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Exceptional longevity in female Rottweiler dogs is not encumbered by investment in reproduction

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Abstract To better understand the potential trade-off between female reproductive investment and longevity in an emerging model of human healthspan, we studied pet dogs to determine whether intensity of reproduction (total number of offspring) encumbered the likelihood of exceptional longevity. This hypothesis was tested by collecting and analyzing lifetime medical histories, including complete reproductive histories, for a cohort of canine "centenarians" — exceptionally long-lived Rottweiler dogs that lived more than 30 % longer than the breed's average life expectancy. Reproductive intensity (number of litters, total number of pups) and tempo of reproductive effort (age at first reproduction, mean interbirth interval, age at last reproduction) in 78 exceptionally long-lived female Rottweilers (>13 years old) were compared to a cohort of 97 female Rottweilers that had usual longevity (age at death 8.0–10.75 years). We found no evidence that a mother's physiological investment in offspring was associated with disadvantaged longevity. Instead, similar to some studies in women, our data showed an inverted U-shaped trend, suggesting that moderate investment in reproduction may promote longevity. Late reproductive success, a much-studied surrogate of maternal fitness in women, was not a strong predictor of longevity in this canine cohort. Instead, independent of reproductive investment, the duration of lifetime ovary exposure was significantly associated with highly successful aging. Our results from exceptionally long-lived pet dogs provide rationale for further investigative efforts to understand the ovary-sensitive biological factors that promote healthy longevity in women and pet dogs.

Keywords Aging · Trade-off · Parity · Comparative biology · Cost of reproductive effort · Ovarian conservation

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Introduction

Life history theory proposes that reproduction and longevity are constrained by physiological trade-offs (Kirkwood and Holliday 1979; Kirkwood and Rose 1991; Williams 1966). Westendorp and Kirkwood

(1998) presented compelling data from studying the British aristocracy that reproductive effort comes at a cost — diminished longevity. Since then, a freshly motivated field of investigators has reported mixed results in human populations, in some cases even showing a positive association between the number of offspring and longevity (reviewed by Helle et al. 2005; Hurt et al. 2006; Le Bourg 2007). This positive association may imply that successful reproduction, especially at advanced age, is a surrogate for increased fitness or quality of the mother (Doblhammer and Oeppen 2003; Gagnon et al. 2009; Korpelainen 2000; McArdle et al. 2006; Smith et al. 2002; Yi and Vaupel 2004). The reported inconsistency in the relationship between reproductive measures and longevity likely results from the difficulty in untangling the complex interplay between the biological determinants and physiological consequences of successful reproduction with social factors and decisions that also determine the tempo and number of offspring.

Researchers are counting on comparative biologists to find useful mimics of the human aging process that will advance the study of successful aging. Our work is championing the idea of harnessing pet dogs as one of biogerontology's new workhorses to test hypotheses relevant to human healthspan, such as cellular aging and the aging-cancer connection (Waters 2011; Waters and Wildasin 2006). By establishing a cohort of canine "centenarians" — exceptionally long-lived Rottweiler dogs who lived more than 30 % longer than the average life expectancy for the breed — we discovered that longer duration of lifetime ovary exposure was associated with increased likelihood of exceptional longevity (Waters et al. 2009). This finding remarkably parallels recent data on the possible lifespan- and healthspan-promoting effects of ovaries in women (Parker et al. 2009; Rivera et al. 2009; Rocca et al. 2006, 2009). Here, we compare the complete reproductive histories of this valuable cohort of exceptionally long-lived female Rottweilers to a cohort of female Rottweilers with usual longevity. Our specific aim was to examine the extent to which the intensity of reproductive effort (i.e., number of offspring) or advanced age at last reproduction influences the likelihood of successful aging in this emerging model of human healthspan. Furthermore, we evaluated whether duration of lifetime ovary exposure, independent of reproductive investment, is strongly associated with exceptional longevity.

Methods

Study population

A database was established in the Center for Exceptional Longevity Studies to construct lifetime medical and reproductive histories for a cohort of Rottweilers with exceptional longevity that lived in North America (Exceptional Longevity Group). Rottweilers with exceptional longevity lived >13 years, i.e., more than 30 % longer than average life expectancy for the breed (9.4 years). 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 different ages throughout the life course. Information on medical and reproductive 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 (Cooley et al. 2003). Information gathered from females with exceptional longevity was compared to another cohort of female Rottweilers living in the same catchment area that died between 8.0 and 10.75 years (Usual Longevity Comparison Group). A summary of the geographic distribution, body weight, height, and cause of death in the entire cohort of 83 females with Exceptional Longevity and 100 females with Usual Longevity has been reported (Waters et al. 2009).

Parameters evaluated from reproductive histories

To assess the relationship between reproduction and longevity, the following parameters related to reproductive effort were assessed: Number of litters, Total number of pups, Age at first reproduction (AFR), Age at last reproduction (ALR), Mean interbirth interval (MIBI) calculated as $[(\text{ALR} - \text{AFR})/(\text{number of litters} - 1)]$. Because the decision to breed in this population of pet dogs was largely dictated by pet owners and because ovariohysterectomy prevents subsequent reproduction, we collected detailed information on age and reason for ovariohysterectomy (spay) by telephone interview with owners. Among nulliparous females, reason for spay was categorized as: (1) owner did not want pups; (2) substandard physical conformation/recognized physical impairment; or (3) infertility or reproductive problems that precluded live births. Among parous females, reason for spay (which limits reproduction to less than maximal) was categorized as: (1) owner did not want any more pups; or (2) reproductive problem, e.g., uterine infection, dystocia, or infertility. For each dog, duration of ovary exposure was expressed as number of years of ovary exposure during the first 8 years of life, which in Rottweilers is approximately equivalent to the first 62 years of life in humans (Patronek et al. 1997). Eight years was selected as the cut point because all dogs in the Usual Longevity and Exceptional Longevity groups lived at least 8 years.

Data analysis

All statistical analyses were performed using IBM SPSS Statistics version 20.0. The data analysis of 175 female Rottweiler dogs includes 78 Exceptional Longevity females and 97 Usual Longevity females for whom complete reproductive histories were available. Mann–Whitney *U* and Fisher's exact tests were used to compare the descriptive demographic and clinical characteristics of the 71 parous females and 104 nulliparous females in the study population.

To evaluate the association between measures of reproductive effort and longevity, binary logistic regression was used to calculate the odds ratio (OR) and 95 % confidence interval (CI) for achieving exceptional longevity. First, we calculated OR and 95 % CI for parous females after setting nulliparous females as the reference group (likelihood of exceptional longevity equals 1.0). Because parous females had significantly longer median ovary exposure than nulliparous females, we conducted a matched-pair analysis after parous and nulliparous females were rank ordered then matched for ovary exposure (members of each pair are within 0.2 years ovary exposure). This enabled us to determine the extent to which controlling for ovary exposure, a factor known to be associated with longevity in this cohort (Waters et al. 2009), weakened or strengthened the observed association between parity and longevity. We also conducted a logistic regression analysis of longevity in parous and non-parous females corrected for ovary exposure as a continuous variable.

To evaluate the dose response, the relationship between number of litters and likelihood of exceptional longevity was evaluated, using parous females with the lowest investment in reproduction (one litter) as the reference group. In addition to evaluating number of litters, we evaluated total number of pups as a measure of reproductive effort that would more strongly reflect inter-individual differences in the overall physiological costs associated with embryonic development, parturition, and lactation. Parous females were divided into tertiles based upon total number of pups and these subgroups were compared for likelihood of exceptional longevity using multivariate logistic regression. Pearson correlation coefficient was calculated to assess the relationship between total number of pups and length of ovary exposure.

To measure the association between indicators of reproductive tempo and exceptional longevity, parous females were subdivided based upon median AFR, median ALR, and median MIBI, then OR and 95 % Cl for reaching exceptional longevity were calculated using logistic regression.

To evaluate the association between parity and cancer mortality, logistic regression was used to calculate crude and ovary exposure-adjusted OR and 95 % CI for parous vs. non-parous females. Because parous females had lower cancer mortality than nulliparous females, multivariate logistic regression was used to assess whether parous females with higher reproductive effort (i.e., higher number of pups) had lower cancer mortality.

Finally, to further evaluate the association between ovary exposure and longevity independent of reproductive effort, we used multivariate logistic regression in nulliparous females to determine the OR and 95 % CI for achieving exceptional longevity in dogs subdivided by median duration of ovary exposure (<12 vs. >12 months).

Results

Complete reproductive histories were available for 78 Exceptional Longevity females and 97 Usual Longevity females. Overall, 71 (40 %) of 175 females were parous; total fecundity in the cohort was 936 offspring from 156 litters. The characteristics of the study population according to parity are summarized in Table 1. Compared to nulliparous females, parous females had longer lifetime ovary exposure ($p<0.001$), were more likely to reach exceptional longevity ($p=0.005$), and less likely to have cancer as cause of death (p=0.04). There was no significant difference between nulliparous and parous females in height, body weight, or likelihood of mother reaching exceptional longevity. Parous females were more likely to be spayed for breast or uterine conditions (p=0.02), whereas 16 of 90 (18 %) nulliparous females were spayed because of substandard physical conformation. Among parous females, the range for parameters of reproductive intensity and tempo were: number of litters (1–6 litters); total number of pups (1–45 pups); AFR (1.4–6.6 years); MIBI (0.5–3.9 years); and ALR (1.4–9.9 years). Table 1 shows the median and interquartile ranges for each of these parameters.

Overall, parous females were 2.5 times more likely to achieve exceptional longevity (p=0.004), compared with nulliparous females (Table 2). Because parous females had longer median ovary exposure than nulliparous females (6.8 vs. 1.1 years, respectively; p<0.001), parous and nulliparous females were subsequently matched for ovary exposure. After controlling for differences in ovary exposure using matched pair analysis, the relationship between parity and longevity was abrogated; likelihood of exceptional longevity for parous females was no longer significantly greater than nulliparous females (OR, 95 % CI=1.4 (0.5–4.1); p=0.58) (Table 2). Similarly, after adjusting for years of ovary exposure in all parous females, females with reproductive investment were not more likely to reach exceptional longevity than nulliparous females (OR, 95 % CI=1.5 (0.7–3.6); p=0.33).

Among parous females, increasing the amount of reproductive effort, measured by number of litters, did not confer a longevity disadvantage. Females with two litters and females with three to six litters did not have a decreased likelihood of exceptional longevity, compared to females with a single litter (OR=1.4, p=0.58; OR =1.4, p=0.55 for two litters and for three to six litters, respectively).

Next, we examined the association between reproduction and longevity using total number of pups as the measure of reproductive intensity. None of these analyses revealed an adverse effect of reproductive intensity on longevity. Among parous females, there was an inverted U-shaped trend between number of pups and likelihood of exceptional longevity. Females with a moderate number of pups were 2.7 times more likely to reach exceptional longevity than females with fewest pups (p=0.10), despite equivalent duration of ovary exposure (Fig. 1a). Likelihood of exceptional longevity in females with the largest number of pups did not differ from females with fewest pups (p=0.28). A multivariate analysis of number of pups and exceptional longevity adjusted for ovary exposure and height showed a similar dose response between pups and longevity (Fig. 1b). Likewise, logistic regression of number of pups as a continuous variable with likelihood of exceptional longevity failed to indicate a longevity cost to reproductive effort in this study population. For each additional pup, likelihood of exceptional longevity increased by 4 % (OR, 95 % CI=1.04 (0.98–1.10); p=0.19). In all dogs, using stepwise logistic regression with the terms years of ovary exposure, ovary exposure^2, number of pups, and pups^2 to test for possible nonlinear effects, only years of ovary exposure was selected in the final model (OR, 95 % CI for ovary exposure=1.19 (1.07–1.32); p=0.002).

Three parameters that reflect the tempo of reproduction — AFR, ALR, and MIBI — were evaluated for their association with exceptional longevity (Table 3). Females with late reproduction (last litter at >5.2 years) were not more likely to reach exceptional longevity than females with earlier age at last litter [OR, 95 % CI=1.3 (0.4–3.8); p=0.69 after adjustment for ovary exposure] (Table 3). Neither AFR nor mean MIBI significantly influenced the likelihood of exceptional longevity in parous females (Table 3).

The relationship between cancer mortality and reproductive investment was evaluated. Compared to nulliparous females, parous females had a significantly reduced likelihood of cancer mortality (OR, 95 % CI=0.51 (0.28–0.95); p=0.03). But after controlling for number of years of ovary exposure, there was no longer a significant difference in cancer mortality in parous vs. nulliparous females (OR, 95 % CI=0.63 (0.27–1.49); p=0.29). Within parous females, the intensity of reproduction, measured by number of pups, did not significantly influence risk of cancer mortality. Multivariate logistic regression adjusted for ovary exposure, height, and mother reaching exceptional longevity showed no difference between tertiles of reproductive intensity (Fig. 2). Within parous females, using pups as a continuous variable, number of pups did not significantly reduce the likelihood of cancer mortality (OR, 95 % CI=0.99 (0.94–1.05); p=0.79).

Table 1 Summary of demographic, clinical, and reproductive data in female Rottweiler dogs with usual longevity (UL) or exceptional longevity (EL) according to parity

	Parous[a] (n=71)	Nulliparous[b] (n=104)	p value
EL dogs, % (n)	57.7 (41)	35.6 (37)	0.005
Year of birth (range)	1980–1998	1982–2000	
Residence			
Geographic distribution	23 states and Canada	29 states and Canada	
UL	15 states and Canada	22 states and Canada	
EL	19 states and Canada	17 states and Canada	
Number of households	60	96	
UL	29	64	
EL	39	35	
Body weight (lbs), median (IQR)	85.5 (83.8, 91.0)	90.0 (83.0, 98.0)	0.07
UL	88.0 (85.0, 95.0)	92.0 (85.5, 100.0)	0.11
EL	85.0 (80.3, 90.0)	85.0 (75.5, 90.0)	0.70
Height (in), median (IQR)	23.5 (23.0, 24.3)	24.0 (23.0, 24.5)	0.73
UL	24.0 (23.0, 24.4)	24.0 (23.0, 25.0)	0.71
EL	23.5 (22.7, 24.0)	23.5 (22.6, 24.4)	0.96
Lifetime ovary exposure (years), median (IQR)	6.8 (5.5, 8.0)	1.1 (0.6, 3.6)	<0.001
UL	6.5 (5.1, 7.9)	0.9 (0.6, 3.0)	<0.001
EL	7.0 (5.7, 8.0)	2.0 (0.7, 4.6)	<0.0001
Number of litters, median (IQR)	2 (1, 3)	NA[c]	
UL	2 (1, 3)		
EL	2 (1, 3)		
Total pups (n), median (IQR)	12 (7, 20)	NA	
UL	10 (6, 18)		
EL	14 (8, 22)		
Age at first reproduction (years), median (IQR)	3.3 (2.8, 3.9)	NA	
UL	3.6 (2.8, 4.4)		
EL	3.3 (2.9, 3.8)		
Mean interbirth interval (years), median (IQR)	1.3 (0.9, 2.0)	NA	
UL	1.1 (0.9, 1.7)		
EL	1.5 (1.1, 2.0)		
Age at last reproduction (years), median (IQR)	5.1 (4.1, 6.2)	NA	
UL	5.0 (4.0, 5.7)		
EL	5.3 (4.5, 6.5)		
Reason for spay (n)			
Owner does not want any more pups	41	63	0.80
UL	15	39	0.45
EL	26	24	0.89
Reproductive problems including treatment of breast/uterine conditions	16	11	0.02
UL	4	8	0.84
EL	12	3	0.02
Substandard physical conformation	0	16	
UL		10	
EL		6	

Table 1 (continued)

	Parous[a] (n=71)	Nulliparous[b] (n=104)	p value
Mother achieved EL, n (%)	7 (21)	5 (11)	0.34
UL	0 (0)	1 (4)	NA
EL	7 (26)	4 (17)	0.39
Cancer as cause of death, n (%)	31 (44)	62 (60)	0.04
UL	21 (70)	49 (73)	0.75
EL	10 (24)	13 (36)	0.29

[a] "Parous" are females with reproductive investment in offspring

[b] "Nulliparous" are females with no offspring

[c] *NA* not applicable

Finally, we evaluated nulliparous females to test whether the association between ovary exposure and longevity could be independent of the duration of gestational hormone influence or reproductive investment throughout the life course. In nulliparous females, who had zero gestational hormone exposure or reproductive investment, longer ovary exposure was associated with a longevity advantage. Nulliparous females with greater than 12 months ovary exposure were 2.4 times more likely to reach exceptional longevity than those with shorter ovary exposure (p=0.04) (Fig. 3). Repeating the analysis of nulliparous females after excluding 16 dogs that were spayed for conformational defects did not markedly weaken the relationship between ovary exposure and longevity (OR=2.2; p=0.08). In multivariate analysis that adjusted for mother with exceptional longevity, ovary exposure of more than 12 months was associated with a 3.4-fold increased likelihood of exceptional longevity (OR, 95 % CI=3.4 (0.9–12.4); p=0.06).

Discussion

Investigators are working to decipher the cryptic relationship between reproduction and longevity — attempting to sift through the bidirectional, competing factors that situate reproductive success as a physiological cost and at the same time an upsided surrogate of high maternal fitness. Add to this combatant context the fact that the timing and extent of reproductive effort are simultaneously the products of both biological and

Table 2 Parity and likelihood of exceptional longevity in female Rottweiler dogs

	OR (95 % CI) of exceptional longevity	Ovary exposure (years)[a]
All female		
Nulliparous	1.0	1.1
Parous	2.5 (1.3–4.6)	6.8
	p=0.004	p<0.001
26 pairs matched for ovary exposure[b]		
Nulliparous	1.0	6.0
Parous	1.4 (0.5–4.1)	6.0
	p=0.58	p=0.94

[a] For the females in this study population, there was a significant correlation between total number of pups and number of years of ovary exposure (R=0.33; p=0.006). This served as rationale for repeating the comparison of nulliparous and parous females in pairs matched for years of ovary exposure

[b] Among the 52 females matched for ovary exposure, there were no significant difference between parous and nulliparous dogs with respect to median height (inches), % that had mother with exceptional longevity, or % that had cancer as cause of death [median height: parous=23.2, nulliparous=24.0 (p=0.72); % with long-lived mother: parous=7 %, nulliparous=20 % (p=0.56); % with cancer mortality: parous=58 %, nulliparous=50 % (p=0.78)]

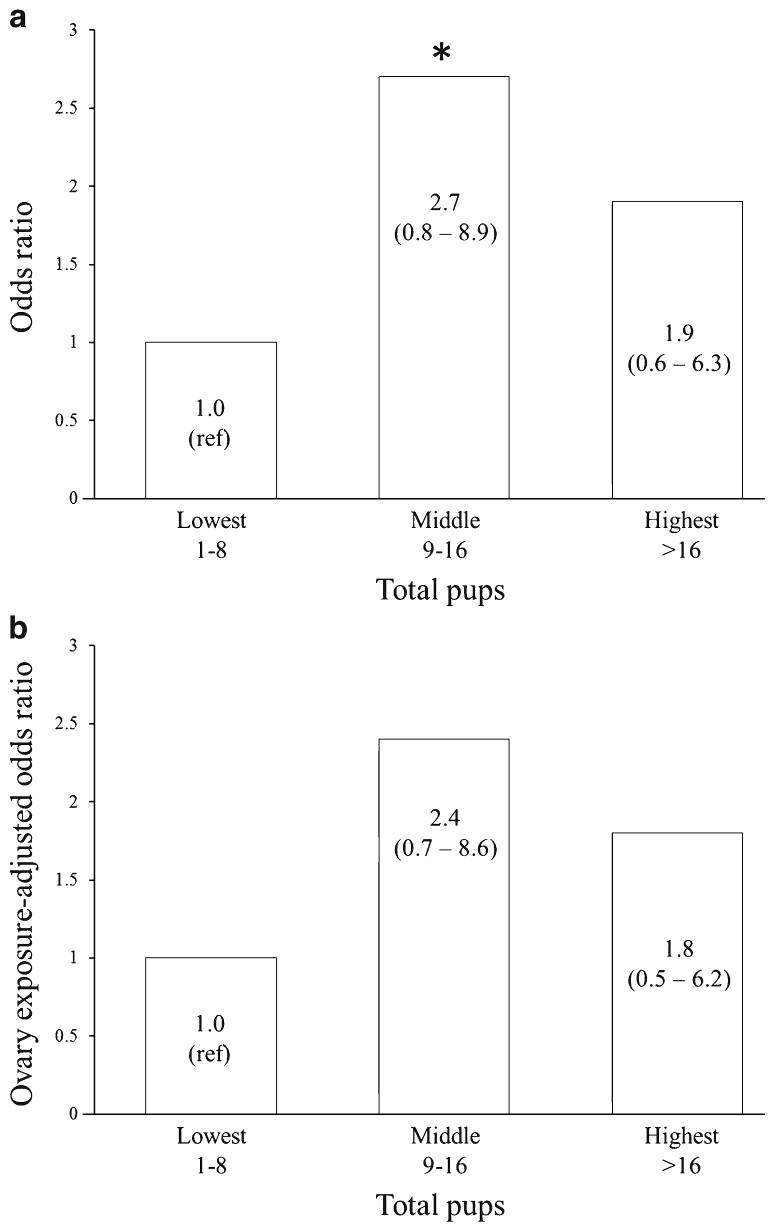

Fig. 1 Increasing intensity of reproduction (total number of pups) does not diminish the likelihood of exceptional longevity in female Rottweiler dogs. (Ovary exposure in the lowest, middle, and highest groups was 6.8, 6.1, and 7.3 years, respectively. Number of female dogs in each group was 23, 24, and 21.) **a** Unadjusted odds ratios; *$p=0.10$ compared to lowest number of pups (reference group). The p value for comparison of highest and lowest group is $p=0.28$ and between highest and middle group is p=0.59. **b** Adjusted odds ratios (adjusted for ovary exposure, height). The p value for comparison of middle and highest with lowest are $p=0.18$ and $p=0.37$, respectively; between highest and middle groups is $p=0.46$. The directionality of the odds ratios (OR>1.0) calculated by logistic regression indicates there is no apparent longevity cost to increased reproductive effort in this study population

social inputs, and it is not surprising that the ideas regarding the real relationship between reproduction and longevity escape consensus. To move closer to better understanding the longevity cost of female reproductive effort in an emerging model of human healthspan, we studied a unique cohort of pet dogs with highly successful aging. We found no evidence that the physiological cost of increased number of offspring was associated with disadvantaged longevity. Instead, our data show an inverted U-shaped trend, suggesting that moderate investment in reproduction may promote longevity. Late reproductive success, a suggested surrogate of maternal fitness in women, was not a robust predictor of longevity in the cohort of dogs studied here. Instead, duration of lifetime ovary exposure, independent of reproductive investment, seems to be a stronger predictor of successful aging.

Our research approach to better understanding the biology of cellular aging and the aging–cancer connection capitalizes on investigating pet dogs sharing the same environment as humans. Compared to laboratory-confined model organisms, our subjects

Table 3 Tempo of reproduction (age at first reproduction, mean interbirth interval, age at last reproduction) and likelihood of exceptional longevity (EL) in female Rottweiler dogs

	Unadjusted OR (95 % CI)	Ovary exposure-adjusted OR (95 % CI)
Age at first reproduction (AFR)		
Early (<3.3 years), $n=38$	1.0 (ref)	1.0 (ref)
Late (>3.3 years), $n=33$	0.6 (0.2–1.6)	0.5 (0.2–1.4)
	$p=0.32$	$p=0.21$
Mean interbirth interval (MIBI)		
Short (≤1.3 years), $n=24$	1.0 (ref)	1.0 (ref)
Longer (≥1.3 years), $n=24$	2.4 (0.7–7.9)	2.3 (0.7–7.8)
	$p=0.14$	$p=0.18$
Age at last reproduction (ALR)		
Early (<5.2 years), $n=36$	1.0 (ref)	1.0 (ref)
Late (>5.2 years), $n=35$	1.5 (0.6–3.9)	1.3 (0.4–3.8)
	$p=0.39$	$P=0.69$

are studied under less artificial conditions and encounter environmental triggers — pathogens, pollutants — at dose ranges and frequencies relevant to human health (Waters 2011). A wealth of medical data based on clinical and biochemical evaluation, medical imaging, and pathology is available for pet dogs. Moreover, the compressed lifespan of dogs relative to humans provides an opportunity to apply a life-course perspective to the study of healthspan. Our study design — a comparison of exceptionally long-lived, "centenarian" dogs that lived 30 % longer than a breed-matched, usual longevity comparison group — does not permit the construction of age-specific mortality curves. Instead, comparison of these two discontinuous Exceptional Longevity and Usual Longevity groups enables us to report the association between reproductive parameters throughout adulthood and the likelihood of achieving highly successful aging. Because the decision to breed in these pet populations is largely dictated by pet owners, reproduction may be less dependent on individual maternal quality than in free living, non-domesticated animal populations (Ricklefs and Cadena 2007). Therefore, we reasoned that any relationship in our study

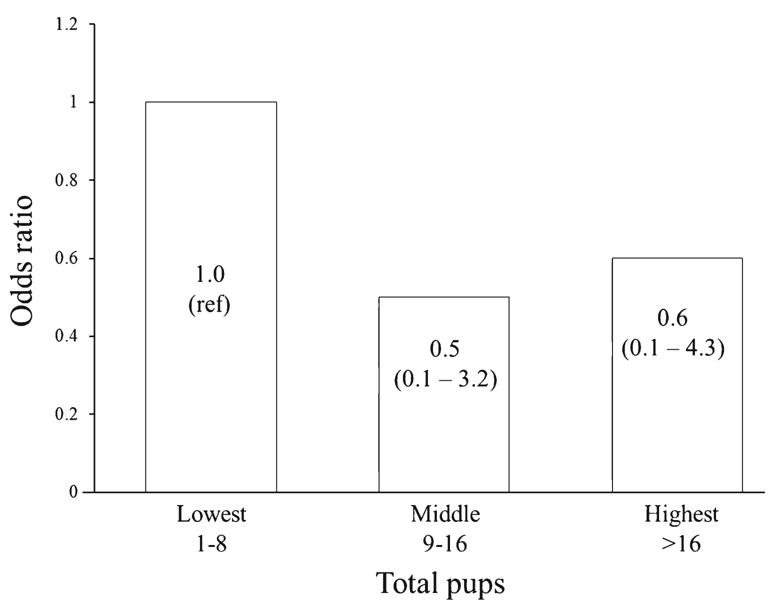

Fig. 2 Intensity of reproduction (total number of pups) and likelihood of cancer mortality in female Rottweiler dogs. (Ovary exposure in the lowest, middle, and highest groups was 6.8, 6.1, and 7.3 years, respectively. Number of female dogs in each group was 23, 24, and 21.) Odds ratios calculated by logistic regression are adjusted for ovary exposure and mother with exceptional longevity. The p value for comparison of middle and highest with lowest are $p=0.46$ and $p=0.60$, respectively; between highest and middle groups, it is $p=0.88$)

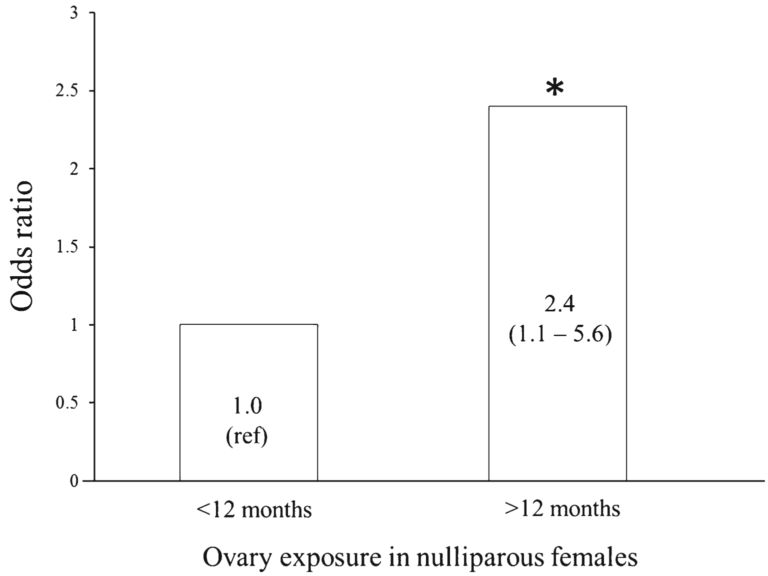

Fig. 3 Lifetime ovary exposure and likelihood of exceptional longevity in 104 female Rottweiler dogs without offspring (nulliparous). (Number of female dogs in each group was 51 and 53.) *p=0.04 compared to shortest duration of ovary exposure (reference group)

population between the number of offspring and life span should more strongly reflect the direct physiological consequences of producing pups. By analyzing detailed reproductive histories, we sought to accurately capture the costs of reproductive effort in our dogs, including the consequences of altered hormonal profiles, as well as the demands of embryonic development, parturition, and lactation. We concede that our findings are less likely to increase our understanding of the relationship between longevity and indicators of reproductive tempo (e.g., AFR, MIBI, ALR) (Pettay et al. 2005), because these parameters are more strongly imposed by social, rather than biological factors in non-natural reproducing populations, such as pet dogs and humans (Grundy 2009).

To probe the longevity cost of reproduction in our dogs, we relied upon two different measures of reproductive intensity. We used number of litters as a measure of reproductive effort that would reflect the amount of lifetime in which females were under the influence of gestational hormones. We expected that our second measure of reproductive intensity, total number of pups, would more strongly reflect the physiological cost associated with embryonic development, parturition, and lactation. Our analysis using number of litters revealed no deleterious effects of reproductive effort on longevity. Interestingly, our analysis using number of pups revealed an inverted U-shaped trend between the number of offspring and exceptional longevity. This trend toward a beneficial effect of a moderate number of offspring in our female dogs mimics the inverted U-shaped relationship between number of offspring and mortality risk in women that has been reported in four different study populations (Doblhammer 2000; Kumle and Lund 2000; Kuningas et al. 2011; Mejer and Robert-Bobée 2003). Taken together, our results do not support the notion that reproduction per se negatively influences the likelihood of successful aging in pet dogs. We believe that in this well-nourished, medically protected population, the physiological cost of reproductive effort did not divert sufficient resources away from somatic maintenance to move females significantly closer to a threshold for age-related diseases or earlier mortality. These results are consistent with those reported in studies of reproduction and longevity in protected zoo animal species (Ricklefs and Cadena 2007). The possibility that a modest number of offspring may represent a hormetic stress that beneficially increases the physiological resilience of females deserves more detailed study.

In humans, a positive association between late reproduction and longevity has been reported by some investigators (Helle et al. 2005; McArdle et al. 2006; Müller et al. 2002; Yi and Vaupel 2004). Notably, Perls and colleagues (1997) reported that late childbearing (after age 40 in an 1896 birth cohort) was associated with a 4-fold increased likelihood of exceptional longevity. The biological underpinnings of this association likely reflect an advantaged overall fitness or sustained fertility in individuals that can execute successful late reproduction. Our study provides the first evaluation of the relationship between ALR and exceptional longevity in dogs. Our motivation was that if a strong relationship between late reproduction and longevity emerged, then pet dogs could provide a model system to identify gene variants that might simultaneously promote late female fertility and slow somatic aging. Our null results are disappointing, but not altogether unexpected, because social factors (i.e., pet owner decisions) likely had a strong influence on ALR in this study population, rendering it an imprecise biological surrogate of late fertility. Although studies in humans are beginning to reveal a common genetic background controlling earlier start of reproduction, late fertility, and lifespan after age 50 (Gögele et al. 2011), we believe that pet dog populations, as studied here, are not likely to accelerate the discovery of genes that co-segregate with late fertility and longevity (Corbo et al. 2008; Kuningas et al. 2011).

Cancer is the major cause of death in Rottweilers that die with usual longevity. Females that reach exceptional longevity are more resistant to cancer mortality (Cooley et al. 2003). In this study population, parous females were less likely to have cancer as the cause of death than nulliparous females. But this apparent upside of having offspring could not be related to intensity of reproductive effort. Within parous females, we found no significant association between total number of pups and likelihood of cancer mortality. Moreover, controlling for ovary exposure abrogated the association between parity and resistance to cancer mortality. The extent to which the intensity of reproduction in women adversely influences the onset or severity of frailty or particular diseases, such as cardiovascular disease or cancer, should be more extensively investigated.

Previously, we discovered a direct positive association between years of lifetime ovary exposure and likelihood of exceptional longevity in this cohort of pet dogs; this association persisted in subgroup analysis that excluded cancer mortality, the major cause of death in female Rottweilers (Waters et al. 2009). Here, by carefully collecting and analyzing reproductive histories, we were able to test the hypothesis that females with longer ovary exposure live longer because of the influence of gestational hormones, not as a consequence of ovary retention per se. Our analysis revealed that among nulliparous females free of gestational hormone influence or other consequences attributable to investment in reproduction, longer ovary exposure was associated with a more than 2-fold increased likelihood of exceptional longevity. When we took steps to minimize selection bias by conducting a subgroup analysis that excluded females in the nulliparous group that were spayed early because of conformational defects which may have favored diminished longevity, our confidence in the relationship between ovaries and longevity was increased. Further, our finding that controlling for ovary exposure in parous females weakens the association between longevity and parity lends additional support to the idea that, independent of reproduction, ovaries are part of a system that promotes longevity. Taken together, our findings from this canine cohort echo results from women in which longer ovary retention is associated with a lowering of overall mortality (Parker et al. 2009; Rocca et al. 2006). Moreover, our conclusions are consistent with the hypothalamic–pituitary–gonadal (HPG) axis hypothesis of longevity proposed by Atwood and colleagues, in which longer lifetime gonad activity (i.e., delayed onset of menopause), rather than number of offspring, predicts longevity in women (Yonker et al. 2011). Future studies in women and dogs are warranted to define specific ovarian longevity factors and to identify the ovary-sensitive biological factors that promote healthy longevity. Pet dogs should provide a tractable mammalian model system with a broad range of lifetime ovary exposure for investigating the mechanisms of how ovaries orchestrate extended longevity in both species.

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