

## LETTER

## Ecology of arthritis

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## Abstract

Osteoarthritis (OA) is a widespread degenerative disease of skeletal joints and is often associated with senescence in vertebrates. OA commonly results from excessive or abnormal mechanical loading of weight-bearing joints ('wear-and-tear'), arising from heavy long-term use or specific injuries; yet, in the absence of injury, the aetiology of OA remains obscure. We show that poor nutritional conditions experienced by moose (*Alces alces*) early in life are linked to greater prevalence of OA during senescence as well as reduced life expectancy. Moreover, we also found a negative relationship between kill rate by wolves (*Canis lupus*) and prevalence of OA, suggesting a potential connection between senescence of prey and the population ecology of predator–prey systems. This association between OA and early malnutrition also provides a basis for explaining the observation in anthropology that OA became more prevalent in native Americans as their diet become poorer – the result of relying more on corn and agriculture and less on hunting and gathering.

## Keywords

Dynamics, early nutrition, moose, osteoarthritis, predator–prey, population, senescence, wolf.

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## INTRODUCTION

Osteoarthritis (OA) is a chronic and progressively crippling condition caused by degeneration of cartilage in the articulating surfaces of moveable joints (Greene 2001). Patterns of incidence for OA among certain lineages of humans and dogs suggest that OA may have a heritable, genetic basis (Van Sickle 1984; Valdes and Spector 2008). Nevertheless, OA is commonly believed to result primarily from 'wear-and-tear', or excessive or abnormal mechanical loading of joints (Greene 2001). Limited evidence suggests that low birth weight is associated with late-onset OA (Jordan *et al.* 2005). Nevertheless, in the absence of injury, the aetiology of OA is poorly understood (Stacy and Basu 2009). We show how malnutrition early in life is a significant risk factor for late-onset OA in a wild population of moose (*Alces alces*), how OA in moose is associated with kill rate by grey wolves (*Canis lupus*), and how these findings may relate to archaeological interpretation of OA prevalence in human skeletal remains.

## MATERIALS AND METHODS

We examined arthritis in the well-studied population of moose on Isle Royale, an island (544 km<sup>2</sup>) and U.S. National

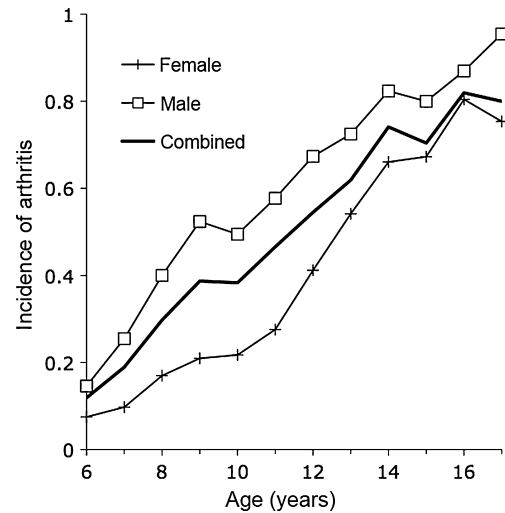
Park in Lake Superior, MI (USA). Between 1959 and 2008, population level fluctuated fourfold in response to weather, forage quantity and predation (Vucetich and Peterson 2004). The primary causes of death in this protected population were predation by grey wolves and malnutrition during winter (Peterson 1977). Throughout the 50-year study period, we found and necropsied the carcasses or skeletal remains of > 4000 moose from Isle Royale. For 1099 of these moose, we determined the sex, year of birth and death, age at time of death, and length of the metatarsal bone, an index of early nutritional health (Palsson and Verges 1952). For these moose, we also recorded the presence/absence of OA anywhere in the skeleton (Fig. 1).

Metatarsal length represents a quantitative index of perinatal nutrition, integrating the effects of forage abundance, weather, and predation risk on maternal condition and early growth of offspring. In ungulates, the metatarsus has a high growth priority early in life (Peterson 1977) and is approximately half its adult length at the time of a moose's birth. Metatarsal length in moose typically ceases growth by the age of 28 months, when the epiphyseal growth plate is fully calcified (Peterson 1977). For moose, in general, poor nutrition and slow early development are associated with small adult stature (Geist 1998: 239).

## RESULTS

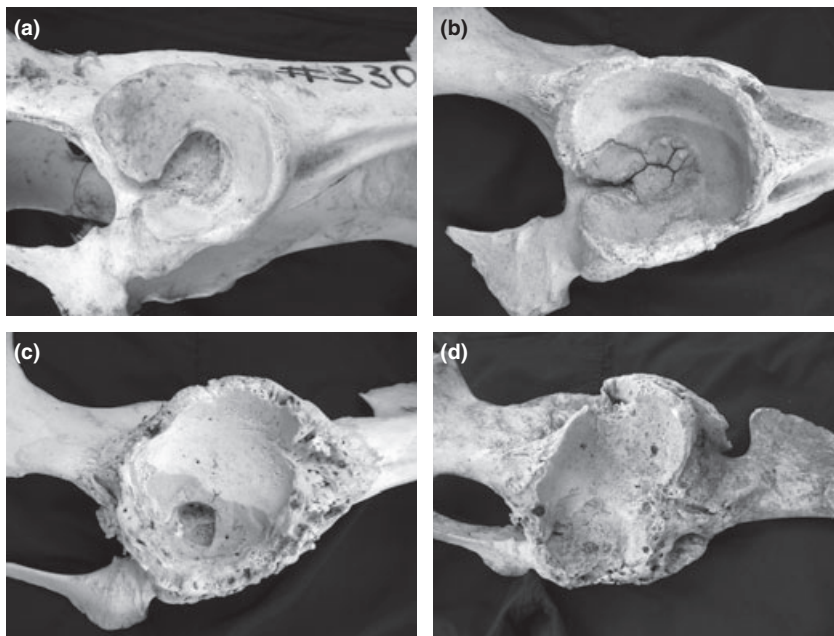
Osteoarthritis is rare in moose less than about 7 years old but increases thereafter with age (Fig. 2). As moose on Isle Royale approach maximum longevity (17 years for males and 21 years for females), virtually all exhibit OA, most commonly in the coxofemoral (hip) and lumbrosacral (posterior spine) joints, but also in other vertebrae. Higher age-specific incidence of OA among males is associated with males having lower age-specific survival rates than females (Hindelang and Peterson 2000).

To assess whether the presence of OA at the time of death was associated with nutritional conditions early in life, we fit our data to a logistic regression model (Fig. 3). That model indicates, for moose that survived to at least the age of 6 years, the odds of dying with OA are substantially higher for moose with shorter metatarsal bones. For a logistic model with terms for sex, age and metatarsal length, the best-fitting model was:  $P[\text{OA}] = \text{logit}[2.99 - 1.19I_{\text{male}} + 0.35(\text{age}) - 1.65 \times 10^{-2} (\text{ML})]$ , where  $P[\text{OA}]$  is the probability of dying with arthritis,  $I_{\text{male}}$  is an indicator variable (0 for females and 1 for males) and ML is the length (mm) of the metatarsal bone. For this model, all the coefficients were highly significant ( $P < 0.001$ ). More specifically, the smallest moose in this sample (i.e. < 33<sup>rd</sup> percentile) had a *c.* 32% greater odds of dying with arthritis

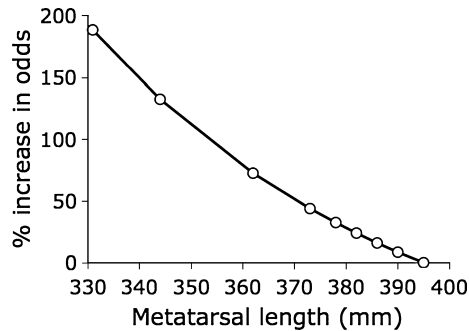


**Figure 2** Incidence of osteoarthritis (OA) in relation to sex and age for moose in Isle Royale National Park, Michigan. Most data points are based on > 55 observations (for all age and sex groups, minimum N = 22), in a composite sample collected from moose skeletons, 1959–2008.

than moose larger than the 66<sup>th</sup> percentile. Moreover, the odds for the very smallest moose in the population (i.e. < 10<sup>th</sup> percentile) dying with arthritis is 2.9 times greater



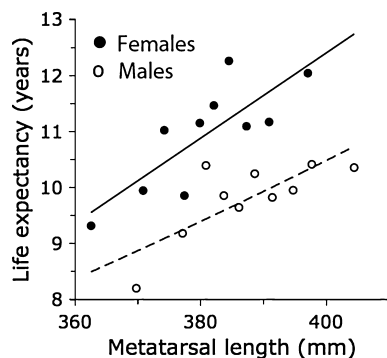
**Figure 1** Right pelvic (coxofemoral) joints of moose from Isle Royale, illustrating the progressive bony deterioration associated with osteoarthritis (OA). Normal joint capsule with open acetabular fossa (AF), which contains the ligament of the head of the femur (a), yields to closure of the AF, cartilage deterioration and dorsal eburation (bone-on-bone articulation) (b), then dorsal displacement of joint articulation from biomechanical weight-bearing forces (c) and, finally, continued displacement as a prelude to dislocation (d). The progression of pathology from (b) to (d) probably occurs in less than a year.



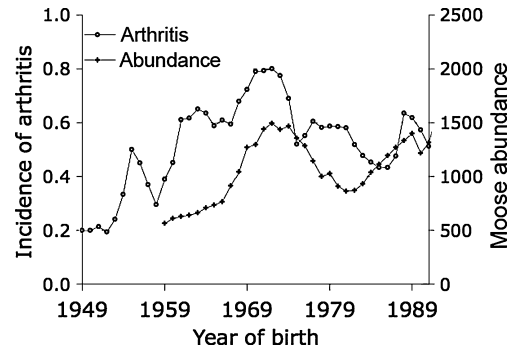
**Figure 3** The relative risk of a moose dying with osteoarthritis (OA) is increased for moose with relatively short metatarsal length ( $P < 0.001$ ), which is an index of early nutrition. The effect of metatarsal length is strongest for younger moose. The relative risk is in relation to moose with metatarsal length equal to the 90th percentile of measured lengths ( $n = 1099$ ).

than it is for the largest moose (i.e.  $> 90$ th percentile). The association between OA and early nutritional status is likely stronger than we describe, because metatarsal length is also a significant predictor of longevity (Gaillard *et al.* 2000; Fig. 4). That is, the smallest moose, with the greatest risk for late-onset OA, tend to die before they have a chance to develop OA.

At the population level, there is a degree of synchrony in prevalence of OA that probably reflects density-dependent fluctuations in the average nutritional welfare of the moose population. Maximum population density in the early 1970s coincided with the highest observed level of OA for moose



**Figure 4** The influence of metatarsal length (ML) on life expectancy for male (●) and female moose on Isle Royale (○). Life expectancy is conditioned on surviving to age 3 years. Each data point represents the mean ML for moose belonging to each ductile (every tenth percentile) of our sample. The lines are best-fit linear regressions, each of which are significant ( $P < 0.01$ ;  $R^2 > 0.58$ ). Analysis is based on skeletal remains of 1656 moose born between 1953 and 2004 for which we could estimate sex, metatarsal length and age at time of death (estimated by counting cementum lines in teeth).



**Figure 5** The incidence of osteoarthritis (OA) at the time of death for moose born during 1949–1989 (circles) and, for comparison, moose population abundance in the same years (crosses). High abundance leads to poor nutrition early in life, followed by high prevalence of OA late in life.

at least 7 years old that were born at that time (Fig. 5). Subsequently, as moose density declined over the next 15 years, the prevalence of OA among moose also declined.

To further assess the ecological significance of OA, we constructed several multiple, linear regression models that predicted kill rate (number of moose killed per day each winter from 1974 to 2008). The candidate variables were wolf abundance (*wolf*), moose abundance (*moose*), North Atlantic Oscillation (*NAO*, an index of winter severity), proportion of wolf-killed moose belonging to a vulnerable age class (calves or  $> 9$  years; *age structure*) and proportion of wolf-killed moose that died with OA (*arthritis*). Because each variable is plausibly an important predictor of kill rate (Post *et al.* 1999; Vucetich *et al.* 2002; Vucetich and Peterson 2004), we used the backward elimination procedure to generate a set of models. We compared these models on the basis of AICc,  $P$ -values and proportion of variation explained (Table 1). The best-performing model included only *wolf* and *arthritis*. More specifically, the best-performing model was  $kill\ rate = 0.50 + 7.1 \times 10^{-3}(wolf) - 0.35(arthritis)$ . The standardized regression coefficients for this model were  $\beta_{wolf} = 0.463$  ( $P < 0.01$ ) and  $\beta_{arthritis} = -0.298$  ( $P = 0.05$ ). This model also outperformed another that was not selected by the backward elimination algorithm, but seemed plausible (i.e. a model including only *wolf* and *age structure*; see Table 1). This analysis suggests that *arthritis* was a more important predictor of kill rate than *NAO*, *moose* and *age-structure*.

## DISCUSSION

If OA among these moose had been attributable to ‘excessive’ use or wear of joints, the widely appreciated cause of OA, then one would expect increased OA during years when moose travel farther to forage, as when moose

**Table 1** Performance of multiple, linear regression models predicting kill rate (kills per day during each winter between 1974 and 2008,  $n = 35$  years) from predictor variables including wolf abundance (*wolf*), moose abundance (*moose*), North Atlantic Oscillation (*NAO*, an index of winter severity), proportion of wolf-killed moose belonging to a vulnerable age class (i.e. calves or  $> 9$  years of age; *age-structure*) and proportion of wolf-killed moose that were arthritic (*arthritis*). Each model was estimated from the backward elimination procedure, except the last model was selected for comparison with the best-performing model\*. The predictors for each model are shown with  $P$ -values (in parentheses)

Predictors	SSR	AICc	$\Delta$	$R^2$
<i>Wolf</i> (0.01), <i>moose</i> (0.42), <i>NAO</i> (0.95), <i>age-structure</i> (0.18), <i>arthritis</i> (0.18)	0.540	-127.86	7.9	0.35
<i>Wolf</i> (0.01), <i>moose</i> (0.41), <i>age-structure</i> (0.78), <i>arthritis</i> (0.18)	0.541	-130.94	4.8	0.35
<i>Wolf</i> (0.01), <i>moose</i> (0.40), <i>arthritis</i> (0.12)	0.542	-133.81	1.9	0.35
<i>Wolf</i> ( $< 0.01$ ), <i>arthritis</i> (0.05)	0.555	-135.71	0.0	0.34
<i>Wolf</i> ( $< 0.01$ )	0.627	-134.00	1.7	0.25
<i>Wolf</i> ( $< 0.01$ ), <i>age structure</i> (0.33)	0.608	-132.52	3.2	0.27

SSR, residual sum of squares; AICc, Akaike's Information Criterion (corrected for small sample size);  $\Delta$ , delta-AICc (the difference between the model of interest and the best performing model in this set);  $R^2$ , proportion of variance explained by each model.

\*The best-performing model was  $kill\ rate = 0.50 + 7.1 \times 10^{-3}(wolf) - 0.35(arthritis)$ .

density is high and therefore food is scarce. Contrary to the 'wear-and-tear' hypothesis, Isle Royale moose were more likely to develop late onset OA if they experienced poor nutritional conditions early in life, as indicated by their metatarsal length (Fig. 3).

This physiological association also has ecological implications. Specifically, the debilitating effects of OA would inhibit a moose's ability to kick or dodge a lunging wolf, behaviours that are important for avoiding predation (Peterson 1977). Consequently, the incidence of OA is associated with the rate at which wolves kill moose on Isle Royale (Table 1). The coefficient associated with OA was negative, indicating that a higher prevalence of OA among wolf-killed moose is associated with lower kill rates. This relationship may indicate that kill rates tend to be low when arthritic moose predominate among wolf-kills and that higher kill rates are associated with wolves' ability to kill moose that are not crippled by arthritis. For example, winter kill rates tend to be higher during winters when calves comprise a larger proportion of wolves' winter diet. That is, winter kill rate and proportion of calves in the winter diet on Isle Royale are positively correlated for the 38-year period (1971–2008) during which such data are available ( $P = 4.5 \times 10^{-4}$ , R.O. Peterson & J.A. Vucetich, unpublished data). Alternatively, the unexpectedly negative relationship could have been caused by some unknown factor that would make wolves less efficient at killing moose during years when moose with OA were common.

In many systems, predation is complicated by predators' tendency to kill prey belonging to vulnerable age classes. Among moose, these vulnerable ages classes are calves and old adults (Peterson 1977). On Isle Royale, OA is an important reason why older moose on Isle Royale become vulnerable. These connections between nutrition early in life, late-onset arthritis and its association with kill rates

make already complicated circumstances even more complex. Age-structured predation would be complicated if the only challenge was to understand how kill rates alter and are altered by temporal fluctuations in prey age structure and to understand how conditions giving rise to a cohort's abundance will affect the abundance of senescent individuals many years later.

However, understanding age-structured predation also requires understanding whether a future cohort of older individuals will be more or less vulnerable than average. Our work suggests that the vulnerability of an older age class depends on the nutritional status those individuals experienced early in life (Fig. 3). These nutritional conditions would be affected by density-dependent competition for forage, winter severity and non-lethal effects of predation during the first year of life. Because the incidence of OA depends on all these factors, it is not surprising that the temporal fluctuation in incidence of OA appears lagged and only somewhat synchronized with the density of moose. In any event, OA is more than a mere proximate mechanism for underlying age-structured dynamics. Instead, our results suggest that for the Isle Royale system the ecologically dynamic nature of arthritis, and senescence in general, is likely responsible for substantial complexity. Such complexity is likely the norm for systems with age-structured predation.

Our results suggest that winter severity was not an important predictor of kill rates (Table 1). However, previous analyses suggest that winter severity was an important predictor of growth rate for the Isle Royale moose population (Vucetich and Peterson 2004). This apparent discrepancy may be attributable to differences in the response variable being analysed. Also, previous work concluded that kill rate was influenced by winter severity (indexed by NAO) by showing that NAO was associated

with pack size and that pack size was associated with kill rate (Post *et al.* 1999). Moreover, although some analyses suggest that moose density is an important predictor of kill rate (Vucetich *et al.* 2002), other analyses, focusing on other aspects of predation ecology suggest otherwise (Table 1; Post *et al.* 1999). Although it seems reliable to conclude that moose density, winter severity and incidence of arthritis are all important for understanding predation, our results and prior analyses suggest the difficulty of bringing all these pieces into resolution at the same time.

Our findings for the moose of Isle Royale also provide insight for understanding OA in humans. For example, the skeletal remains of Native Americans in the Florida peninsula exhibited an increase in OA over a 500-year period when their economies changed from primarily foraging on wild plants and animals to an increased reliance on farming as these societies became increasingly centred on Spanish missions (Larsen *et al.* 2001). A similar change was documented for a mid-continental population of native Americans about 1000 years ago as they came to rely increasingly on cultivated maize. For this population, OA increased 65% and that increase was attributed to increased mechanical joint stress from agricultural activities (Goodman *et al.* 1984). However, these populations were also characterized by growth-retarded children and young adults, and shortened life-spans suggested nutritional deficiencies early in life. These deficiencies and our findings suggest that nutritional deficiencies early in life may have played an important role in the increased incidence of OA of these populations.

Studies of humans and other animals have increasingly linked many chronic adult diseases with nutritional deficiencies early in life. This linkage is likely mediated through processes involving gene expression, cell energetics and hormone systems (Gluckman and Hanson 2006). Our study suggests the need to consider more carefully whether OA is like other late-onset pathologies, including heart disease, diabetes and hypertension that appear to have risk factors established early in life (Barker *et al.* 2002).

The apparent link between early nutrition and OA indicates that the aetiology of OA is more complex than commonly assumed and seems to involve connections among several levels of biological organization, including physiology, life histories, populations and communities. The complexity of these manifestations would seem to make predicting or understanding such dynamics an exercise in humility.

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