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Probing the perils of dichotomous binning: How categorizing female dogs as spayed or intact can misinform our assumptions about the lifelong health consequences of ovariohysterectomy

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Abstract

In 2009, we reported findings from the first study evaluating the relationship between canine longevity and number of years of lifetime ovary exposure. All previous studies examining gonadal influences on canine longevity relied upon categorizing females as "intact" or "spayed" based on gonadal status at the time of death. Our study of Rottweilers generated a novel result: Keeping ovaries longer was associated with living longer. This result challenged previous assumptions that spayed females live longer. In the present investigation, we explored a methodological explanation for the apparent contradiction between our results and those of others, so we might better understand the impact that timing of spaying has on longevity. We hypothesized that naming female dogs as "spayed" or "intact" based upon gonadal status at time of death – a method we refer to as dichotomous binning – inadequately represents important biological differences in lifetime ovary exposure among bitches spayed at different ages. This hypothesis predicts that a strong relationship between years of lifetime ovary exposure and longevity in a population could be obscured by categorizing females as spayed or intact. Herein, we provide support for this hypothesis by reanalyzing longevity data from 183 female Rottweilers. In this study population, there was a three-fold increased likelihood of exceptional longevity (living ≥13 yr) associated with the longest duration of ovary exposure. However, categorizing females in this population as spayed or intact yielded the spurious, contradictory assertion that spayed females (presumed to have the least ovary exposure) are more likely to reach exceptional longevity than those that are intact. Thus, by ignoring the timing of spaying in each bitch, the inference from these data was distorted. It follows from this new understanding that dichotomous binning—naming females as spayed or intact—is inadequate for representing lifetime ovary exposure, introducing misclassification bias that can generate misleading assumptions regarding the lifelong health consequences of ovariohysterectomy.

Keywords: Aging; Longevity; Misclassification bias; Ovarian conservation; Spaying; Oophorectomy

1. Introduction

Clinicians are always looking for ways to create categories that will enable them to make better sense of complex biological systems. Categories confer a comforting either-or-ness to the study of wellness and disease. For example, observations are considered normal or abnormal, lesions categorized as severe or not severe, exposures referred to as yes or no. Although thinking in terms of either-or-ness may serve as a satisfying, simplifying strategy, it has the potential to obscure relationships and promote misleading assump-

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tions. Clearly or not, we see and understand the world through our categories [1–3].

For more than a decade, we have studied dogs to gain clues regarding factors that promote healthy longevity [4,5]. By studying a cohort of Rottweilers with highly successful aging, we discovered an intriguing result: There is a direct relationship between keeping ovaries longer and increased likelihood of achieving exceptional longevity [6]. This result challenged previous assumptions that spayed dogs live longer [7]. Our Rottweiler study measured gonadal influence in terms of actual number of years of lifetime ovary exposure. In contrast, all previous studies examining gonadal influences on longevity [8,9] relied upon dividing female dogs into two categories—naming them as "intact" or "spayed" based upon gonadal status at the time of death, a method we refer to as dichotomous binning. Could this categorizing scheme account for the apparent discrepancy between the conclusions reached from these different study populations?

To date, no canine studies have explored whether populations analyzed using actual years of lifetime ovary exposure or dichotomous binning would yield concordant inferences regarding the association between ovaries and adult health outcomes. The purpose of the present investigation was to probe the perils of employing dichotomous binning in the study of canine longevity. We hypothesized that naming female dogs as "spayed" or "intact", based solely upon gonadal status at the time of death, inadequately represents important biological differences in lifetime ovary exposure among bitches spayed at various ages. Further, we reasoned that these methodologic differences in categorizing gonadal status might be at the root of why our results linking longer ovary exposure with increased longevity oppose previous assumptions regarding spaying and longevity. In this report, we present a reanalysis of our Rottweiler longevity data, providing the first direct comparison of dose-response and dichotomous binning methods.

2. Methods

2.1. Study population

A database was established in the Center for Exceptional Longevity Studies to construct lifetime medical histories for a cohort of Rottweilers with exceptional longevity that lived in North America (Exceptional Longevity group). Rottweilers with exceptional longevity lived ≥13 yr, i.e., more than 30% longer than the average life expectancy for the breed (9.4 yr). In each case, American Kennel Club registration records were used to validate date of birth and purebred status. These pet dogs lived with their owners and bitches underwent elective ovariohysterectomy at various ages. Information on medical history, diet and vaccination, reason for spaying, age at death, and cause of death was collected by questionnaire and telephone interviews with pet owners and veterinarians, as previously reported [4]. In this analysis, information gathered from 83 females with exceptional longevity was compared with another cohort of 100 female Rottweilers living in the same catchment area that died between 8.0 and 10.75 yr (Usual Longevity comparison group). A summary of the geographic distribution, reproductive history, body weight, height, and cause of death in the 83 females with exceptional longevity and 100 females with usual longevity has been reported [6].

2.2. Data analysis

To determine if an increased duration of lifetime ovary exposure is associated with increased likelihood of exceptional longevity, we first defined the dose-response relationship between ovaries and longevity. For each dog, lifetime exposure was expressed as number of years of ovary exposure during the first 8 yr of life. Eight years was selected as the cut point, because all dogs in the Usual Longevity and Exceptional Longevity groups lived at least 8 yr. This enabled us to address the question: Is the number of years of ovary exposure during the first 8 yr of life associated with an increased likelihood of achieving exceptional longevity? The 83 females in the Exceptional Longevity group and 100 females in the Usual Longevity group were combined and then subdivided into tertiles based upon ovary exposure during the first 8 yr (shortest exposure, 0.4 to 2.0 yr; middle exposure, 2.1 to 6.0 yr; longest exposure, 6.1 to 8.0 yr). Odds ratios (OR) and 95% confidence intervals (CI) were calculated after setting females with the shortest ovary exposure as the reference group (likelihood of achieving exceptional longevity = 1.0). This enabled us to determine if females with longer ovary exposure were more likely to reach exceptional longevity than those spayed during the first 2 yr of life.

Next, we employed a second method to analyze the relationship between ovaries and longevity in the same data set—the dichotomous binning method used by other investigators [8,9]. Each dog in the Exceptional Longevity and Usual Longevity groups was categorized as "spayed" or "intact" based upon gonadal status at the time of death. Using this classification method,

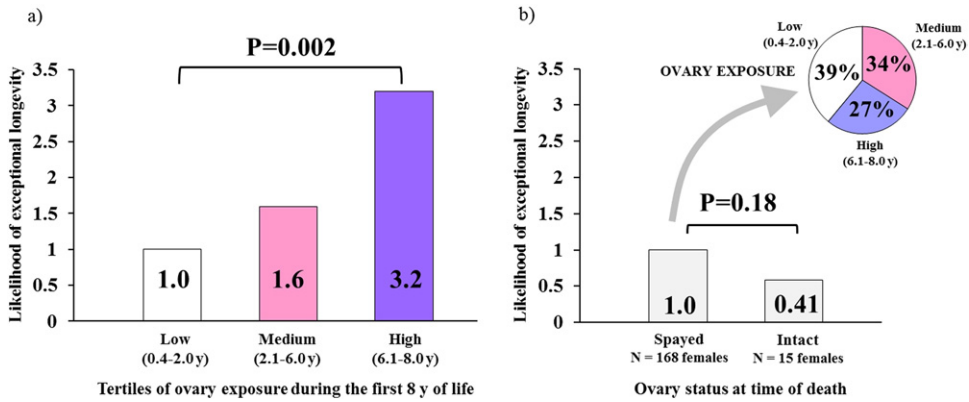

Fig. 1. The perils of dichotomous binning: naming females as "spayed" or "intact" can mislead assumptions regarding the relationship between timing of spaying and longevity. (a) Increased longevity is associated with increased number of years of ovary exposure. The relationship between number of years of lifetime ovary exposure and likelihood of achieving exceptional longevity was analyzed in 183 female Rottweilers. Females that had the most years of ovary exposure during the first 8 yr of life were 3.2 times more likely to achieve exceptional longevity than those with the lowest ovary exposure (P = 0.002). (b) The association between increased ovary exposure and increased longevity is obscured when females are named as "spayed" or "intact" at time of death. When the same population of female Rottweilers was categorized as either "spayed" or "intact" based upon gonadal status at time of death—a method called dichotomous binning—the strong association between increased ovary exposure and increased longevity was obscured. By ignoring the timing of spaying in each bitch, the misleading assertion is reached that intact females (individuals presumed to have more ovary exposure than spayed females) were 59% less likely to achieve exceptional longevity. The discrepancy between these two results is explained in part because females named "spayed" represented a heterogeneous group in terms of lifetime ovary exposure. (b) The pie chart has the frequency distribution of spayed females in the low, middle, and high ovary exposure categories shown in (a). Females binned together as "spayed" have up to a 20-fold difference (8.0 versus 0.4 yr) in lifetime ovary exposure.

naming females "spayed" confers no information regarding the number of years that each dog had their ovaries. Instead, this approach uses "spayed" as a proxy for ovary removal at some undisclosed time prior to death. The proportion of dogs in the Exceptional Longevity and Usual Longevity groups that were spayed and intact was compared using Fisher's exact test. Then, the likelihood of intact females to achieve exceptional longevity was calculated and expressed as OR and 95% CI, with spayed females (presumed to have less ovary exposure than intact females) set as the reference group (likelihood of exceptional longevity = 1.0). This enabled us to determine if dichotomous binning—naming females as spayed or intact—generated results concordant with the relationship between actual number of years of ovary exposure and likelihood of exceptional longevity revealed in the first analysis.

3. Results

3.1. Analysis of longevity data based on number of years of ovary exposure

The association between years of ovary exposure and exceptional longevity is summarized (Fig. 1a) and published previously [6]. An increased number of years of ovary exposure was associated with an increased likelihood of exceptional longevity in Rottweilers. Females with the longest ovary exposure (6.1 to 8.0 yr) were 3.2 times more likely to reach exceptional longevity than females spayed during the first 2 yr of life (P = 0.002). In multivariate analysis, a significant association between ovary exposure and exceptional longevity remained, even after considering other factors that might influence longevity, such as height, body weight, and whether the mother achieved exceptional longevity [6].

3.2. Analysis of longevity data using dichotomous binning: dogs categorized as spayed or intact at time of death

Four of 83 (5%) females in the Exceptional Longevity group were intact when they died at ≥ 13 yr of age. In contrast, 11 of 100 (11%) females in the Usual Longevity group were intact when they died at 8.0 to 10.75 yr of age. Overall, 79 of 168 (47%) bitches that were spayed (i.e., not intact at time of death) reached exceptional longevity, whereas only four of 15 (27%) bitches that were intact at the time of death reached exceptional longevity (P = 0.18, Fisher's exact test two-sided). Thus, naming bitches in this data set as spayed or intact obscured the significant association between greater number of years of ovary exposure and

greater likelihood of exceptional longevity. This was because "spayed" females represented a heterogeneous group in terms of lifetime ovary exposure (Fig.1b, inset). Sixty-five (39%) spayed females had brief lifetime ovary exposure (< 2 yr). However, 46 (27%) spayed females had at least 6 yr of ovary exposure.

To investigate further the extent to which dichotomous binning could misrepresent the relationship between lifetime ovary exposure and longevity, we calculated the likelihood of intact dogs achieving exceptional longevity. Compared with dogs that were spayed at the time of death, intact dogs were 59% less likely to achieve exceptional longevity (OR, 0.41; 95% CI, 0.13 to 1.34; Fig. 1b). This prompted the spurious assertion that those females presumed to have the longest ovary exposure (i.e., "intact" bitches) were 59% *less* likely to reach exceptional longevity. Actually, dogs with the greatest number of years of ovary exposure were *more* likely to reach exceptional longevity—greater than three-fold more likely than females with the shortest ovary exposure.

4. Discussion

At first glance, this sort of analytic exercise may seem far removed from the clinical practice of theriogenology. It is not. Conclusions reached from studies on the relationship between spaying and adult health outcomes have enormous impact on optimizing the wellness of millions of pets. We need studies that will clarify the extent to which the timing of spaying contributes to a range of risk for particular health outcomes. Previously, we reported that the number of years of ovary exposure is directly related to the likelihood of exceptional longevity [6]. In the present study, we demonstrate that this relationship, which offers new insight into the possible role of ovaries in successful aging, is obscured when naming females "spayed" versus "intact" is used as a dichotomous substitute for actual years of lifetime ovary exposure. For future studies to be correctly interpreted, it is important that investigators specify gonadal status of female dogs in number of years of ovary exposure.

In the literature, ovariohysterectomy has been shown to be associated with extended longevity in only one peer-reviewed study [9]. That study used dichotomous binning, naming female dogs as either "spayed" or "intact" at time of death, and then showed that longer-lived dogs were more likely to be in the spayed category; spayed females had a significantly higher mean age at death than intact females, 12.0 versus 10.8 years, respectively [9]. However, there is an important obstacle that stands in the way of making any sound conclusion based upon this study. Rather than representing each dog's lifetime exposure to ovaries in number of years, dogs were subjected to dichotomous binning. It is not difficult to see how this kind of approach can lead to misclassification bias. For example, a dog that is spayed at 7 and lives to be 13 yr of age. This long-lived dog would be allocated to the "spayed" bin, even though she experienced 7 yr of ovary exposure during her lifetime. Similar to naming people as "smokers" or "nonsmokers" at the time of death instead of recording lifetime smoking exposure as number of pack-years, naming dogs as spayed or intact at the time of death fails to register in any consistent way biologically important differences in the amount of lifetime ovary exposure.

We can only speculate as to why, compared with previous dog studies, the work suggesting an ovary-longevity connection in Rottweilers revealed such a novel result. First, we studied a single breed instead of an assortment of small and large breeds with different life spans, so that age at spaying could be reliably standardized according to breed-specific life expectancy. Further, for the first time in dogs, we explored factors associated with exceptional longevity. Studying the differences between usual and extremely successful aging may have magnified our ability to identify previously unseen associations between exposures and outcome. Perhaps the ovary-longevity association we found is peculiar to the Rottweiler breed—a hypothesis whose merit must await the careful study of other breeds.

Instead of resting on the assumption that the Rottweilers we studied were unreliable informants regarding the possible connection between ovaries and canine longevity, we pursued an alternative line of inquiry: Could different conclusions reflect different methods used to assess ovary exposure? To test this possibility, we analyzed the relationship between ovaries and longevity in bitches using two methods. When each female was scored on the basis of the number of years they retained their ovaries, females with at least 6 yr of ovary exposure were 3 times more likely to reach exceptional longevity than females spayed during the first 2 yr of life. These were the conclusions we have reported [6]. However, when each dog was categorized as "spayed" or "intact" based upon gonadal status at the time of death, the association between keeping ovaries longer and longer longevity was lost. This analysis demonstrates that to reveal the true impact that differ-

ences in duration of ovary exposure exerts on physiology and health outcomes, the wrong question is, "Do spayed females live longer than intact females?" It provides no clarity. However, when we ask the question: "What is the relationship between the timing of spaying and longevity?", we ask a better one.

In conclusion, our results demonstrate that dichotomous binning is inadequate for representing lifetime ovary exposure, introducing serious misclassification bias, which can lead to misleading assumptions regarding the association between ovariohysterectomy and longevity. The potential danger of using dichotomous binning in studies of longevity and age-related diseases has been alluded to by other investigators [10,11]. A risk for spurious conclusions is fully expected in study populations in which females that are named "spayed" have a broad range of ovary exposure. Here, we show this risk to be very real. Categorizing bitches as "spayed" or "intact" without regard for the timing of spaying can only hinder us as we continue to define the life-long, system-wide influences of ovaries on physiology and health outcomes.

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