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Sex differences in telomeres and lifespan in Soay sheep: from the beginning to the end.

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There is tremendous diversity in aging rates and lifespan not only among taxa but within species, and particularly between the sexes. Women often live longer than men and considerable research on this topic has revealed some of the potential biological, psychological, and cultural causes of sex differences in human aging and lifespan. However, sex differences in lifespan are widespread in non-human animals suggesting biology plays a prominent role in variation in aging and lifespan. Recently, evolutionary biologists have borrowed techniques from biomedicine to identify if similar mechanisms causing or contributing to variation in aging and lifespan in humans and laboratory animals also operate in wild animals. Telomeres are repetitive non-coding DNA sequences capping the ends

of chromosomes that are important for chromosomal stability but that can shorten during normal cell division and exposure to stress. Telomere shortening is hypothesized to directly contribute to the aging process as once telomeres shorten to some length, the cells stop dividing and die. Men tend to have shorter telomeres and faster rates of telomere attrition with age than women, suggesting one possible biological cause of sex differences in lifespan. In this issue of *Molecular Ecology*, Watson et al. (2017) show that telomere lengths in wild Soay sheep are similar between females and males near the beginning of life but quickly diverge with age since males but not females showed reduced telomere lengths at older ages. The authors further show that some of the observed sex difference in telomere lengths in old age may be due to male investment in horn growth earlier in life, suggesting that sexually dimorphic allocation to traits involved in sexual selection might underlie sex-differences in telomere attrition. This study provides a rare example of how biological mechanisms potentially contributing to sex differences in lifespan in humans may also operate in free-living animals. However, future studies using a longitudinal approach are necessary to confirm these observations and identify the ultimate and proximate causes of any sex-differences in telomere lengths. Collaborations between evolutionary biologists and gerontologists are especially needed to identify whether telomere lengths have a causal role in ageing, particularly in natural conditions, and whether this directly contributes to sex differences in lifespan.

Keywords: Aging, senescence, sex differences, Soay sheep, telomeres

In most modern human societies, women outlive men though the magnitude of this sex difference may be influenced by culture or fertility rates (Austad, 2011). Interestingly, sex differences in lifespan are often found in non-human animals, and in species with polygynous mating systems females often outlive males (Austad, 2011; Clutton-Brock and Isvaran 2007). These patterns suggest a biological basis to variation in aging rates and lifespan and hint at the value of investigating whether there are common mechanisms causing underlying sex differences in aging rates and lifespan across the animal kingdom.

Why would the lifespan of males be considerably shorter than females? One leading possibility is that selection acts differently between the sexes. Enhanced longevity in favor of slower reproduction may increase lifetime reproductive success in females more so than in males (Bonduriansky et al., 2008). The observed sex differences in lifespan may further reflect some unavoidable by-product of sex differences in lifetime exposure to stress, sex, or growth hormones, which facilitate sex-specific reproductive allocation but have knock-on effects on other mechanisms contributing to variation in aging (Brooks and Garratt, 2016).

Telomeres are suspected to be a contributor to the aging process where individuals or species with shorter telomeres or higher rates of telomere attrition tend to have shortened lifespans (Monaghan, 2010; Dantzer and Fletcher, 2015). Across many species, females generally have longer telomeres than males, though it is important to note that in some species females have longer telomeres and shorter lifespans (Barrett and Richardson, 2011). This has led to some speculation that sex differences in telomere lengths contribute to the observed sex differences in lifespan. Although there are a variety of studies examining age-related changes in telomere lengths in wild animals, especially birds (Barrett and Richardson, 2011; Dantzer and Fletcher, 2015), there is a dearth of studies investigating if sex differences in telomere lengths exist in wild mammals.

Soay sheep are an early form of domesticated sheep that have lived on Hirta, an uninhabited island in the St. Kilda Archipelago in the Outer Hebrides, since ~1932 when they were introduced from adjacent islands. Sheep on Hirta are not managed but have been the subject of a long-term individual-based study since 1985 (Clutton-Brock and Pemberton, 2004). Male sheep compete for access to receptive females and there is high reproductive skew among males (Clutton-Brock and Pemberton, 2004). Males are larger than females and have a shorter maximum lifespan (females: 16 yrs; males: 11

years: Clutton-Brock and Pemberton, 2004). Watson et al. (2017) measured telomere lengths acquired from leucocytes within blood samples obtained from individuals ranging in age from <1 to 14 years (females: <1 to 14 yrs; males: <1 to 8 yrs). As in most previous studies in humans and captive mammals, Watson et al. (2017) show that females and males start out at similar telomere lengths early in life but that sex differences emerge in adult sheep >3 years of age, and increase in magnitude with age. Females did not exhibit age-related changes in telomere lengths but male telomere lengths were significantly shorter in older males, as has been reported across other taxa (Barrett and Richardson, 2011).

There are at least two alternative explanations for this inference that telomere lengths decline with age in rams but not ewes. First, telomere lengths were measured in leucocytes and different types of leucocytes may vary in their telomere lengths. Watson et al. (2017) show that the rate of age-related decrease in a specific type of lymphocyte (CD4+ naïve T cells) with advancing age was slightly steeper for males than females. Because naïve T cells have relatively longer telomere lengths than other types of T cells, this could suggest that their main result is a consequence of sex differences in age-related shifts in the proportion of different leucocytes. However, they found little evidence that the proportions of these different types of leucocytes were related to telomere lengths and after accounting for this variation in the proportion of the different types of leucocytes present, it did not affect their main conclusions. This is an important finding for others endeavoring to measure telomeres in wild mammals as it suggests that variation in telomeres is robust to age-related changes in the proportion of different leucocytes in the blood.

The other alternative explanation that Watson et al. (2017) deftly acknowledge is that their study was a cross-sectional rather than longitudinal. In the latter, the same individuals are followed over their lifetime to document within-individual changes in telomere lengths. Because Watson et al. (2017) conducted a cross-sectional study, selective disappearance of individuals with particular telomere lengths in either sex is a plausible explanation for their observation (Nussey et al. 2009). Additionally, biases in capture rates could contribute to the observed pattern given that the sample sizes in older age classes was substantially greater for females than males.

If telomeres do in fact decline with age in rams but not ewes, there are several possible hypotheses to explain this observation. Soay sheep are polygynous and males are heavier than females and investment in increased growth is often expected to come at some cost in terms of shortening telomeres (Monaghan, 2010). Infection may decrease telomere lengths (Monaghan, 2010) and rams experience heavier infection from a gastrointestinal nematode than ewes (Hayward et al. 2009). However, Watson et al. (2017) found no association between telomere lengths and body mass or an index of parasite burden suggesting that sex-differences in growth and body size (see also Barrett and Richardson, 2011) or parasite exposure did not cause sex differences in telomere lengths.

Watson et al. (2017) did find some evidence suggesting that early life investment in a secondary sexual characteristic in males may reduce their telomere lengths (Fig. 1). Horns are a secondary sexual characteristic that rams use in intra-sexual competition. Males with longer horns have higher annual reproductive success but decreased survival (Johnston et al. 2013). Although there was no relationship between horn and telomere length in older males (>1 year), Watson et al. (2017) show that young (<1 year) male sheep with long horns have shorter telomeres. This suggests that investment in horn growth, particularly in early life when males are growing, could carry some physiological cost that reduces telomere length. Again, this result is cross-sectional, but it hints that sex-differences in the timing/nature of reproductive allocation could contribute to sex-differences in telomere attrition. Such sex-specific reproductive allocation is also expected to underlie sexual dimorphism in aging. Future manipulative studies are now required to determine whether different aspects of reproductive allocation directly influence telomere length in wild mammals. This could occur due to the direct allocation and cell proliferation required for the development of such reproductive traits, and/or be a consequence of differences in sex-hormone production that underlie reproductive development in either sex.

Whether or not telomere lengths cause sex differences in lifespan or just simply reflect some metric of condition or a biomarker of biological age needs to be tackled in much greater detail. Evidence that telomere attrition directly contributes to aging in mammals, particularly mice, under laboratory conditions is weak (Simons, 2015). However, in the more challenging environments experienced by wild animals, telomere attrition might increase either intrinsic or extrinsic mortality risk. Conveniently, the causes and consequences of variation in telomere lengths and attrition in telomere lengths is a topic that yokes both evolutionary biologists working with wild animals and those working in humans and captive animals. This nexus is surely to produce more insights into the evolutionary causes and biological mechanisms causing sex differences in lifespan.

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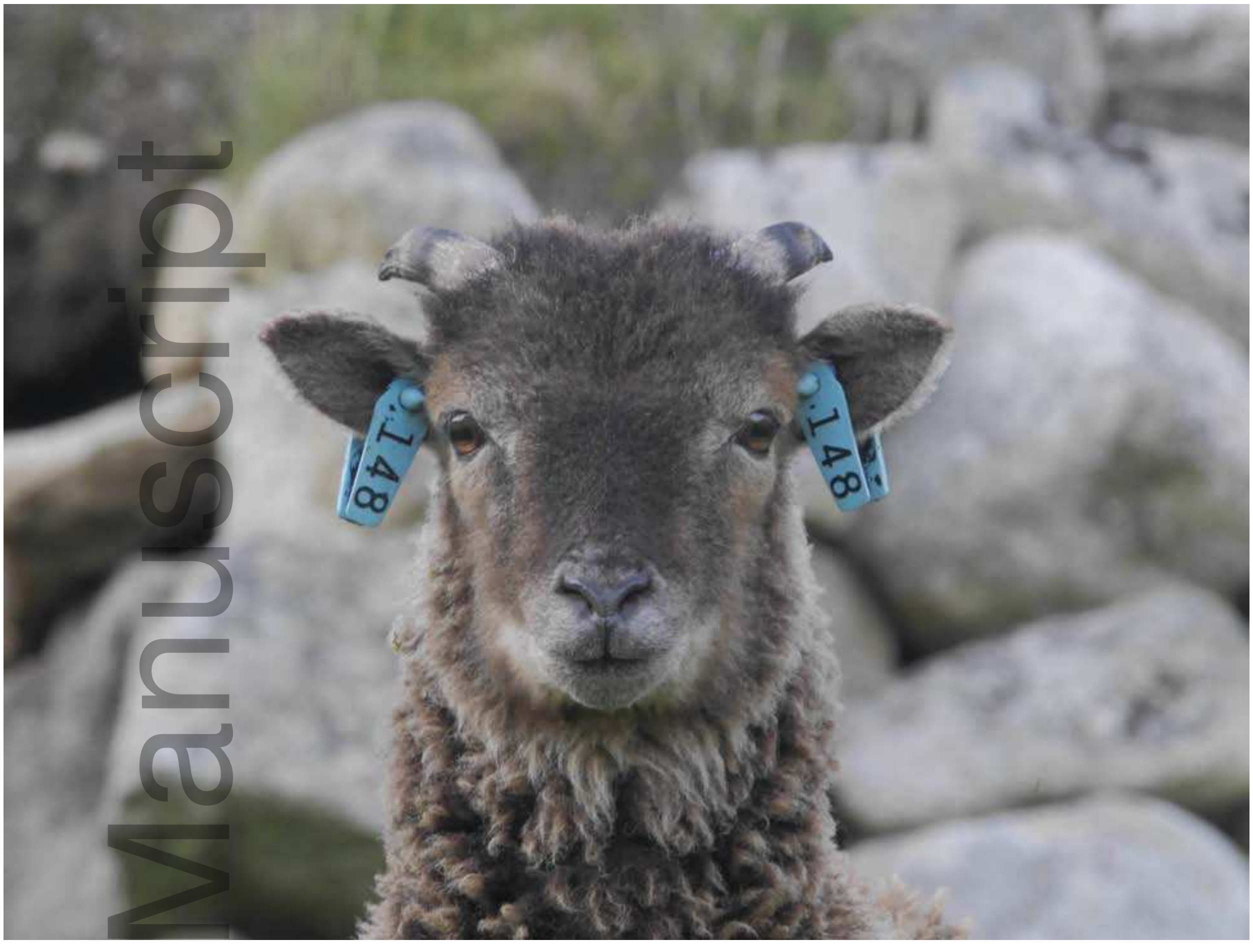
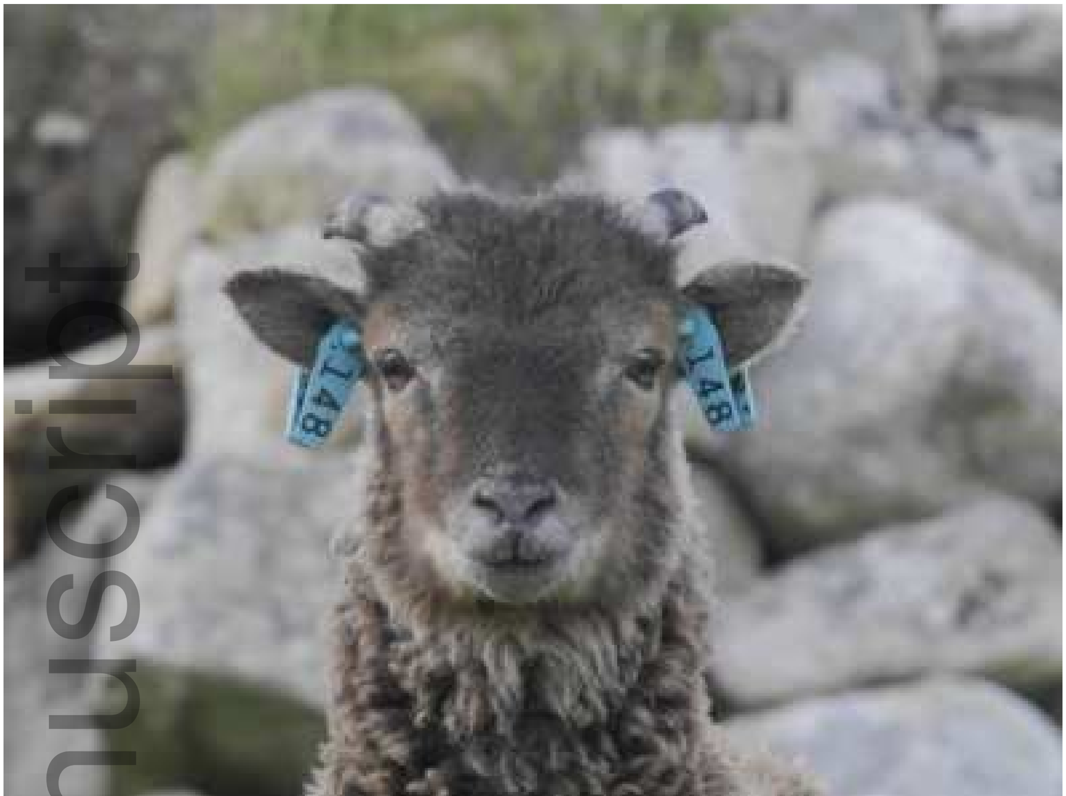
Figures

Figure 1. Watson et al. (2017) show that older female Soay sheep have longer telomeres than older males and some of this sex-difference may be driven by investment in horn growth in males. Young males (<1) with longer horns have shorter telomeres than males with shorter horns though this effect disappears

with age. Photo by Kara Dicks.

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