0.0007</b>
I	<b>0.11 ± 0.03</b>	0.02 ± 0.01	<b>0.009 ± 0.002</b>
J	0.04 ± 0.02	<b>0.05 ± 0.01</b>	0.002 ± 0.002
K	0.05 ± 0.03	<b>0.08 ± 0.02</b>	0.0005 ± 0.0003
L	<b>0.1 ± 0.03</b>	<b>0.04 ± 0.02</b>	<b>0.003 ± 0.0009</b>
M	Not estimable	Not estimable	Not estimable

Table 8 shows the mean EBV for the different COD for the candidate population and the bottom 10% selected of this population based on their EBV for COD, top 10% for COD I. For all COD except I, the selection differential (S) gives the percentual decrease in disease occurrence of the offspring when this 10% is used for breeding compared to the average of the disease occurrence in the candidate population. This decrease ranges from 0% to -8.7%, for COD I this would be an increase in the occurrence of +2.7%.

Table 8: Mean EBV per COD for the candidate population, animals born between the start of 2015 and the end of 2019 who are assumed to be alive, and for the bottom/top 10% animals of this population, based on their EBV for COD. The selection differential (S) for every COD is also given.

COD	Mean EBV candidate population	Mean EBV bottom 10%	S (%)
A	0.026	-0.022	-4.7
B	-0.157	-0.243	-8.7
C	0.011	-0.005	-1.6
D	-0.014	-0.043	-2.9
E	0	0	0
F	-0.001	-0.0009	-0.1
G	0.003	-0.006	-0.8
J	0.006	-0.009	-1.4
K	-0.001	-0.006	-0.5
L	0.015	0.005	-1.4
M	0	0	0
<b>Mean EBV top 10%</b>			
I	0.038	0.066	2.7

Both the heritabilities of longevity and COD are higher in the results for model 4 compared to models 1, 2 and 3. By running models 1, 2 and 3 without the dam effect, it was shown this higher heritability in model 4 was most likely due to the exclusion of the dam effect.

Table 9 shows the estimated genetic and residual correlations between COD and longevity, along with the heritability of COD. Many COD do not have correlations significantly different from zero with longevity, but they do have a heritability significantly different from zero for both COD and longevity. COD I has a positive residual and genetic correlation and COD A has a rather small but significantly different from zero positive residual correlation. The other COD, when significantly different from zero, have negative correlations between COD and longevity.

Table 9: Results from the bivariate analysis of longevity and cod from model 4. Shown are the heritability of COD and the genetic and residual correlations between COD and longevity.  $h^2_{Longevity} = 0.33 \pm 0.025$  for all cod. All estimates are  $\pm$  the SE and estimates that significantly different from zero are in bold.

COD	$h^2_{COD}$	$r_e$	$r_g$
A	<b>0.17 ± 0.03</b>	<b>0.06 ± 0.02</b>	<b>-0.24 ± 0.09</b>
B	<b>0.2 ± 0.03</b>	0.01 ± 0.02	0.1 ± 0.09
C	<b>0.07 ± 0.02</b>	-0.01 ± 0.02	-0.25 ± 0.13



D	<b>0.1 ± 0.02</b>	-0.03 ± 0.02	-0.009 ± 0.11
E	0.007 ± 0.02	-0.01 ± 0.02	0.69 ± 0.8
F	<b>0.06 ± 0.02</b>	<b>-0.11 ± 0.02</b>	-0.3 ± 0.15
G	0.04 ± 0.02	<b>-0.09 ± 0.02</b>	-0.02 ± 0.17
I	<b>0.17 ± 0.02</b>	<b>0.34 ± 0.02</b>	<b>0.6 ± 0.07</b>
J	<b>0.08 ± 0.02</b>	<b>-0.24 ± 0.02</b>	<b>-0.3 ± 0.12</b>
K	<b>0.24 ± 0.03</b>	<b>-0.05 ± 0.02</b>	-0.17 ± 0.09
L	<b>0.13 ± 0.03</b>	-0.02 ± 0.02	0.02 ± 0.1
M	0.0003 ± 0.00	<b>-0.07 ± 0.02</b>	0.89 ± 1.75

Using the EBV for COD the correlated change in EBV for longevity can also be calculated. The change in EBV of longevity when selecting the bottom/top 10% based on EBV of COD can be seen in table 10. Where for all COD the mean EBV of longevity for the candidate population is +244. Correlated changes range from -121 to 111, indicating that selection against one specific COD can have a wide range of effects on longevity. When selecting the bottom 10% of animals based on EBV for COD G as parents, the offspring are expected to live 121 shorter than the average longevity of the candidate population. And when selecting the bottom 10% of animals based on EBV for COD D as parents, the offspring are expected to live 111 days longer compared to the average of the candidate population.

Table 10: Mean EBV of longevity when selecting the bottom/top 10% based on EBV of COD from the candidate population, all animals alive between the start of 2015 and the end of 2019. The mean EBV of longevity for the candidate population is +244, the selection differential (S) for every COD is also given.

COD	Mean EBV bottom 10%	S (days)
A	352	108
B	173	-71
C	241	-3
D	354	111
E	204	-40
F	231	-13
G	123	-121
J	212	-32
K	192	-52
L	185	-59
M	268	24
<b>Mean EBV top 10%</b>		
I	265	21

## 6.1 Discussion

This study found that longevity is a heritable trait (0.27) with a standard deviation of 482 days and there is a significant difference in longevity between some COD. When correcting for COD it was seen that most COD have a similar effect and only explain a small part of the genetic variance of longevity. Most COD had a heritability (0.06 - 0.16) and a standard deviation (0.05 - 0.19) significantly different from zero, although both were relatively low. The correlations found between longevity and COD were generally small (-0.05 to -0.3), except for COD I (0.34 and 0.6). For many COD, the correlation to longevity did not significantly differ from zero.

### Precision and interpretation of estimates

For both traits examined you know neither the longevity nor the COD of the breeding animals, as the animals are still alive and you would not breed animals you know are sick. Therefore, the breeding

values are based on pedigree data, which means siblings would have the same EBV which could increase sib-selection and this could cause problems with increased inbreeding. But considering the number of offspring per sire or dam is generally low for this dataset, the number of siblings would also be low. So, this is not expected to cause a large effect.

Collecting accurate data is difficult for both longevity and COD, as this is dependent on the willingness of other people to share and be correct in sharing information. For longevity, you are dependent on people accurately passing on the birthdate and death date of their dogs. Even if people give slightly inaccurate dates, they are unlikely to make their dogs years older or younger so it should be close to the real date. But for COD, data collection is more difficult, as the cause of death needs to be established first. There is not always one clear cause of death either and then the primary cause of death needs to be established. Owners themselves might not always be clear on the cause of death for their dog and might unintentionally pass on wrong information. Using data from veterinarians would give more clearly determined causes of death. But this would also be more difficult to gather since it would need both owner and veterinarian permission. It also requires owners to either allow veterinarians to perform an autopsy after death or for the animal to have died while in veterinary care. This would exclude information from dogs whose owners do not wish to have an autopsy performed or dogs that died at home and cause a reduction in the amount of data gathered.

The IWDB gathered longevity information on 11558 dogs in total and COD information on 6839 dogs in total. The dataset used for modelling includes the information on the longevity of 10122 animals and COD information of 6057 animals. Even with the difficulty in gathering information on these traits, the IWDB managed to gather a large amount of data and with the increase in the amount of data gathered, the accuracy of the trait estimates also increases. Also, data was gathered on many other traits, like the date of birth, date of death, sex, sire, dam and many others which made it possible to set up the models used. With the large amount of data, the estimates made for longevity and COD are generally reliable.

#### Potential of breeding and inbreeding

When looking at the heritability (0.27) and genetic standard deviation (482) of longevity, selection for increased longevity would be possible for this population. As most COD are also heritable (0.04 - 0.16) and with standard deviations ranging from 0.05 - 0.19, although both are lower in magnitude than for longevity, selection against disease would also be possible. Selection for longevity would be easier if an indicator trait that can be measured early in life was known. Now longevity is only known after the death of the animal and selection would be based on EBV from the pedigree. Every COD has been shown as a bad indicator trait for longevity when considering the low correlations between these traits, also because COD cannot be measured earlier in life than longevity.

It was shown that when selecting the top 10% on EBV for longevity, their offspring would have an expected increase in longevity, compared to the average of the candidate population, of +252 days. When looking at the correlated response in longevity when selecting the bottom 10% based on EBV for COD, the effect ranges between -121 days and +111 days compared to the average of the candidate population, the response when selecting the top 10% for COD falls within this range. This shows that selection against a specific COD can have a wide range of effects on longevity. And that direct selection on increased longevity has a larger effect than indirect selection on decreased disease occurrence. As it seems that selection against only one specific COD has, on average, a small effect on disease occurrence, decreasing a specific COD with -0% to -8.7%. You would generally like to select against multiple COD at the same time. However calculating selection response for selection against multiple COD requires the genetic correlations between all COD, which cannot be estimated with this dataset. When considering the negative genetic correlations between COD and longevity. It was expected that when selecting animals with the lowest EBV for COD, longevity would show an increase, however for many COD a decrease in longevity is shown. This negative response could be

explained by the effect of the genetic correlations between COD along with the inaccuracy in estimating the EBV. This inaccuracy has to do with the assumption that the EBV estimates the true breeding value without error, which might not be correct. This accuracy influences the selection response, with a lower accuracy in estimating the EBV the selection response would also decrease. Because a lower accuracy would decrease the correlation between the EBV and the true breeding value. In all these calculations the estimate is a specific estimate of response for the animals available for selection, the true response to selection would likely be lower. The possible inaccuracy in estimating the EBV is one of the reasons for this difference. Another reason is that these calculations do not include the effect of inbreeding on longevity and almost equal contributions between males and females are assumed, normally a fewer number of males are used to contribute most of the genes to the next generation. The inbreeding effect would be relatively small compared to the estimated response. To account for unequal contributions males can be more intensively selected, by selecting EBV for males and females separately instead of grouped as was done here. Lastly, for the specific response estimate, selection was only done on one trait, longevity or COD. Normally selection is done on many traits, for example selecting against multiple COD, for increased longevity and to maintain the breed standard at the same time. This is done to achieve a balanced response, but by selecting on more traits the response per trait lowers. These calculations show that selection for longevity or against COD can affect longevity and disease occurrence. It also shows that if selection is applied, both traits should be included in the breeding goal as there is a correlated effect.

The effect of inbreeding on the selection response for longevity could be calculated by looking at the difference in mean kinship between the candidate and selection populations. When considering that inbreeding negatively affects longevity, with a 1% increase in inbreeding causing a decrease in longevity of 9.6 days. As it was expected to have a relatively small effect compared to the estimated response, the inbreeding effect was not included in the response calculations. The decrease of 9.6 days with an increase in inbreeding of 1% is the linear effect of inbreeding as defined by model 1, this would not be the true effect, it is shown to exemplify the magnitude of the effect. So, considering the negative effect inbreeding has on longevity, selecting should not be for increased longevity alone. Controlling the inbreeding level should also be included when selecting for longevity. A possibility for this is to constrain the mean kinship in the population (Malm et al, 2013). The kinship between parents is equal to the inbreeding coefficient of the offspring. Kinship can be calculated from the pedigree and then be considered when making breeding decisions. This is a form of optimal contribution selection (OCS), computing the optimal genetic contribution of each selection candidate to the next generation (Meuwissen, 1997). In this case, it would be aimed towards increasing longevity while constraining mean kinship in the breed. But many dog breeds have low genetic diversity, partly due to historical bottlenecks which have also occurred in the Irish wolfhound breed (Flatberg, IWDB). If the genetic diversity in the breed is too low to avoid the negative consequences of inbreeding by only constraining mean kinship in the breed, outcrossing could be considered. Especially if the breed has a small effective population size since this would increase inbreeding. Outcrossing has a short-term effect unless it is continuously performed. It can be used as a method to buy time to change the population structure and increase the effective population size. Continuous outcrossing is rare in dog breeds, it is usually followed by backcrossing to preserve the breed characteristics, even if this lowers the effect of outcrossing (Windig & Doekes, 2018). Further, it was seen that when correcting for COD in the model the inbreeding effect decreases further, except for COD I. But when considering the SE for these responses the effects are not significantly different from what was seen in model 1.

### Correlations between COD and longevity

It was shown that all diseases influence longevity, from the COD estimates of model 2, but not all these effects are significantly different from zero. Both the genetic and environmental correlations between longevity and COD are generally low and almost all COD, except COD I and J, explain only a small part of the genetic variance of longevity. This indicates that COD and longevity are mostly

independent traits, both genetically and environmentally. This means genetic and environmental associations between COD and longevity cannot be estimated with high reliability.

The low correlations observed could be due to multiple reasons. If one COD has a large impact on the longevity of the animals affected, but this COD is very rare, then this would not give a large impact on the mean longevity. Another reason could be the heterogynous COD categories. In combination with the low accuracy of collecting data for this trait, this would also explain the relatively low heritabilities found for COD. The heterogeneity of COD categories could be caused by the fact that 133 different causes of death were compressed into 13 COD and this might cause variations within one group. The 133 different causes of death were compressed into 13 COD because only 9.8% of 133 causes of death had more than 100 records included. Most of the causes of death would have a too low number of records to infer any significant connections. The effect of the heterogeneity of a COD category can be exemplified by looking at COD B (cancer). This group includes many different types of cancer and most of them have a genetic background and a heritable component. It has been shown that although some cancer types are genetically correlated to each other, others are not or with low correlations (Lindström et al, 2017). So even if some cancer types have a significant correlation to longevity, the correlations between cancer types within the group can make this overall correlation of COD B to longevity insignificant. As mentioned before many cancer types do have a genetic background and a heritable component. This was also shown here, as COD B still had a heritability that was significantly different from zero. A more in-depth study with a more defined COD should be undertaken for further explanations of correlations between COD and longevity.

#### COD A

COD A (heart disease) has genetic and residual correlations between COD and longevity which are significantly different from zero and a COD effect not significantly different from zero. It has the combination of a positive residual and a negative genetic correlation. This seems counterintuitive, but both correlations can be explained. The genetic correlation can be explained by the simple fact that heart disease is a heritable trait. There is a genetic basis for the occurrence of heart disease and it is a polygenic trait. Longevity is also known to be a highly polygenic trait (Donlon et al, 2018; Vijg & Suh, 2005). With many genes involved in both traits it is more likely they share at least partially the same genetic architecture. Added to this is the fact that disease is a known risk factor for longevity, which makes it more likely for them to be genetically correlated. So, when you consider the genetic correlation found, suffering from this disease will decrease your longevity. Exemplified by one of the heart diseases which has a genetic background and which frequently occurs in Irish wolfhounds, dilated cardiomyopathy, as this disease is known to cause death at a young age (Vollmar et al). But when looking at the COD effect values the negative effect on longevity is not significantly different from zero. This might be explained by the positive residual correlation, as this indicates that if an animal does not suffer from heart disease due to genetic causes, they will live longer than average. This could be because aging is a convergence of processes that makes the heart more susceptible to heart failure. Aging also causes an overall decrease in exercise tolerance (Strait and Lakatta, 2012; Guglielmini, 2003). So, if an animal dies from a heart attack due to strenuous exercise, this is more likely to happen when they are older than when they are younger. So, the genetic correlation indicates that if you die from genetic heart disease you are more likely to die at a younger age. While the residual correlation indicates that if you die from a non-genetic heart disease you are unlikely to die earlier than average. Given the two opposite correlations found, heart disease seems to have two almost independent sources of variation. Since both types of heart disease are included in COD A, the overall COD effect on longevity is not significantly different from zero.

#### Genetic background for dilated cardiomyopathy

Dilated cardiomyopathy (DCM) is one of the most frequent heart diseases found in Irish wolfhounds (IW). Other studies have researched the genetic background of this disease in IW and specific loci and genes associated with dilated cardiomyopathy have been found. On chromosomes 1, 21 and 37 three

loci were found to be significantly associated with DCM in IW (Simpson et al, 2016; Philipp et al, 2021). Loci on chromosomes 10, 15 and 17 were moderately associated with DCM in IW. With these last three SNPs respectively found to be associated with the genes *ARGHAP8* (part of RhoA activating protein family, regulate many aspects of intracellular actin dynamics), *FSTL5* (a prognostic marker for medulla-blastoma) and *HMGCS2* (encodes a mitochondrial enzyme) (Philipp et al, 2012). The SNP on Chr 21 had a DCM-associated SNP in the intergenic region of *PDE3B*, which has been shown to have a role in cardiac function (Simpson et al, 2016). Also, the RNA expression of *PDE3B* is different between males and females, this has been proven in rats (Wang et al, 2012). This might be an explanation for the different ages of onset between sexes (Simpson et al, 2016). Of the other two SNPs with strong DCM association, the one on Chr 37 is associated with the genes *MOGAT1* and *ADSL3*, two enzymes associated with lipid synthesis. The SNP on Chr 1 is nearest to gene *TSHZ3*, which is a zinc finger transcription factor (Philipp et al, 2012).

For the SNPs identified on loci 1, 21 and 37 none of the genotypes in themselves or in pairs caused an increased or decreased risk compared to the overall population risk of disease. But an individual with the riskiest genotype at all three loci had a significantly increased risk compared to the overall population risk. Similarly, combining the lowest disease risk genotypes was thought to possibly give a protective effect. But this combination did not show a significant decreased risk compared to the overall population risk. This does not discount the idea that there might be genes with a protective effect against DCM, just that they have not been identified yet (Simpson et al, 2016).

### COD I

COD I (old age/weak rear) is the only COD with positive genetic and residual correlations and is the COD with the strongest correlations to longevity. COD I also showed a large positive COD effect on longevity, 1048 days. This connection was expected as this is the only COD compared to the others where animals are not expected to die sooner than average. A weak rear is a disease commonly occurring in older dogs. There can be many underlying causes for a weak rear but these animals are often euthanized because of the discomfort caused by this disorder when they are older (Mercer, M. 2017; IWCAa).

### Other COD

All other COD have, when significantly different from zero, negative residual and/or genetic correlations to longevity. These same COD also have negative COD effects significantly different from zero, calculated from model 2. This indicates that suffering from these diseases would decrease longevity, as was expected. This includes, among others, COD G (infections) which has a low residual correlation and COD J (Accident/Injury/Poison/Surgery complications) which has the highest negative residual and genetic correlations. COD J does not have a significant heritability but does have a significant maternal effect according to model 3. Accidents are known as one of the most common causes of death among young dogs (O'neill et al, 2013). COD F (liver disease), COD K (epilepsy) and COD M (autoimmune and bleeder disease) showed correlations significantly different from zero. However, the estimates for these COD are very low and when considering their SE the estimates are not very different from zero. All estimates and SE are calculated based on the assumption that COD is a normally distributed trait, as was assumed for all traits in this study. COD is actually a binomially distributed trait and, in general, a binomial distribution can be approximated with a normal distribution when the sample size is large enough (Kwak & Kim, 2017). For most COD, this approximation would be reasonable, but with the small sample size of COD F, K and M their binomial distribution is unlikely to be approximated by a normal distribution, which would mean the estimated correlations for these COD might be unreliable. To ensure more reliable estimates a larger sample size would be needed.

### Possible implementations

To gather information on indicators of age and disease over the lifetime of the animals could be interesting, to increase background knowledge on the animals. For this, the implementation of a yearly or bi-yearly health check of all known Irish Wolfhounds could be used. Also, when considering the health screening test results which are now collected, this health check might be more all-encompassing as the health screenings are not performed for all dogs and only for specific aspects. Owners might be willing to respond to a short (online) questionnaire on the health aspects of their dog, like mobility and appetite. It would provide additional information when a dog dies with or without a specific COD known. When including a possibility for owners to pose questions, this could increase response and help owners manage the health of their dogs.

Genomic selection could also be implemented, not only would it increase the accuracy of longevity and COD before selection, but you could specifically select against known disease-causing genes. For example, for DCM the combination of three genes is known to increase disease risk compared to the overall population risk. By using genomic selection, you could prevent the mating of animals that could result in this combination genotype. As the increased risk requires the riskiest genotype at all loci, it does not require exclusion of (many) animals from the breeding population. It does require genotypes of all animals to be known. It is important to be careful in managing a breeding program when selecting for specific genetic conditions, to prevent other genetic diseases from emerging or increasing in frequency. Except for being able to help decide on which animals to mate, knowing the genotypes is also useful for helping animals who might suffer from DCM. Animals that are known to have the riskiest genotype for DCM can be more intensively monitored for signs pointing to the development of the disease. For heart disease certain drugs are known to increase the time to when the disease causes significant welfare issues, possibly increasing both welfare and longevity for these animals (Simpson et al, 2016). In general, having genotype information on many animals can increase knowledge on the genetic background of longevity and diseases specifically for the Irish wolfhound. Which would increase the possibilities for selection against disease-causing genes and/or for protective genes. But genomic selecting requires centralized data collection on genotypes and a breeding program that includes all/most of the animals. In dog breeding, this is difficult as breeding decisions are mostly made by individual breeders, not by an overarching organization. But if breed clubs can show that collecting genotypes and making breeding decisions based on this data has a positive effect on the breed, implementation is possible. Unfortunately, genomic selection is a relatively expensive implementation as many animals need to be genotyped, therefore it is not usually used in dog breeds. But if a dog is known not to carry specific diseases and is likely to live a longer life this dog might be worth more than a dog for which this is unknown, both to prospective owners and for using this dog as a breeding animal.

Another possibility is implementing optimal contribution selection (OCS). This is a selection method that can effectively balance rate of inbreeding and genetic gain, by maximizing the genetic gain for the next generation and constraining the rate of inbreeding by restricting the mean kinship to the breed. By using OCS the optimal genetic contributions to the next generation of all selection candidates can be computed. Implementing OCS in and of itself is not difficult, as for this breed there is an extensive pedigree available for kinship calculations. But, finding the animals which are seen as 'best' under OCS is not the same as breeding them according to this. The same problem applies here as for applying genomic selection, dog breeding is often done by individual breeders who would be unlikely to take OCS into account by themselves. The breed club could use the OCS results for guidance, possibly by establishing a maximum number of litters per sire or dam. Implementing OCS might be easier than genomic selection as it does not require the collection of genotype data, only the data that is already being collected. OCS on longevity and against disease might also give a higher response in the short term as the genetic background of longevity and many diseases is still unknown. But genomic selection is more accurate and changes would be permanent and accumulating over generations.

A possibility to increase longevity and decrease disease occurrence without needing to increase accuracy on these traits would be to breed for a less extreme phenotype. Breeding for smaller-sized dogs, as there is a proven negative correlation between size and age, size and heart problems and size and joint problems in dogs (Kraus et al, 2013; Goddard, 2005). Specifically, it has been shown that for the average lifespan of over 90 breeds, body mass and lifespan are negatively correlated and that when considering the size of Irish wolfhounds, they live shorter than would be expected according to this correlation (Fan et al, 2016). So, the same increase in weight seems to cause a larger effect on longevity in Irish wolfhounds than it does in other large-sized breeds. Breeding for smaller-sized dogs would require an estimate of the genetic correlation between size and lifespan. Then both size and lifespan could be included in the breeding goal. This would ensure you will not select dogs of too large size with a shorter lifespan, nor too small dogs with a longer lifespan. This would ensure the breed standard can be followed, as the size of the Irish Wolfhound is one of its most imposing qualities and an important breed standard, while still making it possible to breed for longer-lived dogs.

#### Further study

As neutering/castration has been suggested as a variable that influences both longevity and certain causes of death (Corp-Minamiji, 2013). Collecting information on the neuter state of the animals might provide additional information in further studies about longevity and COD.

An interesting follow-up study would be looking into other traits that might be used as indicator traits for longevity. Using one COD at a time, all of them are shown to be bad indicator traits. Preferably, it would be a trait that can be measured early in life and with a high correlation to longevity. This would give a more accurate EBV for longevity while the animal is still alive. As it is thought that the rapid growth of large-sized breeds might be the reason these breeds have a shorter lifespan than smaller dogs (Urfer et al, 2007) and it is known that body mass is correlated to longevity (Fan et al, 2016). Growth rate, weight or weight gain might be interesting traits to consider as possible indicator traits for longevity.

### 7.1 Conclusion

Both longevity and COD are heritable traits, 0.27 and 0.06 – 0.016 respectively, with genetic standard deviations of 482 days and 0.05 – 0.19, selection for or against these traits is possible. Considering the large standard deviation for longevity, there is potential for significant improvement in longevity by breeding. Similarly, the two most common causes of death, heart disease and cancer, also have genetic standard deviations that indicate a potential for decreasing the occurrence of these diseases by breeding. Most COD influence longevity (-1063 – 1048 days) but correcting for COD generally only explains a small part of the genetic variance of longevity. Longevity and COD generally have low genetic and residual correlations between them, indicating that they are almost independent traits, thereby separately selecting for longevity and against diseases should be possible. But due to low trait accuracy and heterogynous distribution of COD, these correlations might not be completely accurate. Different possibilities have been suggested to either increase accuracy or apply selection differently. Implementing a health check, genomic selection, optimal contribution selection and selecting for less extreme phenotypes.

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