Breed Predispositions to Disease in Dogs and Cats

Third Edition

Alex Gough • Alison Thomas • Dan O'Neill

WILEY Blackwell

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Alex Gough
Bath Veterinary Referrals, Bath, UK

Alison Thomas
Blue Cross Animal Hospital Victoria, London, UK

Dan O'Neill
Royal Veterinary College, London, UK

WILEY Blackwell

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Alex Gough

To loved ones, friends and colleagues, and of course to my wife Naomi and daughter Abigail for bearing with me through another huge project.

Alison Thomas

To all the wonderful colleagues I have had the pleasure of working with over the years. Most of all to my partner Richard, and children Tom and Harry, for making my life so much fun.

Dan O'Neill

To my wife, best friend and inspiration, Joanne. And to my three children and lights of my life, Alistair, Megan and Clodagh. Thank you each for being you.

This book is also dedicated to all those vets suffering from mental illness, and particularly to those who have lost their lives due to this common condition affecting our profession.

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Author Biographies

Alex Gough MA VetMB CertSAM CertVC PGCert MRCVS
Head of Medicine Referrals, Bath Veterinary Referrals
Alex graduated from Cambridge University Vet School in 1996 and achieved RCVS certificates in Small Animal Medicine and Veterinary Cardiology, as well as a human Postgraduate Certificate in Neuroimaging for Research from Edinburgh University. He worked in mixed, mainly small animal practice for six years, then in referral practice, seeing referrals in medicine, cardiology and neurology, with a particular interest in medical neurology. He is the author of *Differential Diagnosis in Small Animal Medicine* (2007), has written a column summarizing the latest research for the *Veterinary Times* since 2003 as well as chapters on neurology and clinical genetics in two BSAVA manuals, and sits on the advisory clinical board of a large veterinary group. In his spare time, he writes historical fiction novels and plays guitar.

Alison Thomas BVSc, Cert SAM, MRCVS
Senior Veterinary Surgeon, Victoria Hospital, Blue Cross
Clinical Leadership Team, Blue Cross
Alison graduated from Liverpool University in 1987 and has spent most of her career working in charity small animal practice. After two years in private practice in Aylesbury, she moved to Asia, spending two years in private practice in Singapore, followed by seven years at the SPCA in Hong Kong. Since 1998 she has worked at Blue Cross in Victoria, London, becoming Senior Veterinary Surgeon in 2007 and joining the newly formed Clinical Leadership Team of Blue Cross in 2016. She gained the RCVS Certificate in Small Animal Medicine in 2001, and was awarded Advanced Practitioner Status in Small Animal Medicine in 2017. In her spare time she enjoys hiking, travelling and reading.

Dan O'Neill MVB BSc(hons) GPCert(SAP) GPCert(FelP) GPCert(Derm) GPCert(B&PS) MSc(VetEpi) PhD MRCVS
Senior Lecturer, Companion Animal Epidemiology, Royal Veterinary College
After graduating from Dublin Vet School in 1987, Dan worked in industry and general practice for 22 years, latterly running his own companion animal practice in Petts Wood, Kent, for 12 years. During these years, he was awarded additional qualifications in pharmacology, general practice, dermatology, feline practice and business management. In 2009 he undertook an MSc supported by BBSRC and then a PhD supported by the RSPCA in veterinary epidemiology at the RVC to develop the VetCompass programme of primary-care veterinary clinical research. After postdoctoral posts supported by Dogs Trust and Kennel Club Charitable Trust, Dan was appointed as Senior Lecturer in Companion Animal Epidemiology at the RVC in 2017. As well as teaching and publishing, Dan focuses on expanding VetCompass internationally, with particular emphasis on breed-related health. In his spare time, he is a keen ITF taekwondo enthusiast and currently holds a 2nd Dan black belt.

Foreword

For anyone interested in the health and welfare of dogs and cats, there are few topics that engender such emotional energy, diverse opinion and heated debate as the potential negative impacts of selective breeding on canine and feline disease occurrence, and the optimal ways to manage and/or eliminate such impacts. But energy, opinion and debate can only bring true positive change when they are based on good evidence. In this respect, the third edition of *Breed Predispositions to Disease in Dogs and Cats* is hugely timely. The book comes not only at a time of increasing awareness of the impacts that breed characteristics may have on health, but also when there is growing appreciation of the glaring underuse of objective data to support traditional perceptions and opinions which have become accepted as 'fact' in breeding folklore and veterinary science. This book aims to remove the roles of speculation, opinion and anecdote from the discussion on breed health issues and instead to refocus and underpin these discussions based on solid evidence-based principles.

There is no doubt that the Bateson Report on pedigree dog health and its far-reaching recommendations (Bateson, 2010), the creation of the Royal College of Veterinary Surgeons' RCVS Knowledge initiative to promote the generation and application of veterinary clinical evidence (RCVS Knowledge, 2017) and a general increase in commitment to evidence based veterinary medicine over the past decade have resulted in a greater appreciation of the need for reliable evidence on the health impacts of breed characteristics in dogs and cats. Fortunately, this awareness of the need for valid evidence has coincided with the development of exciting new tools which allow us to collect and interpret large volumes of relevant data from primary and referral veterinary practices and to analyse these in robust and less biased ways. As a result, for the first time, we are increasingly able to provide some reliable real-world context to the likely impact of breed characteristics on animal health and welfare. The development and international adoption of standardized systems of nomenclature such as the VeNom initiative (VeNom Coding Group, 2017) and ground-breaking research tools such as the Royal Veterinary College's VetCompass Programme (VetCompass, 2017) allow researchers to explore vast amounts of clinical data from first-opinion and referral veterinary practices. These developments have transformed how we can investigate companion animal diseases and their impact on animals, their owners and their breeders. The era of 'Big Data' for companion animals and its impact on animal health and welfare is now truly upon us.

Realization of the powers from developments such as these means that this new edition of Breed Predispositions to Disease in Dogs and Cats really does herald a new and more valid perspective in our understanding of the types of disorders and their likely impact on different dog and cat breeds. The new edition has been completely rewritten using 'evidence-based veterinary medicine' criteria that are applied to international data and consequently provides an accurate reference resource on disease predispositions that is relevant to breeds from all corners of the world. The information is comprehensive and detailed but presented in a readily understandable and searchable format. Prevalence, odds and risk ratio values, as well as study design details, are provided so that the more motivated reader can go beyond an awareness that a predisposition has been reported and start to examine the context and strength of the reported associations. This book truly is a cornucopia of breed health information.

This third edition will become an invaluable and constant resource for students, vets, breeders, owners, scientists and indeed anyone interested in companion animal welfare. We are privileged to live at a pivotal tipping point in the generation and application of evidence for better decision-making in companion animal health. This book will play a key role in centralizing our current knowledge into a single resource, and is thereby a torch-bearer that will finally enable us to move beyond endless circular discussion to positive action that will benefit the welfare of our cats and dogs.

Professor David Church BVSc PhD MACVSc FHEA MRCVS
Deputy Principal
and Professor of Small Animal Studies,
The Royal Veterinary College

Preface

It is widely accepted that almost all dog and cat breeds have specific diseases to which they are particularly prone (i.e. predisposed). Indeed, many textbooks and published research papers include lists of breed predispositions as a standard feature when describing specific disease conditions. To extend this focus, the first edition of *Breed Predispositions to Disease in Dogs and Cats*, published in 2004, aimed to provide a single reference resource for breed predispositions that would better illuminate our understanding of breed health (Gough & Thomas, 2004). The concept for the first edition was born during discussions between the two original authors (Alex Gough and Alison Thomas) while preparing for their RCVS Certificate in Small Animal Medicine exams in 2001. This book was the first of its kind to focus purely on breed-specific predispositions and was widely welcomed by academics, veterinarians, breeders and owners. That original edition was compiled mainly from secondary sources of evidence such as textbooks, reviews and conference proceedings and did not provide detailed reference citations for all the breed–disease combinations reported. The second edition, published in 2010, redressed many of these shortcomings and was updated with more recent publications while also ensuring that every cited disease had at least one supporting reference. However, much of the disease information still came from secondary sources such as textbooks, review articles and conference proceedings. The implication of this was that the second edition was substantially reliant on expert opinion. At that time, almost a decade ago, this approach may have been acceptable, but as we progress into the modern age of evidence-based veterinary medicine (EBVM), expert opinion is now generally considered to be weak evidence, and reliance should instead be placed on the results of original research (Holmes & Ramey, 2007).

In consequence, preparations began for a third edition that would have a strong emphasis on improved academic rigour, better compliance with the modern principles of EBVM and a sound epidemiological infrastructure. To meet these lofty aspirations, Alex and Alison enlisted Dr Dan O'Neill to join as a third co-author, to ensure high epidemiological standards and also to reduce the individual workload for each author. Dan is an epidemiologist working on the VetCompass Programme at the Royal Veterinary College (VetCompass, 2017), but with that rare academic attribute of essentially still being a general veterinary practitioner. We are confident that this third edition has achieved our academic goals – but we must also sadly report that we failed in our aspiration to reduce the workload. Indeed, it was quite the reverse, as the new perspectives introduced by Dan entailed a complete rewrite. Ah well, you can't win them all – but we do hope that you enjoy the end result of our combined labours.

For this new edition, we have consulted and referenced primary sources of evidence almost exclusively (i.e. the original published papers that reported the primary research) and have restricted inclusion to just those diseases where primary research identified sufficient evidence for the existence of a breed predisposition. As might be expected, this new approach led to some challenges and several discussions between the authors on the optimal threshold of evidence for disease inclusion. During our rewrite, we became painfully aware of just how little evidence actually exists for much of what we may 'believe' to be true about companion animal health. When we examined the literature closely, many of the predispositions commonly reported as 'knowns' in textbooks and introductions to peer-reviewed publications had very little, if any, reliable supporting evidence. This realization reinforced our determination that the new edition should follow rigorous evidence-based principles, but it also meant that the new book would entail a total rewrite, with substantial work required to freshly identify those diseases with and without a solid evidence base. We found ourselves painfully deleting many conditions that had been included in the previous book based on expert opinion but which lacked adequate evidence. 'Believing in a predisposition' and 'having evidence for a predisposition' are not always the same thing. The positive side of our new EBVM approach, however, was a refreshing discovery that our new detailed trawl of the primary literature led us to identify many new breed–disease combinations that had not made it into the previous two editions. This may have been because the predisposition was first reported after the second edition was published or because our previous reliance on expert opinion had failed to uncover the association.

Our new search methods and inclusion criteria are described more fully in the *Methods* section. We hope that these changes support a more robust and defensible evidential and scientific body of information in this third edition, which also includes additional supporting information for breed predispositions where possible. Such additional information may describe the population studied in the original papers – such as geographical location, referral or general practice population (many academic papers are based on referral populations, and their results do not necessarily generalize well to the populations of patients commonly seen in general practice) – while the date of the referenced papers may assist with a perspective on the temporal relevance of the results. Information is also provided on the comparator populations used in the studies (e.g. crossbreds or all study dogs) and the numerical results, which show the strength of the reported predisposition (e.g. odds ratio or prevalence). Taken together, these new segments of information should help the reader to piece together the likelihood of the reported predispositions being real and relevant in relation to his or her own personal animals and interests. In the first and second editions, the research was divided between the authors by body system. For this third edition, we have instead divided the research alphabetically by breed. Consequently, some differences in writing style and emphasis may be apparent between the authors' sections. However, by sticking to pre-agreed methods, we hope to have maintained a satisfactory level of consistency across the work. We have also updated the genetics section as well as adding new explanatory sections on methods, longevity and epidemiology. We hope that these will give the interested reader some useful background on these topics as well as suggestions on where to find further information as required.

Companion animals are often bred according to the whims and needs of mankind rather than following the harsh survival rules of natural selection, and therefore breed-related disease has become an important anthropogenic welfare issue. In consequence, it behoves everyone with an interest in companion animals to strive to reduce these animal welfare costs. A critical first step in this process is the need to define which breed–disease combinations (i.e. predispositions) have strong supporting evidence. We hope that the third edition of our book meets this need and provides a solid evidence base from which other companion animal stakeholders can develop effective strategies to improve animal welfare. Breeders and breeding organizations can use this book to identify priorities when considering the genetic health of their breeds. The show community, both those showing and those judging, may use this book to refine their opinions on optimal conformations and temperaments within individual breeds. The strong evidence-based approach of the book can help veterinary students and veterinarians with diagnosis and when advising prospective and current owners on breed-specific disease proclivities. Owners may find the book useful when deciding on breed selection or considering on how best to care for their current or prospective dog or cat. Ultimately, this book aims to enhance the welfare of current and future generations of cats and dogs by increasing our awareness of those diseases which commonly affect individual breeds and which may therefore be prevented or diagnosed earlier. Good evidence on breed predispositions empowers us all to combat disease occurrence and should lead to improvements in the lives of our dogs and cats.

We have thoroughly enjoyed writing this book: it became a labour of love for the three of us and consumed our lives for over a year, but we are very proud of the final product. There will obviously be some parts that we will re-read later and decide we could have done better, and we welcome the reader letting us know about these. There will also be some opportunities that were missed in this edition, and we will be glad to receive suggestions. However, we hope you will forgive these shortcomings for now and simply accept this third edition for what it is: an evidence-based blueprint for the current state of knowledge on breed predispositions to disease in dogs and cats. We hope you enjoy reading this book.

Alex Gough, Alison Thomas and Dan O'Neill

Abbreviations

95% CI	95% confidence interval
AKC	American Kennel Club
ANA	antinuclear antibodies
aPTT	activated partial thromboplastin time
AV	atrioventricular
CI	confidence interval
CYAR	cat years at risk
DYAR	dog years at risk
E. coli	*Escherichia coli*
EBVM	evidence-based veterinary medicine
ECG	electrocardiography
GSD	German Shepherd Dog
Ig	immunoglobulin, including isotypes IgA, IgG and IgM
IR	incidence rate
IRR	incidence rate ratio
KC	Kennel Club
MHC	major histocompatibility complex
MRI	magnetic resonance imaging
OR	odds ratio
PCR	polymerase chain reaction
PR	prevalence ratio
PT	prothrombin time
RR	relative risk, *or* risk ratio
SBT	Staffordshire Bull Terrier
T_4	thyroxine
TRH	thyrotropin-releasing hormone
TSH	thyroid-stimulating hormone
VMDB	Veterinary Medical Database
WHWT	West Highland White Terrier

Introduction

BASIC AND CLINICAL GENETICS

Inherited diseases and breed predisposition

It has long been recognized that many traits, desirable and undesirable, can be passed along family lines. Darwin noted in 1868 that there is a 'unanimity of … belief by veterinaries of all nations in the transmission of various morbid tendencies'. Inherited diseases in dogs and cats can be categorized as those associated with adherence to breed standards and those unrelated to breed standards. The brachycephalic head shape is particularly associated with a number of diseases such as brachycephalic obstructive airway syndrome, dystocia and corneal ulceration (Packer *et al.*, 2015; O'Neill *et al.*, 2017b, 2017c). Diseases not directly related to breed standards include many intraocular diseases, haematological and immune-mediated diseases, and endocrine diseases (although the creation of small gene pools for a breed because of adherence to breed standards may have contributed to the prevalence of these diseases). For ease of use, the accounts in this book have been arranged by body system rather than in relation to breed standards.

It should be noted that while most conditions with breed predispositions are likely to be truly hereditary, this is not always the case. (Note that in our text, we use *hereditary*, *genetic* and *inherited* as synonyms.) Some conditions may arise because of the use to which the animal is commonly put, such as racing injuries in greyhounds, or to their behaviour, such as the searching behaviour of spaniels making them prone to grass awn (grass seed) foreign bodies. Nevertheless, even diseases such as these will have a genetic component, for example in influencing the behaviour of the spaniel, or giving the greyhound the athletic ability that means it is used for racing, and therefore can still be considered to have some inheritabilty.

Domestication and the canine and feline genome

Dogs are thought to be descended from a common ancestor with wolves, with estimates for the timing of the divergence ranging from 15 000 to 100 000 years ago. Domestication may have occurred more than once, and there may have

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been further interbreeding with wolves subsequently. At least two bottlenecks have occurred in canine genetic history, one when they diverged from wolves, and another more recently when modern dog breeds were created. Nevertheless, the dog has an enormous variation in phenotype, as shown by characteristics such as size, colour, coat type and behaviour.

It has been shown that there is more variation in functional genes in domestic dogs than in wolves (Cruz *et al.*, 2008), and alterations in functional genes are often deleterious to welfare. Population bottlenecks and selective breeding may have exacerbated this, and natural selection against these deleterious conditions is less likely in domestic animals than in their wild counterparts. Domestic dogs may therefore be more prone to inherited diseases than wolves.

Dogs were originally bred to fulfil many different purposes, such as hunting, fighting, guarding, herding and companionship. Sighthound type hunting dogs have been noted in archaeological records dating back 4000 years, and in Ancient Roman times, Columella described the division of dog breeds into working and hunting types. However, most modern dog breeds originate in the last 150 years, with the development of dog breeding as a hobby of the middle- and upper-class Victorian.

In a study (Parker *et al.*, 2007) that examined the DNA of a large number of dogs representing 161 breeds, the authors were able to divide the breeds into 'clades', that is, breeds with common ancestors. This paper shows how complex the genetic history of the dog is, but certain interesting points stand out. One is that single mutations can cause recognizable changes across multiple breeds within a clade. This has the consequence that dogs in a single clade may be prone to similar inherited diseases. Since most dog breeds are young in evolutionary terms, there has been little time for new mutations to occur, and so most disease-causing genetic mutations are thought to have occurred before the breeds were founded. It is also notable that related breeds came out of certain times and geographical locations. For example, dog fighting was popular in Ireland in the 1800s, and many mastiffs and bull terrier crosses from this location and period later developed into recognized breeds. The introduction of dogs into North America by European settlers and later Asian migrations largely replaced the indigenous domesticated canine population which had been introduced by the first American settlers over 10 000 years previously. However, this study showed that breeds related to animals brought by European settlers likely had some interbreeding with the more ancient American breeds, and so American breeds of European origin retain some of the genetic material of the previous indigenous breeds.

Phenotypic variation (e.g. conformation and behaviour) is much smaller in cats than in dogs. Cats are thought to have been domesticated later than dogs, but are probably of less direct use to humans as working animals than dogs, since they are harder to train. Deliberate breeding was therefore more limited, and domesticated cats show as much genetic diversity as the wildcat.

The canine and feline genomes have both been sequenced, and the body of research into the genome and into genetic diseases in these species is rapidly growing.

Basic genetics

All mammalian life is based on the genetic code stored within the nucleus of a cell. This genetic code is stored in a long molecule called *deoxyribonucleic acid* (DNA). Each DNA molecule is composed of a string of units, called bases. There are four different bases, and they attract each other in pairs – *guanine* to *cytosine* and *adenine* to *thymine*. When attached together, they form the famous *double helix*. The order in which these bases (or base pairs, since they always match together) occur along the molecule provides the code for the synthesis of proteins. Proteins are then responsible for most of the functions of the body, from the structure of tissues, to the biological catalysts called enzymes, to the hormones which regulate the body's metabolic processes.

A length of DNA which codes for a particular protein is called a *gene*. Long strings of genes, interspersed with areas of DNA which do not code for proteins, make up *chromosomes*. Each nucleus of a mammalian cell contains a set number of chromosomes, except the sex cells (*gametes*) – sperm and ovum. For dogs this number is 78, and for cats it is 38.

When a somatic (body) cell divides, the chromosomes shorten and thicken within the nucleus, so they become visible under a microscope. They then replicate, and one copy of each chromosome separates into a new nucleus before the cell splits. This process is called *mitosis*.

However, in the production of the gametes (the process of *meiosis*), the chromosomes line themselves up in the middle of the cell with a companion. This companion is always the same, and two chromosomes that associate together are called *homologous pairs*. These homologous pairs separate, so the gametes have half the number of chromosomes as normal cells. This means that when a sperm and ovum combine at fertilization, the newly formed cell (the *zygote*) has the correct number of chromosomes.

Homologous pairs code for related genes, but are not identical. The two genes, one on each chromosome, interact in different ways. Sometimes one gene is *dominant* to the other, the less dominant gene being termed *recessive*, and the expression of the gene, that is, the protein that is produced, will be determined by the dominant gene. In other cases both genes will play a role in the production of the protein, a situation called *co-dominance*.

The exception to the homologous pairs are two chromosomes called the sex chromosomes (all the other chromosomes are called the *autosomes*). These chromosomes determine the sex of an animal. In most mammals, including dogs and cats (and humans), a female's somatic cells contain two X chromosomes while the male's somatic cells contain an X and a Y. At meiosis, the ova acquire a single X chromosome from the mother, whereas the sperm inherit either an X or a Y from the father. This has significance for the inheritance of conditions carried on the X chromosome, and means that some inherited diseases can be more prevalent in one sex than another.

Although any one animal will carry only up to two versions of a gene, many more can exist within a population because of mutation and natural selection. These different versions of the gene are called *alleles*.

In conditions and characteristics that are inherited in a simple way, that is, the conditions are autosomal dominant or recessive, a system of genetics devised by the monk Gregor Mendel (hence Mendelian genetics) can be used to predict the likely offspring of two parents, if the parents' genetic make-up is known. For example, the gene that codes for Labrador coat colours is dominant for black and recessive for brown. A Labrador with two alleles for black colour (call the allele B) is described as BB and hence the coat will be black. If it has one allele for black and one for brown (call the allele b), it will be described as Bb but the coat colour will still be black since this colour is dominant. However, if the dog possesses two alleles for brown (bb), it will be brown. The genetic make-up is called the *genotype*, whereas the physical expression of the genes is called the *phenotype*.

The situation is slightly more complex when looking at matings, and a matrix can be used to aid prediction of offspring types. Take the example of a BB black male crossed with a bb brown female. The BB male will produce sperm each carrying a single B gene, and the female will produce ova each carrying a single b gene. These are then recombined at random to produce offspring. The matrix would therefore look like this:

		Male	
		B	B
Female	b	Bb	Bb
	b	Bb	Bb

This means that all the offspring would be Bb. They all carry the b gene for brown coat, but because this allele is recessive, the coat colour is black. An animal with two identical alleles (e.g. BB or bb) is called a *homozygote*, while an animal with two different alleles (e.g. Bb) is called a *heterozygote*. If a black Bb female were then crossed with a black Bb male a different pattern would emerge:

		Male	
		B	b
Female	B	BB	Bb
	b	Bb	bb

On average three of the offspring would be black: one a homozygote (BB) and two heterozygotes (Bb). The fourth would be a homozygote for brown coat colour (bb), and, since this b allele is not now being suppressed by the dominant B allele, the brown coat colour phenotype is expressed.

In fact, since the fertilization process is random, a litter of four pups may not be born in the exact 1:2:1 ratio, but if this were repeated enough times, the proportions of pups of the various genotypes would approximate to this.

Generally, the alleles separate randomly from each other. If a parent has two genetic conditions, just because one condition is expressed in an

offspring, that does not mean that the other will be. However, some alleles that are closely positioned on a chromosome tend to be passed on together. Thus, two traits controlled by different genes may often be found together in the same individual, and the presence of one of these traits may act as a marker for the other. This process is known as linkage.

When one allele is not dominant over another co-dominance exists. For example, certain flowers that have alleles for red flowers (R) and white flowers (W) will be coloured red if homozygous for red (RR), white if homozygous for white (WW) but pink if heterozygous (RW).

Some genes, even if dominant, do not always produce a physical effect in the host. For example, the condition polycystic kidney disease in cats is inherited as an autosomal dominant trait, but not all cats with the genes have cysts in their kidneys. This situation is called *incomplete penetrance*. Penetrance is the proportion of individuals with a particular genotype that demonstrate the characteristics normally expected with that genotype.

Some characteristics are carried on the X chromosome, and this can lead to the phenomenon of *sex linkage*. For example, Golden Retrievers are predisposed to a condition called X-linked muscular dystrophy. The allele for muscular dystrophy (call it M) is carried on the X chromosome, as is the allele for a normal dog not suffering from the condition (call it N). M is recessive to N. Therefore a female carrying a single affected X chromosome (genetic make-up X^MX^N) would not show the effects of the disease. If this female were mated with a normal male (X^NY), then the matrix for their offspring would be as follows:

		Male	
		X^N	Y
Female	X^M	X^MX^N	X^MY
	X^N	X^NX^N	X^NY

All of the females born to this cross will be clinically unaffected by the disease, but 50% of the females will be carriers of the disease. These will not show the disease, since they have a normal gene on the other X chromosome which suppresses the abnormal, recessive gene. However, the males only possess a single X chromosome, so the 50% of males born X^MY will show the disease (since they do not possess another X chromosome with a normal gene). The 50% of males born X^NY will not show the disease and will not carry it.

Because of this process, sex-linked diseases usually affect only males, and males cannot normally be asymptomatic carriers. Females are often carriers, but the only way they can express the disease is if their mother was a carrier and their father was affected. This situation is rare in nature, especially for uncommon genes, but can occur in domestic animals due to inbreeding.

Some disease inheritances are more complex still, because more than one gene may determine the expression of a disease, or the interaction of genes and environment can determine the outcome in an individual. For example, more than one gene is considered to be responsible for hip dysplasia but the dog's nutrition, exercise and other factors can also influence the severity of the disease.

Finally, some diseases are not inherited through the DNA of the cell nucleus at all, but through the DNA present within the *mitochondria* (which are intracellular organelles responsible for energy production). Mitochondria are entirely inherited from the mother, hence characteristics and diseases caused by mitochondrial DNA can only be passed down from the mother. Although conditions caused by mitochondrial DNA are rare, some canine myopathies are thought to be inherited this way.

In summary, an autosomal dominant trait is transmitted from generation to generation without skipping. Each affected offspring has at least one affected parent, unless the disease has arisen because of mutation. If the disease is lethal, then it will be very rare. An autosomal recessive disease may skip generations. If the two parents are affected, then all the offspring are affected. With an X-linked dominant condition, affected males mated to normal females transmit the gene to their daughters, who are all affected, but not their sons. Affected females then pass the condition on to approximately half of their sons and half of their daughters. In the overall population, the incidence in females tends to be twice that of males. With an X-linked recessive disease, the condition may skip generations. The incidence is more common in males. Affected males do not transmit the disease when mated to a normal female, but all female offspring will be carriers. Females showing the disease who are mated with normal males will pass the condition on to all their sons, and all their daughters will be carriers.

Clinical genetics

As noted above, genetic diseases may be more frequently encountered in domestic animals than in most wild populations. The process of domestication involves selecting animals for desirable traits from a human point of view. Initially, these traits would have been practical: speed in a horse, fertility and milk production in a cow, herding instincts in a sheepdog and so on. Over time, for animals such as dogs and cats that came to be kept for their companionship and aesthetic appeal, selection pressures switched towards features that made the animals fit in well to the human environment or made them look 'cute' – for example, miniaturization or achondroplasia – but which may have reduced adaptation to survive in the wild. As breeding practices were refined and the science of genetics was developed, inbreeding was used to create breeds that bred true with respect to certain desired characteristics (i.e. offspring greatly resembled their parents).

Unfortunately, inbreeding reduces the genetic variation within a breed, and tends to accentuate the expression of diseases that are due to recessive genes. Population bottlenecks occur through the importation of a small number of founder animals to a new country or because of regenerations of previously extinct breeds, and they are complicated by the *popular sire effect* whereby desirable individuals such as a show champion are overused (particularly males, which can produce many more offspring than a female). Most of the characterized genetic diseases of the dog are inherited as autosomal recessive traits. This may be because of inbreeding, but it is also due to the difficulty in identifying and eliminating recessive traits in breeding programmes.

It should be noted that inbreeding of itself does not cause genetic disease, and some degree of inbreeding can be of benefit for the concentration of desirable genes. In fact, some inbred strains of mice and rats are entirely homozygous and yet are quite healthy (Beck *et al.*, 2000). Inbreeding promotes homozygosity, and thus deleterious recessive genes are exposed by increasing the probability of their expression. However, by exposing these genes, it is possible to eliminate them by further selective breeding.

Data are currently sparse regarding the prevalence of disease caused by the spontaneous appearance of new mutations. It seems likely that most of the genotypic variability of the domestic dog was present in its common ancestor with the wolf. However, it has been suggested that the Canidae family have elevated genome-wide basal slippage rates, meaning an increased rate of creation of new mutations due to errors in replication, compared to humans and cats (Shearin & Ostrander 2010). In most of those limited cases studied, the mutation seems to be uniform within a breed. This suggests that a *founder effect* applies, that is, a single initial mutation was propagated throughout the breed. In some cases, closely related breeds may have the same mutation causing a disease – for example, phosphofructokinase deficiency in English Springers and American Cocker Spaniels (and presumably Sprockers) – suggesting that a common ancestor was responsible for the original mutation. Some diseases, however, have more than one mutation in the same gene (*allelic heterogeneity*) or mutations in different genes which can lead to the same outcome. For example, oculoskeletal dysplasia is caused by mutations of different genes in the Labrador and the Samoyed, while multifocal retinopathy is caused by two different mutations of the same gene (Guziewicz *et al.*, 2007; Goldstein *et al.*, 2010).

When determining whether a disease is heritable, certain typical characteristics increase suspicion of a genetic predisposition. Often the first thing to suggest that a disease is inherited is that the disease occurs with a higher frequency in a group of related animals than in the general population. This can help distinguish an inherited disease from a breed predisposition (although it can be argued that in most cases breed predispositions are related to genetics in some sense, and a breed predisposition is suggestive of a genetic cause). For example, St Bernards are predisposed to osteosarcomas (Egenvall *et al.*, 2007), but it is possible this is merely a reflection of their large size, the faster growth rate leading to more mistakes being made in DNA replication, leading to cancer. However, analysis of pedigrees shows that there is a familial clustering pattern to cases of the disease, which suggests a specific gene or group of genes being responsible.

A hereditary defect often involves the same anatomic site in a group of related animals. This is often seen in congenital heart disease in dogs. Also, a hereditary disease is often seen to increase

in frequency with inbreeding. Hereditary diseases often have an early onset, and those that do not often have a consistent age of onset. Hereditary diseases usually affect a few individuals within a litter, as opposed to intoxications and infectious diseases, which frequently affect higher proportions. Some genetic diseases will cause abortion or resorption, and these are often difficult to recognize clinically. Similarly, some hereditary diseases will cause a failure to thrive, the 'fading kitten (or puppy) syndrome', and again it can be hard to determine the cause in these cases.

There is an extremely wide range of severity of hereditary diseases, from the relatively benign to the invariably fatal. Diagnosis of a hereditary disease is usually based on history, clinical signs, history of disease in related individuals, test matings, specific imaging or clinicopathological tests for diseases and genetic testing.

Test matings are often suggested in order to identify autosomal recessive diseases, but this does have problems. With late-onset defects, the results of the mating will be known too late to be useful in selecting which individuals to use for breeding. Test matings can be more useful for early-onset diseases, but the ethics of keeping a known affected animal purely for test purposes, and what to do with affected offspring, can be problematic. Furthermore, the results of test matings may be unreliable. For example, in the case of a recessive disease in which the N allele is normal and n is abnormal, a mating of a suspected carrier (N?) to a known carrier (Nn) which produced six normal puppies would give only an 82.2% certainty that the N? was not a carrier (NN). However, a single abnormal pup would confirm carrier status.

The results of random matings, if performed often enough and with respect to a sufficiently prevalent gene, can provide useful information without the need to maintain a carrier or affected animal, and with less likelihood of breeding unwanted affected individuals.

Specific tests for diseases include ultrasonography and histopathology for polycystic kidney disease, MRI for syringomyelia, and von Willebrand factor assay for von Willebrand's disease. Some laboratories will test samples using enzyme and immunological assays to detect diseases, and the results may indicate whether an individual is a homozygote or heterozygote. An example of this is testing for haemophilia B. A defect in an affected protein's size, function or amount allows the identification of carriers of a disease in some cases, although there may be an overlap with normal values. Also, compensatory rises in other proteins, such as an isoenzyme related to pyruvate kinase in pyruvate kinase deficiency, may reduce the accuracy of this sort of test.

Causal molecular defects have been identified for some inherited diseases. Examples identified on the X chromosome include haemophilia B, severe combined X-linked immunodeficiency and hereditary nephropathy. Some autosomal recessive traits for which the mutation has been identified include copper toxicosis in Bedlington Terriers, progressive retinal atrophy in Irish Setters, von Willebrand's disease in Scottish Terriers and pyruvate kinase deficiency in Basenjis.

Many specific DNA tests are now commercially available to identify genetic diseases, and the number of tests is increasing rapidly, to include tests for such diverse diseases as degenerative myelopathy, von Willebrand's disease, copper toxicosis and anal furunculosis.

Specific DNA test results for diseases should be interpreted with caution, and what may seem a clear-cut result may often be misleading. For example, a positive genetic test result for degenerative myelopathy means the individual is at some risk for developing the disease. However, it does not mean that developing the disease is inevitable, nor does it mean that a clinically affected individual does not have another cause of its clinical signs, such as disc disease or neoplasia. Another pitfall is that there may be more than one type of mutation responsible for a disease, particularly between breeds. For example, the mutation causing muscular dystrophy in the Cavalier King Charles Spaniel is different from the one causing muscular dystrophy in the Golden Retriever.

DNA tests are either linkage-based or mutation-based. Linkage-based tests look for a marker gene that is physically near the gene of interest. Mutation-based tests look for the specific mutation causing a disease. Linkage tests may be inaccurate in a small number of cases where chromosomal recombination has occurred in the region between the marker and the mutation.

DNA testing shows great promise for the identification and elimination of genetic diseases

in dogs and cats. The inherited diseases can be identified before an animal is bred, and affected animals can either be removed from the breeding pool or, in the case of recessive traits, bred only to normal individuals, to preserve desirable characteristics. This allows the genetic diversity of breeds to be retained while inherited diseases are eliminated.

The limitations of DNA testing, such as the limited availability of tests, and the fact that its utility is largely restricted to single-gene diseases, mean that there is still a vital role for screening programmes to eliminate inherited diseases. Screening programmes currently in operation in the UK include the British Veterinary Association/Kennel Club programmes for hip and elbow dysplasia and eye diseases, and the International Cat Care scheme for polycystic kidney disease.

EPIDEMIOLOGY

The first and second editions of this book applied relatively loose evidence-based approaches to report on predispositions to diseases in dogs and cats. These evidence-based methods were not explicitly defined and were heavily reliant on expert opinion from textbooks, review articles and conference proceedings. Expert opinion is sometimes called 'eminence-based' veterinary medicine; it represents the personal view of recognized experts or self-appointed commentators without explicit external critical appraisal applied to its quality as evidence. Expert opinion is commonly promulgated as 'evidence' in veterinary medicine, particularly at conferences, in editorials and during undergraduate teaching. However, it is widely considered to be weak evidence at best, unless underpinned by a solid and stated evidential platform (Holmes, 2007). This is because many cognitive biases are inevitably inherent within the belief systems of any individual expert, which also explains why experts so often vehemently disagree on specific issues.

This third edition of *Breed Predispositions to Disease in Dogs and Cats* aims to be more explicit about how the epidemiological results for each breed–disease combination were chosen for inclusion. The book also aimed to cite those references that related to the highest available quality of study designs for each disease. Most of the references in this new book describe original research that has been published in high-quality peer-reviewed journals. To support our new emphasis on reporting quantitative results from primary research, we have penned this introduction to epidemiology, to explain the epidemiologic metrics (e.g. prevalence, odds) that are reported throughout the book. Further information on this fascinating science of epidemiology is available in several useful texts (Thrusfield, 2007; Dohoo *et al.*, 2009; Pfeiffer, 2010).

Epidemiology is the study of disease levels in populations and of factors that determine the occurrence of these diseases. Veterinary epidemiology is a structured scientific approach towards collecting, integrating, analysing and interpreting data on health and demographics at a population level. Epidemiology aims to describe quantitatively the population under investigation. For example, we can define the proportion of German Shepherd Dogs among a known population of dogs [demography] or the proportion of these German Shepherd Dogs with aggression [prevalence] or whether male German Shepherd Dogs have a higher risk of aggression than females [risk factor analysis] (O'Neill *et al.*, 2017a). By identifying key relationships in biological systems, we can develop options for prevention or better diagnosis of future disease cases. New epidemiological evidence is interpreted within the wider body of basic scientific knowledge to contribute towards understanding and solving problems. For example, if we know that Pugs are predisposed to corneal ulceration, then we can recommend that owners are diligent with ocular care and more alert to eye problems in this breed, and that veterinarians are more vigilant during ophthalmological examinations, especially to assess for keratoconjunctivitis sicca (dry eye) which predisposes to corneal ulceration (O'Neill *et al.*, 2016a, 2017b). This evidence-based approach is very different to the traditional anecdotal approach where opinion (no matter how expert) and personal experience are the dominant forces. In the new epidemiological paradigm, data reign supreme.

At its most basic level, there are two main types of epidemiology: descriptive and analytic. Descriptive epidemiology describes the world that is defined by the data under examination in order to understand its demographic, disease or risk-factor features. In the context of the current book, descriptive epidemiology is used to report the frequency of the occurrence of disease within specific breeds. One measure of disease occurrence

is prevalence, which is commonly reported as the proportion or percentage of animals in a group that are affected by the disease at any one point in time (*point prevalence*) or during any specified period (*period prevalence*). So, for example, a statement that the 'St Bernard had 19.4% prevalence for elbow dysplasia in the UK' means that 19.4% of the St Bernard dogs in that study group of dogs in the UK had a diagnosis of elbow dysplasia during that particular study. Prevalence does not draw any distinction between long-standing cases that pre-existed the study period and new cases that were first diagnosed during the study period: these all count equally towards the prevalence total. Cases that are newly diagnosed during a specified period are called *incident cases*. These are reported as either the *incidence risk* (the proportion of animals that were not affected at the start of the study and that are newly diagnosed during the study period) or the *incidence rate* (number of new cases diagnosed divided by the sum of the length of time at risk for each animal in the study overall). Incidence rate is a useful measure to assess the rapidity with which animals develop disease over time.

Measures that describe deaths associated with specific diseases are called mortality. These are very useful pieces of data that offer information on the severity and impact of the condition. The *mortality rate* is derived similarly to the incidence rate and reports the number of deaths during a specific period diagnosed divided by the sum of the length of time at risk of death for each animal in the study overall. *Case fatality* describes the probability of death in affected animals. This is generally reported as a proportion (from 0.0 to 1.0) or percentage (0% to 100%) that describes the number of deaths divided by the total number of animals diseased.

Whereas descriptive epidemiology describes patterns of disease and can report absolute values for disease (e.g. prevalence tells us what percentage of a group of animals have a disease of interest), analytic epidemiology explores risk factors for diseases. *Risk factors* are attributes of an animal that affect its probability of developing a specific disease. For example, important risk factors for patellar luxation in dogs include bodyweight, breed, age, sex and neutering (O'Neill *et al.*, 2016b). In the context of this book, breed is the most important attribute that we explore as a risk factor for disease. A key feature of analytic epidemiology is that it requires a comparison group. If we aim to identify whether some category within a risk factor increases the probability of disease, we need to compare this probability to some other category and then report the relative results. For example, in relation to sex as a risk factor, we might choose to compare disease levels in males versus females to assess whether being male is associated with increased probability of a disease such as epilepsy (Kearsley-Fleet *et al.*, 2013). These comparative results can be reported using metrics such as *risk ratio* or *relative risk* (RR), *odds ratio* (OR) or *incidence risk/rate ratio* (IRR). The reader will see these terms used throughout this book. These metrics report the relative value for the risk-factor category of interest compared with the baseline (comparator) category. These ratios can be broadly interpreted in a equivalent way: a value above 1.0 suggests an increased probability of disease whereas a value below 1.0 suggests that the category is protective and may be associated with reduced probability of disease.

When exploring breed as a risk factor for disease, it is very important to select a logical comparator group to assist meaningful inference from the results. Options for the breed comparator group include 'all dogs in the study', 'all remaining dogs in the study', 'all crossbred dogs', or even another specified 'single breed'. Swapping the comparator category from a group with a low risk of disease to a group with a high risk of disease can cause an odds ratio to change from above 1.0 to below 1.0 and give an illusion of reversal of risk. From this, it is clear that we must interpret results with great care. As Mark Twain aptly observed, 'There are three kinds of lies: lies, damned lies, and statistics.'

A *census* is an epidemiological study that examines every animal in a population and can give an exact (true) value for the overall population, provided that all other aspects of the study design are perfect. However, owing to financial and logistical constraints, most epidemiological studies rely on just subsets (*samples*) of the overall population and are therefore restricted to reporting values that can then be extrapolated from the sample to the overall population. Statistical methods allow studies to report the exact value for the sample and then also to provide a spread of lower and higher values between which the study is 95% confident the true value in the wider general population lies.

This spread is called the 95% confidence interval (often abbreviated to 95% CI) and defines the statistical uncertainty associated with the reported measure of disease occurrence. The *power of a study* to confidently report precise results increases as the study sample size increases. This means that larger and possibly more reliable studies can report narrower spreads for the 95% CI; in other words, they have greater *precision*. When interpreting results, it is very important to examine not just the central exact value for the sample but also the width of the 95% CI that describes the inference for the wider population. A wide spread for the 95% CI suggests that the study was low-powered (i.e. a small sample size) and that precise conclusions may be difficult or unsafe to accept (Poole, 2001). The 95% CI for a prevalence value can be interpreted loosely as the range of values within which we are 95% confident that the true prevalence in the wider target population exists. For an odds ratio or risk ratio, if the lower limit of the 95% CI is above 1.0, then we can be highly confident ($p < 0.05$) of an increased odds/risk compared with the comparator group.

The *p-value* is another tool that helps to infer the strength of evidence for statistical results. Ideally, all analytic test results should report an associated p-value. The p-value defines the probability (from 0.0 to 1.0) of obtaining a result equal to or more extreme than what was observed, generally assuming that there is no true difference between the groups under comparison. A very low p-value describes a very low probability that the current result would have been found if there truly was no difference between the groups, and therefore we interpret this as suggesting that the groups are likely to truly differ. Previously, a simplistic approach was taken to the interpretation of the p-value, whereby any value less than 0.05 was taken as being 'statistically significant' and many older papers just reported whether p-values were above or below this cut-off. While many sources continue to use this heuristic, it is preferable to report the actual p-value for fuller interpretation by the reader in conjunction with other aspects of the result such as the size of the effect, the width of the confidence interval and the nature of the comparator groups chosen (Jeffery, 2015).

Causality (causation) deals with interpretation of possible causal relationships between a risk factor and a disease. A true causal relationship (i.e. the risk factor can be stated as an absolute cause of the disease) is often very difficult to establish, even in the face of large volumes of supporting evidence. Most diseases have a complicated web of genetic, epigenetic, environmental and temporal factors that interact to promote disease occurrence. Even then, there may be random elements in play that determine which individuals from an apparently similar group get diseased. The relative effects and directions of causal factors can be problematic to unravel and quantify. For this reason, it is generally wise to avoid ascribing causality to risk factors, but instead to report just what the evidence usually suggests, which is an association. For example, rather than saying that 'being a Yorkshire Terrier causes patellar luxation', it is safer to say that 'there is an association between being a Yorkshire Terrier and having patellar luxation' (McGwin, 2010; O'Neill *et al.*, 2016b).

Many of the diseases investigated in the early days of epidemiological analyses had relatively simple and direct causal pathways. Exposure to a risk factor such as canine distemper virus regularly resulted in a very clear disease outcome called distemper. In such cases, analyses that only took account of a single risk factor (variable) were often adequate to answer the research question about probable causality. Such analyses are called *univariable* and explore associations between just one risk factor and a disease outcome. Nowadays, however, most of these 'simple' questions have already been answered and we are left with the more complex questions where multiple causal factors may be implicated in disease: the web of causation. To answer these multifactorial questions, we need more complex statistics called *multivariable* analyses that account for several variables in a single analysis. Thankfully, modern computing power now enables most researchers to carry out multivariable analysis easily and the cautious reader should seek out multivariable results rather than just to accept the more simplistic and possibly misleading findings from univariable analyses.

Confounding is a critically important concept when trying to understand the web of factors associated with disease occurrence. Confounding (meaning 'mixing up' or 'confusing') occurs when the effects of the risk factor of interest (e.g. breed) are mixed up with some other associated factor that is also associated with the disease outcome. Pet insurance is a good example of possible confounding. It is now well established that insured

pets are more likely to have disease diagnosed than uninsured pets, especially for those diseases that are more expensive or complicated to diagnose. It is also the case that certain dog breeds are more likely to be insured than others because of breed-related owner attitudes or differential pricing of policies by insurers, among other reasons. Consequently, a simple (univariable) analysis that directly reports the odds of diagnosis of a specific disease between two breeds of dog that have differing levels of pet insurance may appear to show the more insured breed as apparently more diseased. However, a multivariable analysis that also takes insurance into account can remove the effects of the differential uptake of insurance across the breeds and give a truer comparison of inherent predisposition between the breeds. Confounders, both known and unknown, should always be considered when planning studies, and especially when interpreting the results from any study.

Epidemiological studies are population-based analyses. This means that they are essentially reporting the cases (the *numerator*) that are identified from some underlying group of animals (the *denominator*). We often place inordinate focus on the numerator animals, because these are the ones with the disease of interest, but we ignore the denominator population at our own peril. It is critical to learn as much as possible about the denominator population so that we can extrapolate study results safely to wider or different populations. We especially need to know where these denominator animals lived (e.g. the UK or the USA), the dates for the study (e.g. 1990 or 2010), and some basic demography on these animals (e.g. ages, breeds, insurance). These key pieces of information are needed to assess the representativeness of the sample animals for the target population within that study. Additionally, this information allows comparison with our own population of interest so that we can evaluate the generalizability of the results, for example, in the same breed but in a different country and 10 years after the original study. The astute epidemiologist recognizes that time and location/setting are associated with many other 'hidden' changes such as economics or DNA testing that may affect the propensity for true or apparent disease diagnosis/occurrence.

Epidemiological studies rarely examine true disease status (i.e. whether an animal is truly diseased or not in the real world) but instead generally apply some belief or knowledge about the disease status. Hence, the same individual animal at the same time point may have differing disease status recorded depending upon how the data are collected. For example, a puppy with a diagnosis of congestive heart failure from a primary-care veterinary practice may be recorded as a congenital ventricular septal defect case by a referral specialist but may also be recorded as having no cardiac disease by an insurance database if the heart disease preceded the inception of the insurance policy or if the policy did not cover congenital diseases. Meanwhile, the owner of this same animal may record the disease as coughing or collapsing. The fact that none of these disease status reports is incorrect in its own context highlights the importance of carefully stating the case definition for the disease of interest and exploring how the disease data were derived. In this book, we try to help the reader by describing where possible how the data were collected – for example, from an owner survey, from an insurance database, or from referral or primary-care veterinary data.

In summary, epidemiology is the best method yet devised to understand the demography and health of dogs and cats. It can unlock secrets of disease that are otherwise impossible to discover. It can tell us which breeds are predisposed to which diseases. But with great power comes great responsibility. It behoves the user of epidemiology to understand the basics of this science so that we do not abuse or misuse its power.

LONGEVITY: UNDERSTANDING AND INTERPRETING THE DATA

Longevity (lifespan) and mortality (causes of death) statistics offer tantalizing prospects for unique insights into health and welfare variation in domestic dogs. However, interpretation of published statistics is fraught with pitfalls for the unwary, who may rush to draw conclusions without deeper consideration about such data drawn from various sources. Longevity (lifespan) is hugely uncertain for any individual animal and can be heavily influenced by unexpected disease, environmental effects or accidents. However, estimating average longevities for general populations of animals (e.g. a specific breed) can

be much more accurate, especially for comparison across breeds within restricted geographical and temporal limits taken from the same dataset.

We considered adding data on longevity for each breed into this edition to provide another perspective on comparative breed health that might act as a proxy value for the summative effects of all diseases within each breed. After all, surely the average duration that a breed lives should be an excellent and trustworthy measure of the health of that breed. But could it really be so simple? Following prolonged consideration, we rejected the option of adding longevity because of current limitations on the availability of reliable comparative population-based data, and because there are many caveats to the use of such data that often go unrecognized or ignored. However, to provide some information on breed longevity, and to highlight some of the pitfalls to the safe interpretation of these data, Table 1 shows some longevity results from the VetCompass Programme in the UK that illustrate apparently wide lifespan variation across breeds. Many other reports have shown similar results (Michell, 1999; Proschowsky *et al.*, 2003b; Adams *et al.*, 2010; Fleming *et al.*, 2011).

Reviewing the data shown in Table 1, the reader may feel very comfortable to accept these longevity values across a range of breeds as incontrovertible evidence that can rank breeds based on the summative effects of their general health, robustness and proclivity to disease. There are several other sources of good published evidence on longevity in dogs and cats that appear to tell a similar story (Proschowsky *et al.*, 2003a, 2003b; Fleming *et al.*, 2011; O'Neill *et al.*, 2013a). However, a good conceptual grasp of longevity is needed before we can safely move from our current position of data access to a position of data understanding and thence to a desired position of new beliefs (Proschowsky *et al.*, 2003a, 2003b; Fleming *et al.*, 2011; O'Neill *et al.*, 2013a). 'Having data' and 'understanding data' are not always synonymous.

Firstly, it is worth emphasizing that longevity in dogs is influenced by many factors other than just breed effects. The domestic dog (*Canis lupus familiaris*) exhibits unparalleled morphological diversity, from the 1 kg Chihuahua to the 85 kg Mastiff (Alderton & Morgan, 1993; Neff & Rine, 2006). There is now substantial evidence that average longevity reduces as breeds increase in average body size (Patronek *et al.*, 1997; Michell, 1999; Galis *et al.*, 2007; Greer *et al.*, 2007; Adams *et al.*, 2010; O'Neill *et al.*, 2013a). Lifespan reduction in larger dogs has been attributed to a range of genetic differences and pathological conditions induced by artificial selection and accelerated growth (Galis *et al.*, 2007; Urfer *et al.*, 2007; Fleming *et al.*, 2011; Salvin *et al.*, 2012; Kraus *et al.*, 2013). Consequently, perhaps we should restrict comparison to breeds of similar bodyweight if we wish to compare reliably true breed-related health as opposed to longevity effects that are related to bodysize irrespective of breed. In other words, is it fair to directly compare the lifespans of the Cairn Terrier and the Great Dane from Table 1 and to assume that we can draw safe conclusions about their relative health from these values alone, or are we really just seeing differences that come mainly from comparing small and large breeds?

Euthanasia is another phenomenon in companion animals that needs to be considered when evaluating longevity as an indicator of health. Most humans undergo unassisted (so-called 'natural') deaths, but the converse is generally true for domestic pet species in developed countries. Reported euthanasia rates for dogs vary from 52% to 86% (Gobar, 1998; Michell, 1999; O'Neill *et al.*, 2013a), while 86% of deaths of UK cats involve euthanasia (O'Neill *et al.*, 2015a). By definition, euthanasia means that these animals have died prematurely before reaching the end of their so-called natural lifespan. The average ages at euthanasia may therefore be a highly reliable indicator of the inflection point at which quality of life dips below an acceptable threshold, and therefore may be a better measure of lifetime health than the maximum achievable lifespan up to a 'natural' death (McCutcheon & Fleming, 2001/2002). However, high euthanasia rates in dogs and cats also mean that longevity is influenced heavily by the opinions and decision-making patterns of owners, which may take welfare and suffering into account but may be additionally influenced by economic, performance and social factors. Varying decision-making on the acceptability and timing of euthanasia across breeds, diseases, countries and time could therefore impact differentially on subsequent longevity results. For example, owners may perceive the need for euthanasia differently between larger and smaller breeds for issues such as canine aggression, incontinence, mobility or even surgery, because larger breeds may cost more to treat, pose more risk to owners or offer shorter potential future lives than smaller breeds.

Table 1
Longevity for common dog breeds attending primary veterinary practices in England ranked by median age at death. The interquartile range (IQR), range and number of study dogs are also shown ($n = 5095$) (O'Neill *et al.*, 2013a).

Breed	Median (years)	IQR	Range	No. of dogs
Miniature Poodle	14.2	11.1–15.6	2.0–19.4	20
Bearded Collie	13.7	12.2–14.3	4.0–17.0	25
Border Collie	13.5	11.5–15.0	0.1–19.1	184
Miniature Dachshund	13.5	9.2–14.3	2.0–19.5	25
West Highland White Terrier	13.5	10.4–14.9	0.2–21.0	128
Cairn Terrier	13.4	10.6–15.4	0.2–21.6	27
Jack Russell Terrier	13.4	9.3–15.7	0.0–24.0	298
Shih Tzu	13.3	9.2–15.6	0.0–18.6	79
English Springer Spaniel	13.3	10.4–14.8	0.3–19.4	111
Dalmatian	13.3	11.5–14.0	0.9–17.2	27
Crossbreed	13.1	10.1–15.0	0.0–22.0	1120
Yorkshire Terrier	13.0	10.0–15.1	0.01–20.6	217
Lhasa Apso	13.0	7.7–15.3	0.0–16.7	32
Bichon Frise	12.7	9.5–14.8	0.1–18.5	56
Weimaraner	12.6	11.1–13.5	6.5–17.0	36
Labrador Retriever	12.5	10.6–14.0	0.0–18.0	418
Golden Retriever	12.5	11.0–14.1	0.1–17.6	114
Shetland Sheepdog	12.5	11.7–13.8	8.5–14.6	20
Rough Collie	12.0	9.4–13.8	1.0–17.1	28
Border Terrier	12.0	8.9–13.1	1.2–21.2	31
King Charles Spaniel	12.0	10.0–14.2	0.0–15.3	26
Scottish Terrier	12.0	9.1–12.7	0.3–15.9	21
Cocker Spaniel	11.5	7.5–13.7	0.0–18.0	145
Bull Terrier	11.2	7.3–13.0	1.4–16.3	36
German Shepherd Dog	11.0	9.2–12.9	0.0–18.0	312
Greyhound	10.8	8.1–12.0	2.5–16.3	88
Staffordshire Bull Terrier	10.7	4.7–14.0	0.0–18.1	300
Boxer	10.0	7.7–11.6	0.0–16.5	91
Cavalier King Charles Spaniel	9.9	8.1–12.3	0.0–17.2	124
Dobermann	9.2	6.2–11.0	2.1–13.0	37
Bulldog	8.4	3.2–11.3	0.4–15.2	26
Rottweiler	8.0	5.5–10.2	0.0–16.6	105
Chihuahua	7.1	1.0–11.9	0.0–19.9	36
Mastiff	7.1	2.0–9.0	0.0–13.8	35
Great Dane	6.0	4.0–9.0	0.0–11.0	23
Dogue de Bordeaux	5.5	3.3–6.1	0.0–8.8	21

In the current context of dog and cat breeds, longevity defines the average lifespan for each breed. These longevity values are generally identified using death data from large populations such as referral or primary-care veterinary records, pet insurance data or owner/breeder surveys (Proschowsky *et al.*, 2003b; Bonnett *et al.*, 2005; Adams *et al.*, 2010; Fleming *et al.*, 2011; O'Neill *et al.*, 2013a, 2015a). A steady state of breed popularity over time is a key assumption when using these data for comparison between breeds, but this assumption is rarely true. If the relative proportion of all puppies born each year is constant over a prolonged period for each breed, then the ages at death for each breed should be a reliable indicator of average breed longevity. However, breeds often rise and fall markedly in popularity over time, resulting in waves of young and old individuals for these breeds that complicate the interpretation of subsequent death data. For example, the popularity of Pugs in the UK has increased sharply in recent years, rising from less than 1% of all puppies born before 2008 to 2.8% of puppies born in

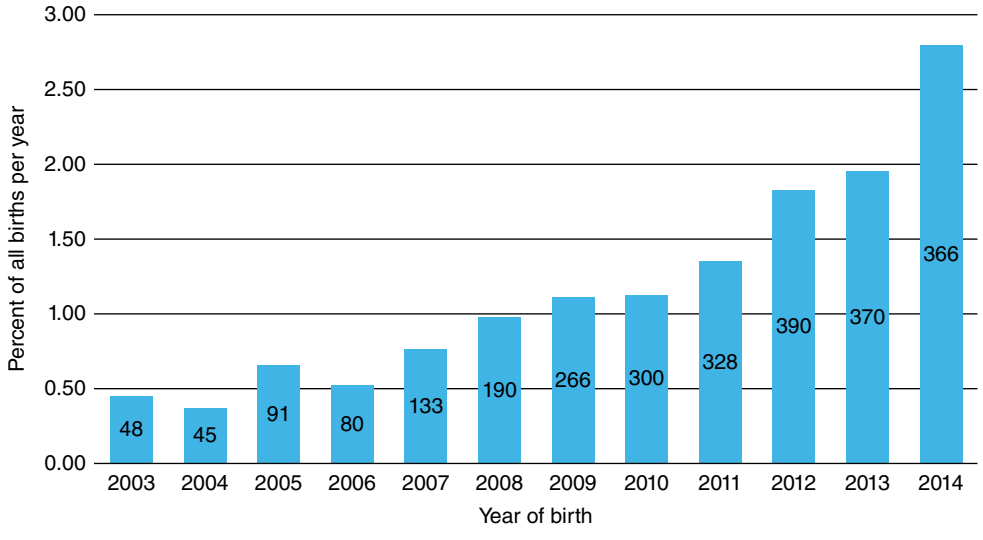

Figure 1
Annual proportional birth rates (2003–2014) for Pugs among all dogs ($n = 263\,456$) attending VetCompass primary-care veterinary clinics in England. The annual birth count of Pugs is shown in each bar (O'Neill *et al.*, 2016a).

2013 (Figure 1). Given that a high proportion of the Pugs that existed in 2014 were therefore young, it follows that younger Pugs have a greater probability of inclusion in mortality statistics compared with breeds that have not recently increased in population counts. Consequently, results from mortality data during 2014 that report the average longevity of Pugs will bias the true age at death for the Pug downwards and give misleading results showing that the breed dies younger than it truly does. The converse effect applies for breeds that are in numerical decline, which have relatively higher proportions of older dogs available to die during any one year. This effect is known as cohort bias, and it renders direct comparisons between average breed longevities highly problematic (Urfer, 2008).

In addition to breed popularity, several other factors that vary across breeds can also influence breed longevity results and complicate comparisons that aim to use longevity as a measure of breed health. Levels of neutering uptake can vary between countries. For example, some Scandinavian countries have historically restricted neutering in dogs to direct health-related purposes, whereas the procedure is routinely promoted in other countries such as the UK for population control and health prophylaxis, with the outcome that much higher proportions of UK dogs are neutered (Anfinsen *et al.*, 2011; O'Neill *et al.*, 2014b). Likewise, pet insurance uptake in dogs varies widely: 0.3–3.0% in America, 4% in Canada, 34.0–40.3% in the UK, 68.4% in Sweden (O'Neill *et al.*, 2014a). Both neutering and pet insurance status are differentially associated with the health status, diagnostic rates and lifespans of dogs, and therefore variable uptake across breeds can influence the longevities achieved by these breeds, independently of inherent breed health characteristics (Egenvall *et al.*, 1998; Hart *et al.*, 2016; O'Neill *et al.*, 2016c; Belanger *et al.*, 2017).

This *Longevity* section started with an unchallenged thesis that longevity, if it could be reliably interpreted, could be a useful metric to evaluate and compare breed health and welfare. But, as we have seen, this is perhaps too simple a perspective, for many reasons. For example, can we even believe that longevity and welfare are linearly related, and that welfare continues to score higher as longevity increases to its maximum? It is not necessarily true that a long life is an indicator of high animal welfare, and perhaps therefore the focus of welfare studies should be more on the quality of the overall life lived, rather than on the quantity. In human medicine, scientists are now turning their attention to the concept of healthspan

(healthy longevity) and towards quantifying both the length and the proportion of lifespan that qualifies as healthspan (Waters, 2011). This is yet another example of how a simple comparative analysis of breed longevity could direct the unwary towards unsafe conclusions.

METHODS

This third edition of *Breed Predispositions to Disease in Dogs and Cats* has substantially bolstered the scientific methods used in the two earlier editions in order to place stronger emphasis on compliance with modern principles of evidence-based veterinary medicine (EBVM) (Holmes, 2007). In line with this progression, this new *Methods* section explains the processes followed during the literature searching and reporting in the current edition, while the *Epidemiology* section (above) describes the epidemiological approaches used.

Information on breed predispositions is available from a wide variety of sources. *Primary sources* of information describe original studies and show the information that was first published. For instance, for a scientific study that describes the common diseases of dogs in England, the primary source is the paper originally published by the scientists who performed the research, 'Prevalence of disorders recorded in dogs attending primary-care veterinary practices in England' (O'Neill *et al.*, 2014b). *Secondary sources* are documents such as websites, the press, books, editorials and review articles that may include information taken from primary sources. In relation to the paper describing the common diseases of dogs in England, a secondary source might be a newspaper article entitled 'Pedigree dogs "as healthy as mongrels", say vets' (Copping, 2014). Such sources often add further discussion or interpretation that extends or does not necessarily reflect the true intent of the original primary research, that may cherry-pick certain aspects of the original research, or that may not be completely accurate. While secondary sources can make for interesting general reading, they may not always tell an accurate story, or the full story, or an unbiased story. Consequently, it is wise to validate secondary reports by following the trail back to the original primary research before accepting the veracity of any conclusions.

Human medicine moved towards applying more rigorous standards for defining information sources that were 'good evidence' in the 1980s, and the Cochrane Collaboration aimed to provide clinicians with valid publications and guidelines to assist improved decision-making in public health from 1993 (Cochrane, 2017). Later, in the 1990s, evidence-based medicine (EBM) was recognized in human medicine as a distinct discipline that should be founded on the best available clinically relevant research (Sackett *et al.*, 1996). Since then, evidence-based veterinary medicine (EBVM) has become increasingly accepted in the veterinary field and is similarly reliant on understanding and using the most reliable sources of evidence when making decisions or developing beliefs (Cockcroft & Holmes, 2003).

A critical aspect of EBVM is to identify the most reliable sources of evidence from the ever-increasing deluge of information that is available in the modern era of electronic publication and data dissemination. The hierarchy of evidence quality is stylized as a pyramid that narrows progressively from the wider volume of lower reliability material at the base to a smaller volume of higher reliability material at the tip (Figure 2). The higher quality evidence towards the top of the pyramid tends to be individual or amalgamated analyses based on well-designed original pieces of research (studies) that have been through the peer-review process. These high-quality studies are designed to reduce selection or information biases, to be large enough to reduce random error, and to have appropriate statistical analytic methods (Vandeweerd *et al.*, 2012). Although there is some debate about whether the study design or the quality of the execution are more important for validating the reliability of the results, it is generally accepted that the pyramid of evidence is a useful model for the quality of evidence (Rosner, 2012). This EBVM aspiration was at the forefront of our minds when we designed the research and reporting methods for the current edition. Where possible, we aimed to reference only original peer-reviewed scientific publications and to avoid the inclusion of conference proceedings, review articles, editorials, websites or veterinary textbooks.

The research and writing process that we used was as follows. Each of the three authors was allocated a random subset of breeds for which

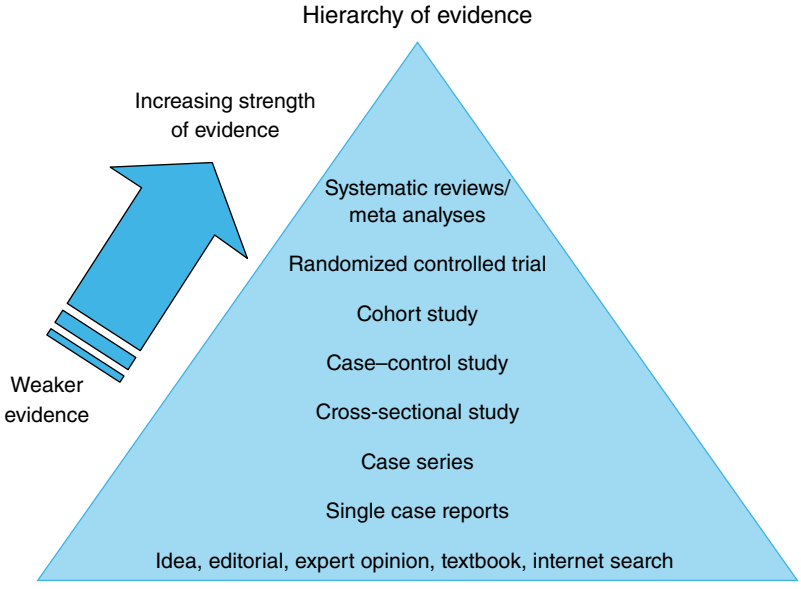

Figure 2
Hierarchy of evidence quality.

we aimed to identify all disease predispositions with sufficient supporting evidence. A breed was considered predisposed to a disease if some available evidence reported an increased incidence, prevalence or risk compared with an appropriate comparator group, preferably within a peer-reviewed primary publication. Specifically, where an odds ratio, a risk ratio or an incidence ratio was the reported metric of comparison, this ratio value would be greater than 1.0 and be supported by a p-value of < 0.05 or by a 95% confidence interval that spanned values entirely greater than 1.0.

Each author followed the same general literature search strategies to ensure that the probability of disease discovery was similar across the breeds. The literature search covered a spectrum of electronic bibliographic databases including *CAB Direct*, *Google Scholar*, *IVIS* (International Veterinary Information Service), *PubMed*, *Science Direct*, *Veterinary Information Network* and *Web of Knowledge*. The precise search strategies included various keyword search combinations from relevant categories, including [BREED NAME], [DISEASE NAME], INHERIT*, HERED*, CONGEN*, GENETIC* and PREDISPOS*.

Relevant findings were merged from multiple searches for each breed. Analytic studies reporting the results of comparative studies that reported increased incidence or prevalence in the breed of interest compared with some other meaningful comparator group (e.g. crossbreds) were prioritized. Where this level of evidence was not available, high-quality descriptive studies were accepted. We also accepted results from genetic studies that identified the mutations for specific diseases or evidence of inheritance within the specified breeds in combination with some evidence of increased incidence or prevalence. Case reports, studies conducted on laboratory research animals, and literature not published in the English language were generally excluded. The constraints of working within the available literature meant that a variety of comparator groups were accepted; these included 'all study dogs', 'all remaining study dogs', 'all crossbred dogs', or single or a combination of other breeds. If an author was in doubt about a source, then all three authors independently reviewed the original article to reach a majority consensus. From the final list of accepted publications, available information was extracted that described (1) the predisposed breed and disease, (2) the strength of the predisposition and the comparator group, (3) the geographic location, (4) the authors and date of the original publication, and (5) any other information of potential relevance such as inheritance and

signalment (e.g. sex or age) associations. These metadata were summarized and reproduced in this book.

For breed predispositions with several supporting publications, we applied some criteria to decide which publications to include in the book. Reports that were larger, more recent and had stronger study designs according to the pyramid of evidence (Figure 2), or those papers that provided evidence on the genetic mechanisms, were favoured for inclusion. Preference was also given to references based on studies with larger underlying denominator populations or those that were deemed more representative of the wider populations. Priority was additionally given to studies based on multivariable statistical analyses rather than univariable results. Multivariable statistical methods take account of multiple risk factors when reporting the breed effects and therefore account for confounding effects from other factors such as insurance status, age and neutering in order to provide less biased inference (O'Neill *et al.*, 2013b).

The lists of breeds included in the current edition have been extended from those presented in previous editions. The current edition includes predispositions to over 650 diseases across 204 breeds of dog and 45 breeds of cat. In line with moves towards international standardization of veterinary language, the breed names and synonyms used in this edition were based on the breed lists available within the VeNom coding system (VeNom Coding Group, 2017) along with additional breed terms identified from the VetCompass Programme database (VetCompass, 2017). This third edition defined breed and purebred as any dog types that were achieved through the process of selective breeding and that would breed true. *Breeding true* was taken to mean that when any two individuals from the same breed are mated, their progeny show consistent, replicable and predictable characteristics typical of the parents. *Pedigreed* animals were defined as that subset of individual breeds with known parentage for several generations. The terms *crossbred* and *mixed breed* were taken as synonyms to describe any dog types that were not a purebred, regardless of whether their parentage was known or not.

In this edition, we have aimed to include only information on disease predisposition. A contrarian approach that we contemplated as a useful adjunct towards improved understanding of breed health was to also include evidence for diseases against which specific breeds are protected (i.e. they are less likely to get this disease than a comparator group of animals). Ultimately, however, we did not tackle this task in the current text because there is little information published on disease protection within breeds, but it may be included in a future edition.

Usage of the term 'inherited' was downplayed in the current edition, because it is now recognized that the majority of diseases in dogs and cats have both inherited and environmental components to their causality. For example, information on the inheritance of hip dysplasia in dogs has been widely published, and so hip dysplasia is widely considered as an inherited disorder (Lewis *et al.*, 2011b; Wilson *et al.*, 2013). However, age and sex are also known to be associated with hip dysplasia (Witsberger *et al.*, 2008). The current edition therefore uses the term *breed predisposition* to cover the combined effects from all factors (including genetic, epigenetic, environmental and owner-related) associated with increased probability of disease in a given breed.

It is also worth noting that the current edition is restricted to breeds and their diseases with published supporting evidence. It is clear that breed-based research is not carried out at random but may be biased towards common or popular breeds, human translational research, working breeds, laboratory breeds or perceptions of priority topics where funding for research may be more readily available. This means that, while this edition may accurately identify the evidenced predispositions within breeds, this does not necessarily mean that these are the only or even a representative selection of the true predispositions for each breed. As always, absence of evidence is not evidence of absence.

PART I

DOG BREEDS

AFFENPINSCHER

Dermatological conditions

Canine follicular dysplasia (seasonal flank alopecia)

- Reported in a small case series
- In this breed, low plasma levels of sex hormones were not considered the cause of the condition

(Waldman, 1995)

AFGHAN HOUND

Cardiovascular conditions

Heart block

- This breed reported to be predisposed to high-grade second-degree or third-degree heart block in a US case series
- Heavier, older and sexually intact female dogs over-represented

(Schrope & Kelch, 2006)

Musculoskeletal conditions

Panosteitis (enostosis, eosinophilic panosteitis)

- Young males predisposed
- OR 1.9 compared to mixed breeds

(LaFond *et al.*, 2002)

Neurological conditions

Afghan myelopathy

- Reported in two case series
- Considered to be inherited in an autosomal recessive fashion
- Onset in young adolescents

(Averill & Bronson, 1977; Cummings & de Lahunta, 1978)

Ocular conditions

Cataract

- Prevalence of primary cataract 2.36%, compared to 1.61% in mixed-breed dogs, in a retrospective study of dogs presenting at North American teaching hospitals (VMDB, 1964–2003)
- Prevalence declined over the years 1964–2003
- Highest prevalence at age 1–2 years in this breed

(Gelatt & MacKay, 2005)

Corneal oedema (due to infection or vaccination with canine adenovirus type 1)

- Increased susceptibility (less commonly seen with the development of canine adenovirus type 2 vaccines)
- Afghans showed a more profound clinical response than Beagles experimentally

(Curtis & Barnett, 1981)

Breed Predispositions to Disease in Dogs and Cats, Third Edition. Alex Gough, Alison Thomas and Dan O'Neill.

Respiratory conditions

Chylothorax
- Usually idiopathic
- Afghan hounds comprised 37.5% of dogs with idiopathic chylothorax and 26.5% of all dogs with chylothorax
- No sex predisposition noted

(Fossum *et al.*, 1986)

Laryngeal paralysis–polyneuropathy syndrome
- Afghans reported to be predisposed
- May be inherited by an autosomal dominant mode

(Burbidge, 1995)

Lung lobe torsion
- Afghans reported to be over-represented compared to hospital population, with 4/22 cases

(Johnson & Feeney, 1984; Neath *et al.*, 2000)

AFRICAN BOERBOEL

Musculoskeletal conditions

Elbow dysplasia
- Common in this breed in South Africa
- >38% incidence
- Males predisposed

(Kirberger & Stander, 2007)

Neurological conditions

Cervical spondylomyelopathy (cervical vertebral malformation, wobbler syndrome)
- Seen in first 2 years of life in this breed
- Reported in a South African case series

(Gray *et al.*, 2003)

AIREDALE TERRIER

Cardiovascular conditions

Dilated cardiomyopathy (DCM)
- Increased prevalence with age
- Approximately twice as common in males as in females
- Thought to be familial or genetic

(Tidholm & Jonsson, 1997)

Electrocardiographic abnormalities
- All 42 dogs of this breed investigated in a screening survey had ECG abnormalities
- Abnormalities included mean electrical axis deviations, low-voltage QRS complexes and first-degree AV block

(Amberger *et al.*, 1996)

Dermatological conditions

Grass awn migration
- Increased prevalence in this breed compared to hospital population
- Common in the summer months

(Brennan & Ihrke, 1983)

Canine follicular dysplasia (seasonal flank alopecia)
- Neutered females predisposed
- A marked predilection in this breed implies a genetic basis for this group of diseases
- Hair loss begins at 2–4 years of age and occurs mainly on the flank

(Miller & Dunstan, 1993)

Endocrine conditions

Hypothyroidism
- Breed at increased risk ($p < 0.01$)
- Genetic component suspected
- May occur at a younger age in breeds at risk (2–3 years)
- Ratio of affected males:females higher in at-risk breeds compared to non-high-risk breeds

(Milne & Hayes, 1981; Larsson, 1986)

Haematological/immunological conditions

Haemophilia B
- Severe factor IX deficiency in this breed
- Familial in this breed

(Brooks, 1999)

von Willebrand's disease (vWD)
- Type I seen in this breed

(Brooks, 1999)

Musculoskeletal conditions

Congenital umbilical hernia
- This breed reported to be significantly over-represented
- Females reported to be at excess risk

(Hayes, 1974a)

Hip dysplasia
- OR 3.9 compared to mixed breeds
- Neutered male dogs predisposed

(LaFond *et al.*, 2002)

Neoplastic conditions

Bladder and urethral tumours
- Airedales significantly over-represented compared to a hospital population
- Male:female ratio 1.95:1, but this was not statistically significant ($p > 0.05$)

(Norris *et al.*, 1992)

Nasal cavity tumours
- Breed at increased risk in a US teaching hospital case series
- Relative risk (RR) 4.6 (95% CI 2.24–9.25)
- Median age 9 years
- Males over-represented in most studies

(Hayes *et al.*, 1982)

Reproductive conditions

Pyometra (cystic endometrial hyperplasia–pyometra complex)
- Breed at moderately increased risk in a Finnish population

(Niskanen & Thrusfield, 1998)

AKBASH

See *Turkish Shepherd Dog*

AKITA INU

See *Japanese Akita Inu*

ALASKAN HUSKY

Endocrine conditions

Hypothyroidism (lymphocytic thyroiditis)
- Breed with a higher prevalence of thyroid hormone autoantibodies (THAA)
- In a cohort study of 287 948 serum samples from dogs in the USA with clinical signs of hypothyroidism, Huskies had an OR of 1.45 ($p = 0.001$) of being affected compared to dogs of all other breeds
- Across the study, females were over-represented, and the highest prevalence was in dogs 2–4 years old

(Nachreiner *et al.*, 2002)

Neurological conditions

Lysosomal storage disease – GM_1 gangliosidosis
- Autosomal recessive inheritance; mutation identified
- Symptoms include proportional dwarfism and neurological deficits (ataxia and dysmetria) from 5–7 months of age

(Kreutzer *et al.*, 2005)

Mitochondrial encephalopathy
- Inherited, mutation identified
- Genetic defect at the level of the thiamine transporter

(Vernau *et al.*, 2015)

ALASKAN KLEE KAI

Haematological/immunological conditions

Factor VII deficiency
- 6/18 client-owned dogs of this breed had this deficiency in an American study
- Inherited condition

(Kaae *et al.*, 2007)

ALASKAN MALAMUTE

Endocrine conditions

Hypothyroidism
- More than 30% of Malamutes had a low T_4 in a sample of 2033 dogs of various breeds, compared to 10% for Dachshunds and Schnauzers
- Median TSH concentration significantly lower in this breed in a series of 693 dogs from 7 different breeds
- American populations studied

(Blake & Lapinski, 1980; Hegstad-Davies *et al.*, 2015)

Gastrointestinal conditions

Pancreatitis
- This breed reported to be predisposed in a Hungarian series of 80 cases

(Pápa *et al.*, 2011)

Haematological/immunological conditions

Stomatocytosis
- Reported in a few cases of Malamutes with chondrodysplasia in a Canadian study
- May be associated with anaemia

(Fletch & Pinkerton, 1972)

Musculoskeletal conditions

Alaskan Malamute chondrodysplasia
- Autosomal recessive inheritance with complete penetrance and variable expression
- American population studied

(Sande *et al.*, 1982; Bingel *et al.*, 1985)

Cranial cruciate ligament (CCL) disease
- Prevalence in this breed 3.25% (OR 1.29, 95% CI 1.10–1.50; $p = 0.018$)
- Population studied was from 27 teaching hospitals in the USA
- Neutered female dogs predisposed

(Witsberger *et al.*, 2008)

Hip dysplasia
- 7.8% prevalence (OR 2.33, 95% CI 2.10–2.58; $p < 0.001$)
- Population studied was from 27 teaching hospitals in the USA
- Neutered male dogs predisposed

(Witsberger *et al.*, 2008)

Neoplastic conditions

Tracheal and laryngeal tumours
- 5/26 dogs in a series and literature review were Alaskan Malamutes
- 10 of the 26 cases in the study were a Spanish population, the rest were a worldwide literature review

(Ramírez *et al.*, 2015)

Sebaceous gland tumours
- Breed at risk of sebaceous adenoma and epithelioma in case series
- American population

(Scott & Anderson, 1990)

Neurological conditions

Idiopathic polyneuropathy in Alaskan Malamutes
- Affects mature young adults
- Previously considered eliminated by breeding programmes, but more cases have arisen recently in the USA and northern Europe
- Autosomal recessive inheritance due to a single gene mutation

(Braund *et al.*, 1997; Bruun *et al.*, 2013)

Ocular conditions

Cone degeneration (hemeralopia or day blindness)
- Autosomal recessive inheritance
- Different underlying mutations reported in American versus Australian populations

(Seddon *et al.*, 2006; Sidjanin *et al.*, 2002)

ALSATIAN

See *German Shepherd Dog*

AMERICAN BULLDOG

See *Bulldog – American*

AMERICAN COCKER SPANIEL

See *Cocker Spaniel*

AMERICAN ESKIMO

See *Eskimo Dog*

AMERICAN PIT BULL TERRIER

Gastrointestinal conditions

Parvovirus enteritis

See under *Infectious conditions*

Infectious conditions

Babesiosis
- High incidence reported in this breed in a number of countries, including USA, Australia and Romania
- In Romania, significantly associated with fighting-dog breeds, especially American Pit Bulls

(Birkenheuer *et al.*, 2005; Jefferies *et al.*, 2007; Imre *et al.*, 2013)

Parvovirus enteritis
- Breed at increased risk in cases series
- Age 6 weeks to 6 months at higher risk

(Houston *et al.*, 1996)

Ocular conditions

Retinal dysplasia
- Reported in one purpose-bred colony from a single affected founder dog in Brazil
- Authors extrapolate that this condition is inherited in this breed
- Autosomal dominant inheritance

(Rodarte-Almeida *et al.*, 2016)

Renal and urinary conditions

Urolithiasis – cystine
- Breed at significantly increased risk in case series

(Case *et al.*, 1992)