VETLESSONS

BY MIKE FARRELL BVETMED CERTVA CERTSAS DIPECVS MRCVS

EVIDENCE-BASED CHOICE: THE RISKS AND BENEFITS OF NEUTERING DOGS

FIRST, DO NO HARM: "Above all, my constant endeavour will be to ensure the health and welfare of animals committed to my care." This is the promise I made with my fellow graduates when I qualified from the Royal Veterinary College in 1997. As veterinary surgeons, we're responsible for helping people make choices on behalf of vulnerable animals. Making decisions for our pets is easiest when we're certain we'd make the same decision for ourselves. For example, if I broke my leg and was suffering unbearable pain, I'd accept a surgeon's advice to operate without hesitation. As an animal lover, I know I'd make the same choice for my pet if they endured a similar injury. Choosing surgery to prevent a *potential* problem is more difficult. For instance, women considering prophylactic mastectomy because of a family history of malignant breast cancer face an agonising decision. When we choose on behalf of a loved one, it's especially hard to accept that an operation *always* inflicts short-term harm and *always* involves long-term risk. An informed choice to neuter requires a high degree of confidence that the long-term benefits outweigh the costs. This article is an evidence-based risk-analysis of canine neutering.

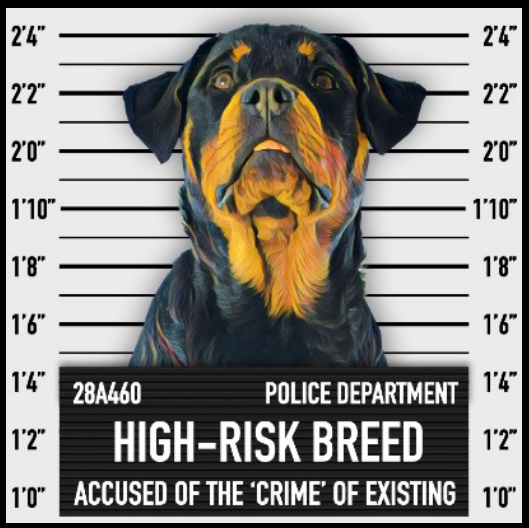
INTUITIVE JUDGEMENT: Which of these dogs is more likely to bite their owner?

Did you make an intuitive judgement? How could you be sure the dog on the left wasn't 'smiling' for the camera? Perhaps the dog on the right is typically sweet but snaps at anyone who approaches her favourite toy? Intuitive judgements are often unfair, and this fact applies equally to scientific publications and smiling dogs.

Dr John Ioannidis, a Tufts University professor, published an essay entitled "Why Most Published Research Findings Are False". Dr Ioannidis is one of the world's most respected medical epidemiologists. When he promoted a sceptical approach, the scientific community listened. At the time of writing, his paper has 11,740 citations on Google Scholar, making it one of the most referenced medical publications of all time. Dr Ioannidis teaches us that blind faith in healthcare publications is misplaced. Consequently, if we're to discover the truth about neutering risk, we must apply his sceptical approach to the veterinary literature.

PROOF BEYOND DOUBT: In 2008, University of Pennsylvania researchers published the final paper in a series of landmark publications assessing the impact of dietary restriction on canine joint disease. They studied a group of 48 Labrador retrievers recruited from family lines with a high incidence of hip dysplasia. Starting at 8-weeks, 24 puppies ate as much as they wanted, causing them to become overweight. A second lean-fed group, matched by gender and bodyweight, consumed 25% less than their paired littermates. This group maintained an ideal bodyweight throughout life. The impact of dietary restriction was dramatic. Lean dogs had a five-fold lower risk of hip dysplasia and their overall risk of arthritis was significantly reduced. They developed less severe chronic pain, which occurred relatively later in life. As a result, the lean dogs enjoyed an average lifespan which was 1·8 years longer than their overweight littermates.

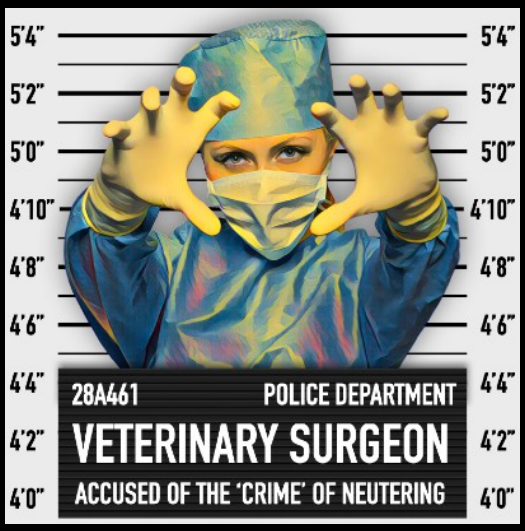
The University of Pennsylvania researchers knew that multiple factors might affect their outcome. To prove overfeeding caused joint disease, they carefully controlled other variables which influence skeletal development. Matching related littermates while controlling gender and exercise meant the only variable was calorie intake. Their excellent study design, data analysis, and presentation serve as a benchmark. These features allow us to make a valid conclusion that overfeeding *causes* canine developmental joint disease.



INNOCENT BYSTANDERS: While one prestigious research team tested the effect of diet, another analysed the impact of genetics. University of Florida researchers measured the outcome of crossing dysplastic Labradors with normal greyhounds. Within two generations, they reduced the incidence of hip dysplasia close to zero. In effect, the harmful genes commonly found in high-risk Labradors were diluted with normal genes found in low-risk greyhounds. Thanks to this research, we learned that humans could rapidly rid the world of hip dysplasia, but only by ridding the world of many popular breeds.

A NEW PRIME SUSPECT? The experimental design of the aforementioned studies allowed researchers to prove a causal relationship. We know, beyond reasonable doubt, that harmful genes and overfeeding cause canine joint disease. This is an unpalatable reality for a society which values breed-specific personality traits and prizes the loving interaction involved in feeding our dogs. So when a third research group exposed a new prime suspect, society was ready and able to pass judgement.

THE CASE AGAINST NEUTERING: In the case against neutering, the jury consists of pet owners. To make an informed decision, these educated laypeople must carefully consider evidence presented by neutering 'prosecutors' and 'defendants'. Evidence for the prosecution was collected and presented primarily by researchers from the University of California, Davis. Four similar papers from one research team form the basis of a campaign to delay dog neutering until at least 2-years or abolish it entirely.

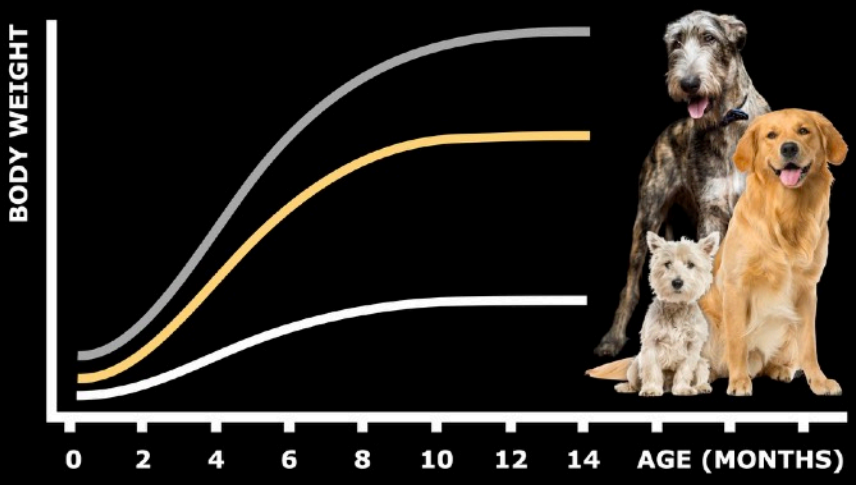


Neutering risk analyses are very different from the aforementioned analyses of diet and breed. To date, every published neutering risk study involves retrospective analysis of hospital records. These so-called observational studies are limited by one irrefutable fact. Although they can highlight correlations, observational studies cannot prove a causal relationship. The highest profile observational study assessing neutering is entitled "Assisting Decision-Making on Age of Neutering for 35 Breeds of Dogs: Associated Joint Disorders, Cancers, and Urinary Incontinence". At the time of writing, this free-access publication has amassed an impressive 1,383,345 views. The Davis research team consists of an expert in anatomy and physiology (B.L. Hart), two population health researchers (A.L. Hart and A.P. Thigpen), and a statistician (N.H. Willits). Prior to publication, this study was reviewed by a veterinary pathologist and an animal breeding and herd health expert. To date, dog neutering hasn't received a fair trial because it hasn't been afforded a proper defence. I volunteered for this role for the following reasons: (1) I've received specialist training in every condition monitored by the study. (2) As an experienced clinical researcher, I've published papers and book chapters on three of these conditions (hip dysplasia, elbow dysplasia, and cruciate ligament disease). (3) As a board certified specialist, I'm statistically literate. (4) As an orthopaedic surgeon, I don't perform neutering surgery. My only personal gain from proving or disproving a relationship is to ensure the public target the true culprit.

SKELETAL DEVELOPMENT: I've read and re-read Hart et al's 2020 publications many times. I'm an expert in developmental joint disease, so I was surprised and confused by an apparent implication that neutering could trigger conditions which occurred in the past.

For illustrative purposes, we can compare a growing dog to a building under construction. Build quality is highly influenced by design, which is defined by an architect. A dog's 'build quality' is defined by their DNA. A poor quality architect designs fragile homes, while poor quality DNA codes for fragile dogs.

Imagine you're having a home constructed by builders with a questionable reputation. Your construction team has one year to complete their work. During that year, you can influence build quality by paying the workforce on time and (if you're a UK resident) supplying them with tea and biscuits. After your builders have finished their work, you can repair any pre-existing faults, but you can no longer influence the original build quality. Sadly, no amount of tea and biscuits can fix a leaky roof occurring six months after construction has finished.



Skeletal maturity occurs when the size, shape and mineralisation of bones can no longer change. Claims that dogs don't reach skeletal maturity until 18 months are popular, but false. There's no library of x-ray images showing open growth plates in 18-month-old dogs. In contrast, there are many studies showing growth cessation after 8-12 months.

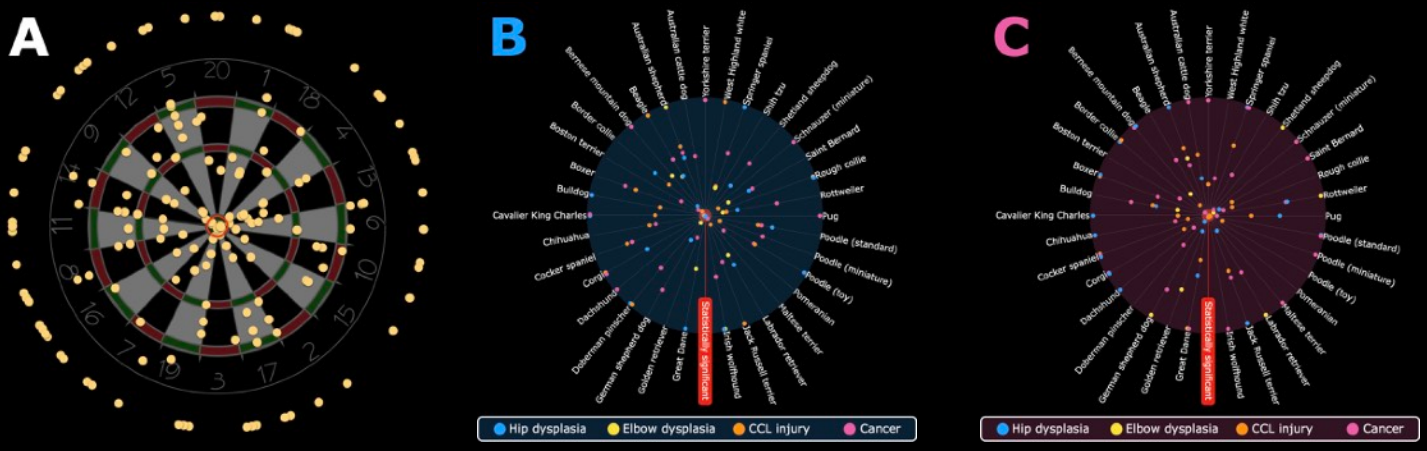
Developmental joint diseases are, by definition, flaws caused by faulty construction. The only way for neutering *after* maturity to cause a condition which develops *before* maturity is for the laws of physics to be rescinded and time to run backwards.

HUMAN ERROR: The likelihood that a research finding is true depends on the prior probability of it being true (plausibility and prior research), statistical power, and the level of statistical significance. Unfortunately, there's a popular notion that medical research articles should be interpreted based purely on statistical significance (i.e. probability or p-values).

In the case against neutering, the prosecution presented data showing p-values below the standard cutoff of p=0.05. This means the likelihood of a tested relationship occurring by chance is less than 1 in 20. Take, for example, the German shepherd dog. A prosecutor might argue that, with a p-value of 0.049, neutering females under 1-year increases their risk of hip dysplasia. However, correlation does not equal causation. Foot size is highly correlated with reading ability, but only because younger children have smaller feet. When we're searching for the truth, p-values viewed in isolation cannot supply it.

Most laypeople aren't trained in statistical analysis. Most prefer simple answers to simple questions; in this case, could neutering before 1-year cause long-term harm to my dog? In the following section, we'll focus on this specific question.

REVIEWING THE EVIDENCE: There's a simple explanation to explain the illogical conclusion that neutering *after* skeletal maturity can affect skeletal development. The developmental conditions tracked by Hart et al (i.e. hip dysplasia and elbow dysplasia) were grouped with a third condition, anterior cruciate ligament (ACL) injury, which typically develops in skeletally mature dogs. Risk of weight gain is strongly correlated with neutering, and ACL injury is strongly correlated with excess bodyweight. Overweight dogs are four-times more likely to injure one or both ACLs. Grouping the three conditions means an apparent increase in developmental joint disease could be entirely attributed to an increased incidence of ACL injury. When the three conditions are disentangled, the lack of any clear relationship between neutering before 1-year and joint dysplasias becomes obvious.

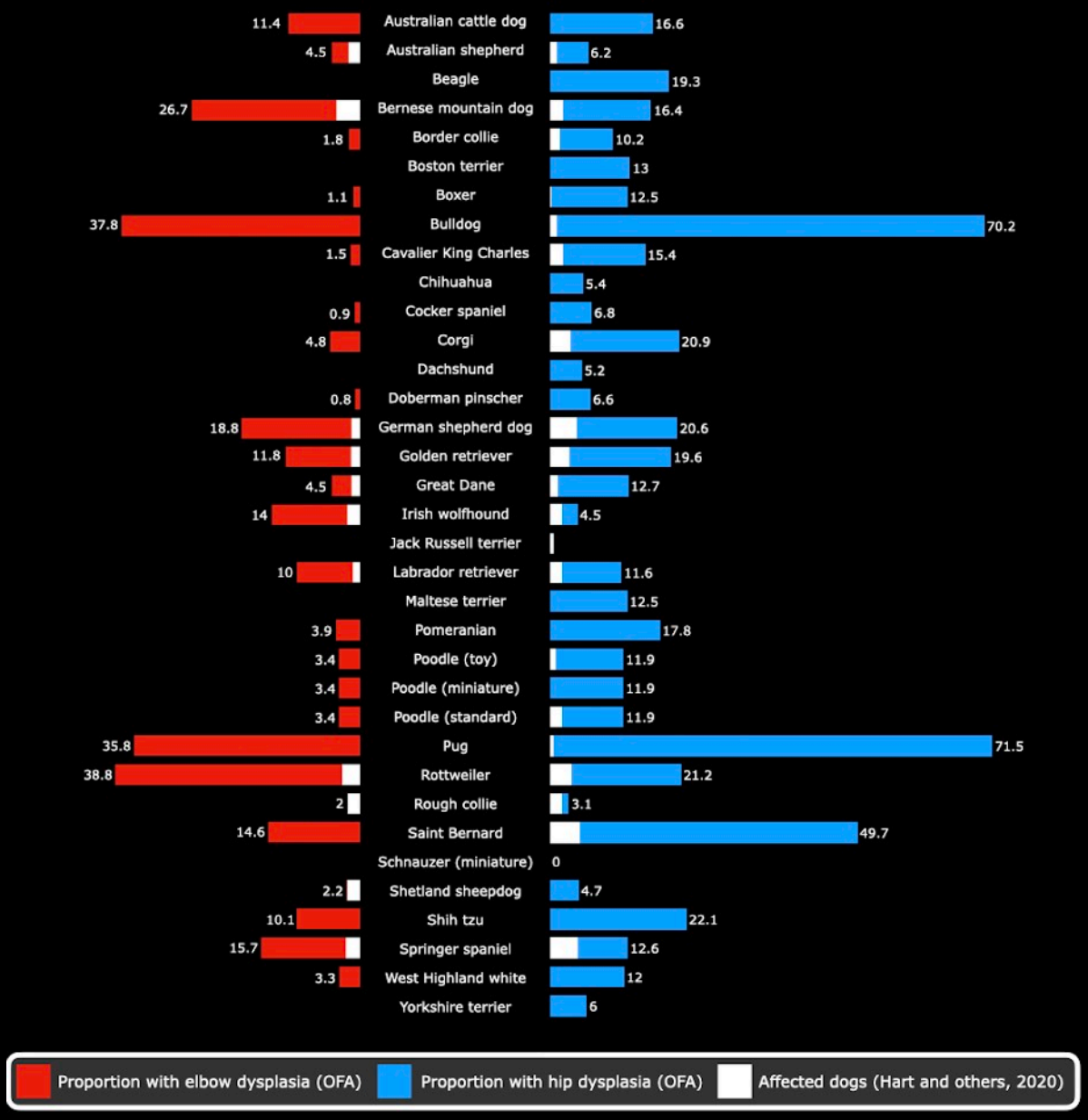


The images above show p-values as dots when dogs neutered before 1-year are compared with dogs who aren't neutered before 1-year. Low p-values hit close to the centre, while high p-values hit far from the centre. The red bullseye marks the p=0.05 cutoff which defines statistical significance. For illustrative purposes, image A shows collated data from males and females. Of the 280 tests performed, 14 statistically significant relationships were identified (Fisher's exact test, $p<0.05$), with 1/14 indicating an apparent cancer-reducing effect of neutering before 1-year in male Labradors. Images B and C show the breakdown for males and females, respectively.

SELECTION BIAS: A population is the entire group that we need to draw conclusions about. In our case, it's 900 million dogs. A sample is the smaller group that data was collected from. For a study to be valid, the sample group must accurately reflect the population. For example, to accurately estimate the average height of British citizens, our sample population shouldn't be recruited from basketball team rosters.

Do samples taken from veterinary hospital databases accurately reflect the dog population? We can answer this question by comparing Hart et al's data to an official registry. The Orthopedic Foundation for Animals (OFA) publishes data which includes radiographic diagnoses of hip and elbow dysplasia. In 2021, bulldogs ranked #3 for hip dysplasia (HD),

with an incidence of 70%, and #4 for elbow dysplasia (ED), with an incidence of 38%. Hart et al's sample population was not similar. They identified HD in 1% and ED in 0.2% of bulldogs. This isn't an isolated example. The image below highlights the extreme mismatch between Hart et al's 2020 sample group and the OFA registry.



Note that the OFA publishes data for dogs intended for breeding. Consequently, the true gulf between the sample population and an average dog is probably larger.

FAIR COMPARISONS: It's not appropriate to argue that selection bias affects neutered and entire dogs equally. Neutering requires pet owners to analyse future risk. They must decide if a potential future problem warrants current surgical intervention. Those who choose neutering see future risk differently to those who don't choose neutering. If the same individuals encounter a problem of intermittent limping, they must perform a similar risk analysis. Owners who are worried about the long-term implications of joint disease are more likely to request referral to the local specialist centre. In this case, that specialist centre is the University of California, Davis. Their clinicians routinely perform diagnostic tests to determine the cause of lameness. In Hart et al's studies, dogs with a diagnosis are not compared to

normal dogs. Rather, they're compared to dogs who have no diagnosis. The commonest manifestation of joint dysplasias is a 'hidden' condition with no identifiable clinical signs. To illustrate this important point, a lifetime study of insured dogs revealed that only 1 in 20 owners of dogs with moderate hip dysplasia made an insurance claim for their condition. With so few dogs diagnosed with joint disease or cancer, Hart et al's studies are very vulnerable to selection bias. This serious limitation must be carefully considered by the public, who should clearly appreciate that "no diagnosis" doesn't mean "normal".

LOW-RISK GIANTS: A plausible hypothesis has been proposed to explain why early neutering might cause joint disease. The hypothesis, which proposes that withdrawal of sex hormones negatively impacts skeletal growth, accounts for the finding that risk is higher in large breed dogs. The largest breed in Hart et al's study was a group of 353 great Danes who, despite their rapid growth rate, had no increased risk of joint disease, cancer or urinary incontinence after neutering at any age. This apparent paradox is easily explained. Compared with other breeds, Danes are experts at maintaining lean body mass. In one study, Danes, Labradors and papillons consumed strict calorie-controlled diets. Danes remained leanest as they aged, averaging only 10.5% body fat. Papillons averaged 14.8%, and Labradors topped the charts at 15.7%. This finding supports an indirect relationship between neutering and health problems. In other words, a strong link exists between neutering and obesity, and neutered dogs are nearly three times more likely to be overweight.

WE HAVE A CHOICE: Healthy people shouldn't move to Mississippi, Alabama, Louisiana, or Tennessee. These US states report obesity rates of 33%, 31%, 30%, and 29%, respectively. All four Southern states differ significantly from neighbouring Colorado, whose residents enjoy a significantly lower risk of obesity, high blood pressure, heart attack, and stroke. The flaw in this argument should be obvious. An individual can choose a healthy lifestyle while living in a high-risk state. Equally, a pet owner can choose to neuter their dog and adjust food intake to maintain a low-risk, lean body mass. The practical problem lies with modern society's reluctance to accept responsibility. Blaming circumstances rather than ourselves is considered easier than accepting the truth that obesity-related illnesses, including arthritis and cancer, are caused by consuming (or feeding) too many calories.

TO PEE OR NOT TO PEE: Spaying and female urinary incontinence are positively correlated. A reduction in luteinising hormone (LH) has been implicated as a trigger for so called "spay incontinence". A genuine link appears likely; however, a causal relationship is difficult to prove because the average onset of incontinence occurs nearly 3-years after surgery. An excellent evidence-based review on this subject is available here.

AVOIDING CANCER: We've established that the University of California's sample doesn't accurately reflect joint disease in the general population. Could the same be true of cancer? The Dog Aging Project collected data from 27 541 dogs, and reported a 2.79% prevalence of malignant cancer. In their 2020 purebred dog study, Hart et al reported an overall cancer prevalence of 5.53%. Golden retrievers were singled out as a high-risk breed. Although golden retrievers have a higher than average cancer risk, Hart et al documented a 6-fold higher risk in this breed, with a reported overall cancer prevalence of 17.6%. Once again, it's important to look at the bigger picture. Another study used data from the same university hospital to show that although neutered female golden retrievers had a higher cancer risk, being neutered didn't affect the risk of cancer-related death, and neutered females had a significantly *longer* average life span than entire females ($p<0.0001$). Golden retrievers are noteworthy for another reason. Published evidence linking neutering to weight gain is strongest in this breed, and there's compelling evidence for a fat-mediated link between neutering and cancer. Body fat releases pro-inflammatory chemicals called adipokines, and fat-mediated chronic inflammation increases cancer risk.

LEST WE FORGET: Most of the public accept that a guilty verdict should't be delivered without proof. Even so, neutering has been tried and convicted based on circumstantial evidence. In the current social climate, it's easy to ignore or forget the benefits of surgery. When we discuss the benefits of neutering, we must distinguish male castration from female ovariectomy, whose benefits are dissimilar. The primary benefits of ovariectomy are prevention of potentially life-threatening uterine infection (pyometra), and a 4-fold decreased risk of dying from mammary cancer.

Pyometra and mammary cancer risk both vary with breed. This table shows the proportion of entire females diagnosed with either or both of these conditions from the ten highest risk breeds.

1	Leonberger	73%
2	Bernese mountain dog	69%
3	Irish wolfhound	69%
4	Great Dane	68%
5	Staffordshire bull terrier	66%
6	Rottweiler	65%
7	English bull terrier	62%
8	Doberman pinscher	62%
9	Bouvier des Flandres	60%
10	Airedale terrier	60%

Although it's reasonable to eschew prophylactic ovariectomy in favour of therapeutic ovariohysterectomy, it's important to recognise that the same operation isn't being performed. Ovariectomy can be performed using keyhole surgery (A), with a 0.009% mortality rate. Ovariohysterectomy for pyometra (B) is associated with prolonged

hospitalisation, high cost and a 10% mortality rate. When animal shelters neuter young puppies before rehoming, they're literally saving millions of lives.

RESPONSIBLE OWNERS: Guide Dogs UK have been caring for blind people and their dogs since 1931. At the time of writing, all of their non-breeding male guide dogs are castrated at 8-months. Here's how Guide Dogs UK justify their neutering policy:

"Working guide dogs need to keep their minds on the job at all times. No flirting, fighting or seeking a mate. For these reasons all working guide dogs are neutered. Un-neutered dogs are easily distracted by female dogs in season and will often try to escape and find a mate. They can also become more aggressive towards other dogs and may become territorial, frequently marking their territory."

Guide Dogs' approach is supported by high-quality science. Testosterone is an anabolic steroid with a role in sexual motivation and aggression. Removing it effectively reduces sexual motivation, and frequently triggers important behavioural improvements. For example, one study reported the following outcomes: 90% reduced roaming behaviour, 80% reduced mounting, 62% reduced inter-male aggression, and 50% reduced urine marking. Another study produced similar results. For urine marking, mounting, and roaming, castration resulted in an improvement of ≥50% in ≥60% of dogs. Multiple independent studies show castrated males are less likely to bite humans.

The case for castration appeared clear-cut until a contradictory study was published which suggested that castration might worsen behaviour. How could this be possible? The answer lies in the way the researchers designed their experiment. The new study collected data via a voluntary online questionnaire. To understand the critical limitation of this method, picture three dog owners with various attitudes to neutering.

- Owner A has a male dog with behavioural problems. She wants to get him castrated because she believes this will help. After his operation, she sees a clear improvement.

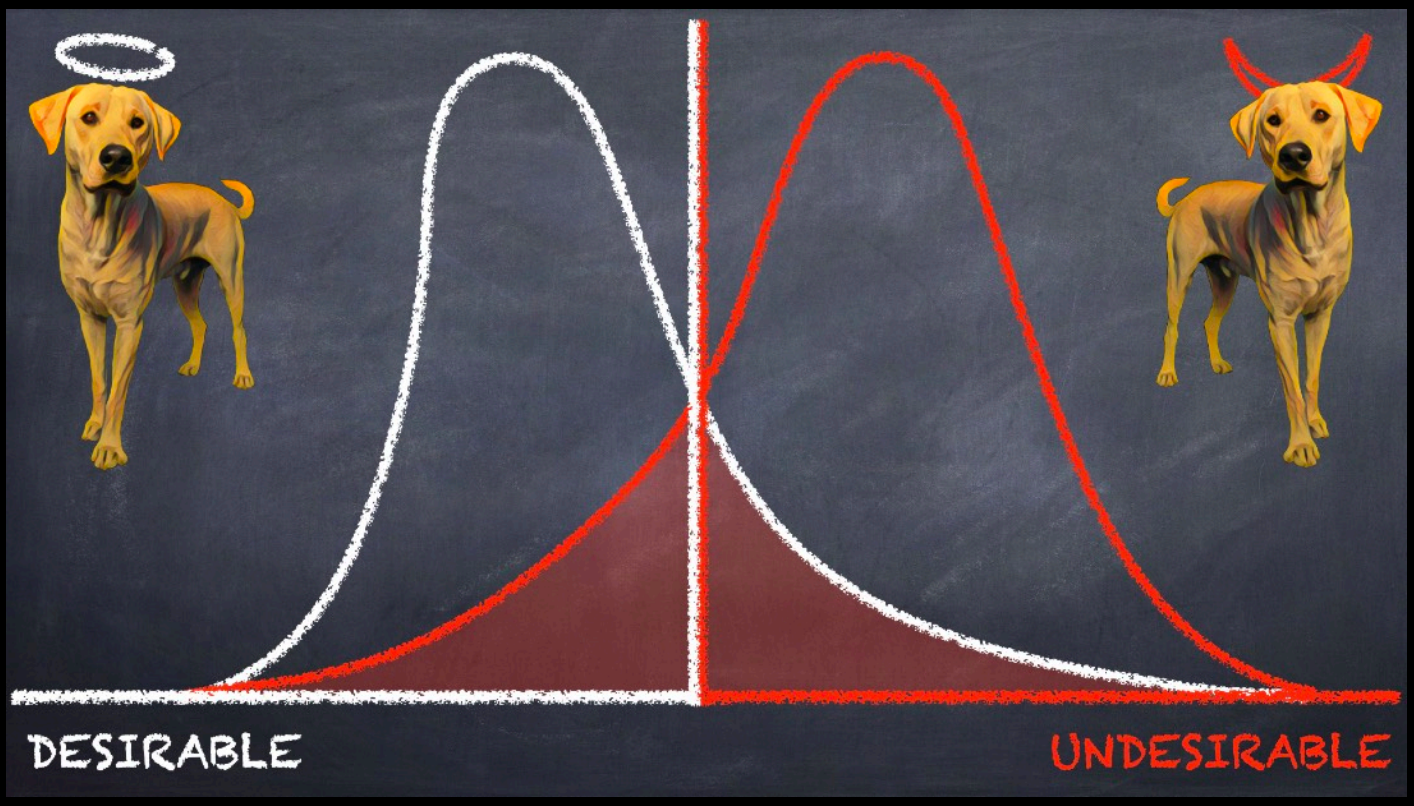
- Owner B has a well behaved male dog. He's a staunch believer that male dogs should not be castrated. Owner B wishes other people could see that male dogs don't need to be castrated to be well behaved.

- Owner C doesn't know what she should do. Her male dog is very well behaved but he's been urinating indoors. Her local veterinarian recommends castration. Surgery goes well and her dog stops urinating indoors.

Owner A's outcome was precisely what she expected. She has no motivation to seek out and complete an online questionnaire. Owner B is different. He hears about the questionnaire and grasps his opportunity. He shares the link with like-minded carers who also complete the

questionnaire. Owner C isn't allowed to contribute to the study because it excludes dogs who were castrated following veterinary advice.

Behavioural psychology has a notorious reputation for generating conflicting opinions and advice. This stylised image illustrates the unpredictability of the canine response to neutering. Castration typically shifts the curve towards improved behaviour; however, neither surgical nor chemical castration can 'switch off' unwanted behaviours. A proportion of dogs will experience little or no improvement (shaded section), and some dogs who don't respond to chemical castration will show improved behaviour after surgical castration.



CLOSING STATEMENT: In the case against neutering, the public have been provided a combination of facts and circumstantial evidence. They should carefully interpret the evidence to ensure the true culprit is convicted. In this case, the only proven crime is overfeeding. Neutering surgery isn't innocent, but its conviction was based purely on circumstantial evidence. In effect, its offence was delivering the genuine culprit to the scene of the crime.

REFERENCES

1. Ioannidis JP. Why most published research findings are false. PLoS Medicine. 2005 Aug 30; 2(8): e124. Free access
2. Lawler DF et al. Diet restriction and ageing in the dog: Major observations over two decades. British Journal of Nutrition. 2008 Apr; 99(4): 793-805. Free access

3. Bliss S et al. Quantitative genetics of traits associated with hip dysplasia in a canine pedigree constructed by mating dysplastic Labrador retrievers with unaffected greyhounds. Am J Vet Res. 2002 Jul; 63(7): 1029-1035. Free access
4. Hart BL et al. Long-term health effects of neutering dogs: Comparison of Labrador retrievers with golden retrievers. PloS one. 2014 Jul 14; 9(7): e102241. Free access
5. Hart BL et al. Neutering of German shepherd dogs: Associated joint disorders, cancers and urinary incontinence. Veterinary Medicine and Science. 2016 Aug; 2(3): 191-199. Free access
6. Hart BL et al. Assisting decision-making on age of neutering for 35 breeds of dogs: associated joint disorders, cancers, and urinary incontinence. Frontiers in Veterinary Science. 2020: 388. Free access
7. Hart BL et al. Assisting decision-making on age of neutering for mixed breed dogs of five weight categories: associated joint disorders and cancers. Frontiers in Veterinary Science. 2020: 472. Free access
8. Kilborn SH et al. Review of growth plate closure compared with age at sexual maturity and lifespan in laboratory animals. Contemp Top Lab Anim Sci. 2002 Sep; 41(5): 21-26. Abstract
9. Adams P et al. Influence of signalment on developing cranial cruciate rupture in dogs in the UK. JSAP. 2011 Jul; 52(7): 347-352 Abstract
10. Malm S et al. Association between radiographic assessment of hip status and subsequent incidence of veterinary care and mortality related to hip dysplasia in insured Swedish dogs. Prev Vet Med. 2010 Feb 1; 93(2-3): 222-232. Abstract
11. Speakman JR et al. Age-related changes in the metabolism and body composition of three dog breeds and their relationship to life expectancy. Aging Cell. 2003 Oct; 2(5): 265-275. Abstract
12. Spain CV et al. Long-term risks and benefits of early-age gonadectomy in dogs. JAVMA. 2004 Feb 1; 224(3): 380-387. Abstract
13. Akil L and Ahmad HA. Relationships between obesity and cardiovascular diseases in four southern states and Colorado. J Health Care Poor Underserved. 2011; 22: 61-72. Free access
14. Stöcklin-Gautschi NM et al. The relationship of urinary incontinence to early spaying in bitches. J Reprod Fertil Suppl. 2001; 57: 233-236. Abstract
15. Schwartz SM et al. Lifetime prevalence of malignant and benign tumors in companion dogs: cross-sectional analysis of Dog Aging Project (DAP) baseline survey. Veterinary and Comparative Oncology. 2022 May 16. Free access
16. Kent et al. Association of cancer-related mortality, age and gonadectomy in golden retriever dogs at a veterinary academic center (1989-2016). PLoS One. 2018 Feb 6; 13(2): e0192578. Free access
17. Simpson M et al. Age at gonadectomy and risk of overweight/obesity and orthopedic injury in a cohort of golden retrievers. PLoS One. 2019 Jul 17; 14(7): e0209131. Free access

18. Lim HY et al. Obesity, expression of adipocytokines, and macrophage infiltration in canine mammary tumors. Vet J. 2015 Mar; 203(3): 326-331. Abstract
19. Jitpean et al. Breed variations in the incidence of pyometra and mammary tumours in Swedish dogs. Reproduction in Domestic Animals. 2012 Dec; 47: 347-350. Free access
20. Beaudu-Lange, C et al Prevalence of reproductive disorders including mammary tumors and associated mortality in female dogs. *Vet. Sci.* 2021, *8*, 184. Free access
21. Shoop-Worrall SJ et al. Mortality related to general anaesthesia and sedation in dogs under UK primary veterinary care. Veterinary Anaesthesia and Analgesia. 2022 Sep 1; 49(5): 433-442. Free access
22. Jitpean S et al. Outcome of pyometra in female dogs and predictors of peritonitis and prolonged postoperative hospitalization in surgically treated cases. BMC Vet Res. 2014 Jan 7; 10:6. Free access
23. Hopkins SG et al. Castration of adult male dogs: effects on roaming, aggression, urine marking, and mounting. JAVMA. 1976 Jun 15; 168(12): 1108-1110. Abstract
24. Neilson JC et al. Effects of castration on problem behaviors in male dogs with reference to age and duration of behavior. JAVMA. 1997 Jul 15; 211(2): 180-182. Abstract
25. Gershman KA et al. Which dogs bite? A case-control study of risk factors. Pediatrics. 1994 Jun; 93: 913-917. Abstract
26. Reece JF et al. Decline in human dog-bite cases during a street dog sterilisation programme in Jaipur, India. Veterinary Record. 2013 May; 172(18): 473. Abstract
27. D'Onise K et al. Mandatory desexing of dogs: one step in the right direction to reduce the risk of dog bite? A systematic review. Injury prevention. 2017 Jun 1; 23(3): 212-218. Free access
28. McGreevy PD et al. Behavioural risks in male dogs with minimal lifetime exposure to gonadal hormones may complicate population-control benefits of desexing. PloS one. 2018 May 2; 13(5): e0196284. Full access
29. A complete reference list is available at www.vetlessons.com/risk/neutering

Mike Farrell graduated from the Royal Veterinary College in 1997. He holds the ECVS Diploma in Small Animal Surgery, and is an EBVS and RCVS board-certified specialist. At the time of writing, he’s published 55 peer-reviewed papers. Mike’s first true love was a golden retriever called Léa. She was neutered after her first season, and lived to the ripe old age of 14.5. This article was written in December 2022.