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Why are some species more commonly afflicted by arthritis than others? A comparative study of spondyloarthropathy in primates and carnivores

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Abstract

Spondyloarthropathy is a painful arthritic affliction of humans that also occurs in wild mammals. Important questions remain concerning the underlying causes of spondyloarthropathy in mammals, particularly regarding whether it is infectious in origin or driven by genetic predisposition and environmental stressors. Moreover, spondyloarthropathy has negative effects on host fitness, leading to potential conservation concerns if it impacts threatened species. Using a comparative data set on the prevalence of joint disease in 34 primate species and 100 carnivore species, we tested predictions involving the epidemiological correlates of spondyloarthropathy in wild mammals. Analyses revealed that 5.6% of primates and 3.6% of carnivores exhibited signs of spondyloarthropathy, with maximum incidence as high as 22% in great apes and 27% in bears. We tested whether prevalence of spondyloarthropathy increases with population density and group size, greater contact with soil, a slower host life history, increased ranging, dietary factors and body mass. We found general support for an effect of body mass, with larger bodied primates and carnivores exhibiting a higher prevalence of spondyloarthropathy. In addition, more threatened species experienced higher rates of spondyloarthropathy, with this association influenced by body mass and phylogeny. The effect of body mass could reflect that larger animals are exposed to more pathogens through greater consumption of resources, or that joints of larger bodied mammals experience greater biomechanical stresses, resulting in inflammation and activation of local joint infections.

Introduction

Wild mammals suffer from a wide variety of infectious diseases (Samuel *et al.*, 2001; Williams & Barker, 2001). In nonhuman primates, for example, more than 400 infectious organisms have been documented in free-ranging animals (Nunn & Altizer, 2005). These parasites exhibit a remarkable diversity of transmission modes, including vector, sexual and faecal transmission, and some of these pathogens, such as Ebola haemorrhagic fever, have been responsible for a rapid decline in primate populations (Walsh *et al.*, 2003; Leroy *et al.*, 2004). Noninfectious diseases are also common in wild animals, including diseases resulting from ingestion of poisons, exposure to pollution and developmental abnormalities (Fairbrother *et al.*, 1996; Deem *et al.*, 2001). Recent comparative studies have improved understanding of specific diseases that occur in wild animals and the factors that drive these patterns (e.g. Nunn & Altizer, 2006). In addition to improving basic knowledge concerning disease risks, this knowledge could be important for conservation planning, especially for diseases that

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reduce the ability of a population to recover from human-induced population declines (Wallis & Lee, 1999; Woodroffe, 1999; Cleaveland *et al.*, 2002).

In this paper, we investigate the phylogenetic distribution of an arthritic joint disease in primates and carnivores. This disease – spondyloarthropathy – defines a subgroup of inflammatory arthritic conditions that in humans includes ankylosing spondylitis, Reiter's syndrome or reactive arthritis, psoriatic arthritis and the arthritic conditions associated with inflammatory bowel disease (McEwen *et al.*, 1971; Rothschild, 1982; Kelly *et al.*, 1985; Katz, 1989; McCarty, 1989; Resnick, 2002). Spondyloarthropathy is characterized by erosive joint disease, ossification of sites of tendon, ligament and joint capsule insertion (enthesial bone formation), and a tendency for fusion of the spine and sacroiliac regions (McEwen *et al.*, 1971; Rothschild, 1982; Woodrow, 1985; Rothschild & Woods, 1991; Rothschild & Martin, 1993; Resnick, 2002). Possible causative agents of spondyloarthropathy include *Salmonella*, *Shigella*, enteropathic *Escherichia coli*, *Yersinia*, *Camplyobacter*, *Chlamydia* and *Mycoplasma* (Granfors *et al.*, 1988). The distribution of spondyloarthropathy in humans might also have an autoimmune component, perhaps related to molecular mimicry and shared antigens between the micro-organisms and human antigens. Reported frequencies of spondyloarthropathy in humans range from 1% to 8% and could result from exposure to infectious agents that cause diarrhoea (Rothschild & Rothschild, 1993).

Spondyloarthropathy has been documented in a wide variety of mammals, including bears (Rothschild *et al.*, 1993), canids (Rothschild *et al.*, 2000) and primates (Rothschild & Woods, 1989, 1991; Rothschild, 1993; Rothschild & Woods, 1996). This broad phylogenetic distribution provides a means to investigate the behavioural, ecological and life-history correlates of spondyloarthropathy. Humans afflicted with this disease experience substantial costs that are likely to impact fitness, including painful locomotion, vision loss and urethritis. These effects would be exacerbated in wild animals that lack opportunities for receiving medical care, thus reducing ambulation, retarding growth and increasing irritability among afflicted individuals (e.g. Neiffer *et al.*, 2002).

We use a new comparative database and phylogenetic comparative methods to test predictions involving links between the prevalence of spondyloarthropathy and characteristics of primates and carnivores. We focus on predictions that are consistent with an infectious causation of spondyloarthropathy in wild populations, with the goal to identify host traits involved with transmission that are responsible for the distribution of this disease across mammalian species. The samples that we used were skeletons in museum collections, with prevalence referring to the percentage of individuals that exhibit symptoms of spondyloarthropathy based on direct observation of these skeletal remains.

We tested the following predictions:

1. Because social contact is a key predictor of parasite establishment in epidemiological models (Anderson & May, 1991), we predict that animals living at higher densities, in larger populations and in larger social groups exhibit a higher incidence of spondyloarthropathy if this disease is spread through an infectious organism (e.g. Møller *et al.*, 1993; Arneberg *et al.*, 1998; Nunn *et al.*, 2003a).
2. Diet may influence the risk of acquiring infectious agents that lead to spondyloarthropathy. Consumption of greater amounts of food resources (e.g. in folivorous primates, Moore, 2002; Nunn *et al.*, 2003a; Nunn & Altizer, 2006) or animal prey could increase exposure to parasites and pathogens. In addition, animals that are larger in body mass require more resources, and are therefore more likely to incidentally ingest parasites while consuming food. Thus, we predict that prevalence of spondyloarthropathy increases with body mass (Moore & Wilson, 2002), and with increases in consumption of leaves (primates) or animal prey (carnivores). Spondyloarthropathy could also increase with body mass if the bones and joints of larger bodied mammals experience greater stresses caused through locomotion or other activities, thus resulting in inflammation and further activation of local joint infections.
3. Life-history traits are another key variable in epidemiological models, with lower mortality rates increasing the basic reproductive number (R_0) of a parasite and thus increasing the probability that it becomes established in a host population (Anderson & May, 1991). We therefore predict that prevalence of spondyloarthropathy increases with life-history traits involving longevity, age at first reproduction and the interbirth interval. These patterns should be found independently of the effects of body mass.
4. Animals that more commonly use the ground could experience greater contact with faecal contamination, including infectious organisms that have been proposed as causative agents of spondyloarthropathy. Thus, we predicted that prevalence is higher in terrestrial primates and carnivores, when compared with prevalence in species that use arboreal substrates to a greater extent. In addition, extensive contact with water in aquatic carnivores could increase exposure to disease (Harvell *et al.*, 1999; Nunn *et al.*, 2003b; Poulin & Morand, 2004).
5. Previous authors proposed that spondyloarthropathy could be transmitted sexually (Rothschild *et al.*, 1993; Rice & Handsfield, 1999). Thus, we predict that measures of mating promiscuity will correlate with prevalence of spondyloarthropathy across species.

As noted above, spondyloarthropathy and similar conditions could represent an unrecognized threat to endangered species. Thus, in addition to testing specific predictions, we also investigated whether primate and

carnivore species that are listed as threatened in the IUCN Red List (Hilton-Taylor, 2002) exhibit higher prevalence of spondyloarthropathy.

Materials and methods

Skeletal data set

The macerated (lye treated to remove the soft tissue) complete post-cranial skeletons were surveyed macroscopically for visible evidence of articular and periarticular joint pathology. Each skeletal element of all sampled individuals was carefully examined by B. Rothschild, R. Woods and C. Rothschild, with concurrence in identifying lesions as representing an erosion, and ruling out artefacts such as post-mortem trauma (e.g. 'drawer damage', a term used to describe lesions of a questionable origin; these are probably attributable to damage incurred during preparation and/or storage of the skeleton). Discrepancies have been less than one in 300 between individuals scoring specimens (Rothschild & Martin, 2006). For purposes of this study, articular surfaces were treated as missing if artefactual damage precluded demonstration of joint disease.

The entire data set involved skeletons examined from collections of 35 museums (see Appendix). Here, we investigate patterns of spondyloarthropathy prevalence (per cent with disease) in a subset of the total data set involving primates and carnivores. Individuals came from wild and captive settings, but previous work revealed no significant differences between wild and captive animals in subsets of the data set used here (e.g. Rothschild & Rothschild, 1996; Rothschild *et al.*, 2000). We calculated prevalence based on the entire sample of males and females to maximize sample size, although we acknowledge that studies have revealed a mixture of results regarding whether sex differences in prevalence exist (Rothschild *et al.*, 1997; Rothschild & Ruhli, 2005a, b). We checked for an association between body mass and sample size because – based on initial results – we were concerned that larger bodied animals are more likely to have spondyloarthropathy, and because afflicted individuals might be more likely to be taken from populations (e.g. if they are weaker). Such a bias would be indicated by a positive association between body mass and sample size and could result in elevated prevalence estimates in larger bodied hosts. However, we found no significant association between these variables in primates ($b = -0.14$, $t_{31} = -1.32$, $P = 0.20$), and a significant negative association in carnivores ($b = -18.8$, $t_{78} = -3.03$, $P = 0.003$). This negative association probably reflects that larger bodied species exist at lower abundance in the wild and in captivity and so are underrepresented in museum collections.

Spondyloarthropathy is typically described as a disorder with reactive new (enthesial) bone formation, predominantly pauciarticular peripheral joint involvement (involving less than five joints) and frequent axial (spine and sacroiliac) joint disease (Bywaters, 1960; Martel, 1968; McEwen *et al.*, 1971; Rothschild, 1982; Rothschild & Woods, 1991; Rothschild & Martin, 1993; Resnick, 2002). Although the classical 'bamboo spine' of ankylosing spondylitis is difficult to misdiagnose in humans, this finding is lacking in most patients with spondyloarthropathy. Inflammatory enthesial bone formation is considered a 'clinical hallmark' for spondyloarthropathy (Ball, 1971; Niepel & Sittaj, 1979; Jacobs, 1983). Although individuals with sacroiliac or spinal diarthrodial joint erosion or fusion are easily recognizable as having spondyloarthropathy, such findings may be lacking in more than half of humans affected by this disease (Rothschild & Martin, 1993). Similar patterns have been found in the zoological record (Rothschild & Martin, 1993). Recognition of spondyloarthropathy in the absence of sacroiliac/spine involvement and distinguishing it from other erosive disorders, such as rheumatoid arthritis, is the challenge. Spondyloarthropathy is herein applied as a generic term inclusive of several disorders which typically, but not invariably, affect the axial joints (spine or sacroiliac joints). Documented skeletal features characteristic of spondyloarthropathy include marginal and subchondral localization of erosions, para-erosional new bone formation, preservation of residual para-erosional trabeculae, enthesial calcification, zygoapophyseal joint fusion and erosions, costovertebral fusion and erosions, syndesmophytes, sacroiliac erosions and fusion, erosion of anterior-superior and anterior-inferior vertebral margins, pauciarticular pattern, limited distribution (fewer joints than in rheumatoid arthritis, even in those with polyarticular disease) and presence of patterns (including arthritis mutilans, all joints on a single digit and distal interphalangeal joint predominant, Rothschild & Woods, 1991).

Although identification of the particular variety of spondyloarthropathy is predicated on fulfillment of specific criteria, not all individuals can be categorized. The term 'undifferentiated spondyloarthropathy' is therefore applied, and this group of cases occurs as frequently as reactive arthritis (Boyer *et al.*, 1990; Kahn & van der Linden, 1990) and actually presents with an indistinguishable pattern of joint inflammation (Mielants *et al.*, 1989; Mielants & Veys, 1990). Reiter's syndrome or reactive arthritis is a form of spondyloarthropathy (Rothschild, 1982; Arnett, 1987; Resnick, 2002), which, in genetically predisposed individuals, frequently complicates infectious agent diarrhoea (e.g. food poisoning) and genital infections. *Salmonella*, *Shigella*, enteropathic *Escherichia coli*, *Yersinia*, *Camplyobacter* and *Chlamydia* and perhaps *Mycoplasma* have been implicated (Granfors *et al.*, 1988).

Comparative data on primates and carnivores

The dependent variable in our analyses was the percentage of specimens (prevalence) that showed evidence for

spondyloarthropathy. We excluded a species if fewer than 10 specimens had been examined, as this could result in poor estimates of prevalence. This resulted in the exclusion of one primate species and 33 carnivore species. Following exclusion, the average number of samples ranged from 12 to 237 for primates ($n = 34$ species, mean sample size per species = 75.0, standard deviation = 58.2), and 10–164 for carnivores ($n = 100$ species, mean sample size per species = 53.4, standard deviation = 40.5). We transformed prevalence (a proportion) by taking the arcsin of the square root (Sokal & Rohlf, 1995). For some analyses, statistical assumptions were violated and could not be rectified through data transformation; we therefore also report nonparametric statistics (the Spearman rank order correlation coefficient).

We acquired data on body mass for primates (Smith & Jungers, 1997) and carnivores (Gittleman, 1985), along with data on life-history traits involving longevity, interbirth interval and age at first reproduction for primates (Ross & Jones, 1999), and longevity and age at sexual maturity for carnivores (Gittleman, 1986, 1989). All of the carnivore data were updated and verified from recent publications (Kitchener, 1991; Creel & MacDonald, 1995; Nowell & Jackson, 1996; Mills & Hofer, 1998; Creel & Creel, 2002; Sunquist & Sunquist, 2002; Macdonald & Sillero-Zubiri, 2004). For primates, data on home range size, day range length, group size, population density and diet (percentage of leaves and dichotomous categorization of fruit vs. leaves) were taken from a previous compilation of comparative data (Nunn & van Schaik, 2001). Diet for carnivores was examined using both the percentage of meat in the diet and with a dichotomous categorization of meat vs. nonmeat (Gittleman & Harvey, 1982; Gittleman, 1986, 1989). Population size was quantified as population density multiplied by geographic range size (Nunn *et al.*, 2003a). As a measure of mating promiscuity in primates, we used relative testes mass because this variable correlates with sperm competition and thus female mating promiscuity (Harcourt *et al.*, 1981). We also used data on discrete categories of the number of mating partners from previous comparative studies of primates (Nunn *et al.*, 2000; Nunn, 2002) and data on mating systems for carnivores (Gittleman, 1989). The presence of sexual swellings in primates was taken from Nunn (1999). Substrate use in primates was coded on a three-part ranked scale: primarily use of the trees (arboreal), mixture of trees and ground and primarily use of the ground (terrestrial, based on data on substrate and habitat in Nunn & van Schaik, 2001). For carnivores, we also included a fourth category for aquatic carnivores (Gittleman, 1986, 1989; Bininda-Emonds & Gittleman, 2000), predicting highest levels of disease risk in these species (Nunn *et al.*, 2003b); we also re-ran analyses excluding aquatic species or including them among terrestrial species. Data on population density and diet for carnivores came from Gittleman & Harvey (1982) and Wrangham *et al.* (1993). Finally, for both sets of species, we used data on threat levels from the IUCN Red List (Hilton-Taylor, 2002). We created a dichotomous variable, with unlisted and low-risk/not-threatened combined into a 'low'-risk category, and vulnerable, endangered and critically endangered into a 'high'-risk category (which also included *Mustela nigripes*, listed as extinct in the wild). All continuous variables were $\log_{10}$-transformed prior to analysis.

Comparative analyses and statistical tests

We analysed the data using standard statistical tests that treated each species value as statistically independent (nonphylogenetic tests), and then repeated the analyses using independent contrasts (Felsenstein, 1985) based on phylogenetic relationships in primates (Purvis, 1995) and carnivores (Bininda-Emonds *et al.*, 1999). Independent contrasts were calculated using the computer program CAIC (Purvis & Rambaut, 1995). We tested the assumptions of CAIC, as recommended by Garland *et al.* (1992) and in the CAIC manual. For all continuous, nondisease traits, we used log-transformed data and branch lengths.

For both the phylogenetic and nonphylogenetic tests, we used multiple regression to identify predictor variables that best account for variation in percentage of specimens that were afflicted with spondyloarthropathy. We performed three main sets of analyses when testing predictions. First, we conducted 'focused' tests, in which we investigated whether individual host traits accounted for variation in the prevalence of spondyloarthropathy. We repeated these analyses with and without controlling for body mass.

Second, we addressed the possibility that multiple host traits influence spondyloarthropathy by analysing the data with a stepwise multiple regression model that included the following traits: body mass, longevity, population density, group size (primates only), home range size, per cent leaves or meat, residual testes mass (primates) or mating system (carnivores), substrate use and population size (carnivores). We used a forward stepwise procedure with all variables initially removed, sequentially adding variables with significance levels of $P < 0.1$ and removing entered variables when significance exceeded this P-value (i.e. a mixed model). To control for correlations between body mass and other host traits, body mass was forced into the multiple regression model at all steps. We also checked for collinearity among the predictor variables using variance inflation factors (VIFs), with VIF > 10 indicating the existence of collinearity (Petraitis *et al.*, 1996). For primates, no variables exhibited VIFs > 10, although body mass approached this cut-off (VIF = 9.05 for nonphylogenetic tests and 5.15 for a contrasts analysis). For carnivores, however, two variables had VIFs exceeding 10 in nonphylogenetic tests (population density and

population size). Collinearity seemed to be less of an issue for contrasts analyses in carnivores, with all VIFs well below 10. Substrate use was treated as a continuous variable in the stepwise model (three or four-categories, see above), with increasing use of the ground (or water) scored as a higher value in the classification. We repeated the stepwise procedure with all variables entered in the model to check whether similar results were obtained.

Finally, we tested whether the prevalence of spondyloarthropathy correlated with host threat level. We repeated analyses that controlled for variables found to be significant in the analyses of host traits. In phylogenetic tests, we treated threat level as a continuous variable, with higher threat levels indicated by larger values. We also repeated analyses of threat status and other discrete variables using the 'Brunch' algorithm in CAIC, which investigates whether evolutionary transitions in a discrete variable are associated with consistent changes in continuous variables.

Analyses were conducted with the significance level $\alpha < 0.05$. Because we formulated *a priori* directional predictions for the effects of host traits on the prevalence of spondyloarthropathy, we used directed tests (Rice & Gaines, 1994) for investigating predictions. Directed tests allocate a disproportionate probability under the null hypothesis to the tail of the distribution in the predicted direction (γ), while retaining a smaller probability in the opposite tail to detect unexpected deviations opposite to predictions ($\delta < \gamma$). Directed tests are subject to the constraint that $\delta + \gamma = \alpha$. We followed the guidelines in Rice & Gaines (1994) by setting γ/α to 0.8, giving values of $\gamma = 0.04$ and $\delta = 0.01$. For the effect of threat level, we had no *a priori* hypotheses and so used two-tailed tests.

Results

General patterns

After removing species with samples of fewer than 10 individuals, the mean prevalence of spondyloarthropathy in the samples was 5.6% in primates (standard deviation = 7.33) and 3.6% in carnivores (standard deviation = 5.35). Great apes showed the highest prevalence among primates (mean of 21.5% among four species), with *Macaca arctoides* and *Theropithecus gelada* also exhibiting high prevalence (18% and 17% respectively). Among carnivores, highest prevalence was found among the bears, *Ursus arctos*, *Ursus maritimus* and *Helarctos malayanus* (26.7%, 20% and 25% respectively). Values of 15% or greater were also found in *Vulpes zerda* and *Crocuta crocuta*.

Spondyloarthropathy in primates

Focused tests using species values revealed that the majority of the primate traits were statistically significant (Table 1). Counter to predictions, population density was negatively associated with prevalence of spondyloarthropathy, with this result statistically significant in a

Table 1 Results from primates†.

	Nonphylogenetic				Phylogenetic (independent contrasts)			
	n	Bivariate test	Include mass	Mass significant?	*n*	Bivariate test	Include mass	Mass significant?
Body mass (female)‡	33	5.07***	n/a	n/a	32	3.14**	n/a	n/a
Longevity‡	30	3.06**	0.23	Yes	29	0.68	−0.81	Yes
Age first reproduction	27	2.99**	−0.33	Yes	26	1.00	−0.80	Yes
Interbirth interval	28	2.60**	−0.36	Yes	27	1.01	−0.36	Yes
Population density‡	34	−2.60*	−0.38	Yes	33	−0.90	0.14	Yes
Group size‡	34	2.22*	1.09	Yes	33	1.39	1.21	Yes
Population size	31	−2.15	−1.44	Yes	30	−2.17	−2.09	Yes
Home range‡	32	2.83**	0.62	Yes	31	0.71	−0.63	Yes
Day range	29	0.77	0.17	Yes	28	−1.21	−1.38	Yes
Diet (per cent leaves)‡	31	1.45	−1.59	Yes	30	1.53	0.10	Yes
Residual testes mass‡	27	0.91	1.25	Yes	26	−0.24	0.33	Yes
Mating partner number§	25	0.21	0.52	Yes	24	−0.13	−0.21	Yes
Substrate use‡,§	34	7.04**	2.11	Yes	33	1.91*	1.48	Yes
Threat status§	34	2.85**	1.53	Yes	33	1.05	0.03	Yes

†For most cells, table shows *t*-statistics, with the direction of the effect indicated by the sign of the statistic. Significance levels: *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, in all cases (except threat status) using directed tests (see text). For mating partner number and substrate use in nonphylogenetic tests, table shows *F*-statistics. For these analyses, monogamous and arboreal species tended to have lower prevalence of spondyloarthropathy (significant only for substrate).

‡Variable included in multivariate model.

§Treated as continuously varying in phylogenetic results presented in this table. See Table 2 for analyses that used the Brunch algorithm for phylogenetic analysis of discrete traits.

directed test. Day range length, percentage of leaves in the diet and residual testes mass were not significant. Of these variables, body mass explained the greatest variance in the prevalence of spondyloarthropathy ($r^2 = 0.44$, Fig. 1).

Given that most of the variables are highly correlated with body mass, many of the significant results in Table 1 could reflect a confounding effect of body mass. The negative association obtained for population density is further consistent with this possibility, as density correlates negatively with mass in mammals (Damuth, 1981). Thus, inclusion of body mass as a covariate eliminated all of the significant results, with only body mass emerging as statistically significant (Table 1). The predominant effect of body mass was confirmed in a nonparametric test (Spearman's $r_s = 0.61$, $P < 0.0001$), and body mass remained significant after excluding the great apes ($F_{1,27} = 2.43$, $P < 0.05$, directed test, see also Fig. 1).

In phylogenetic tests using independent contrasts, only body mass (Fig. 1) and substrate use were statistically significant (Table 1), with species that use the ground having higher prevalence of spondyloarthropathy. Analyses using the Brunch algorithm produced non-significant results (Table 2). As in nonphylogenetic tests, body mass was significant in all focused tests when it was included as a covariate, and body mass remained significant in a nonparametric analysis of independent contrasts ($r_s = 0.48$, $P < 0.01$).

In the multiple stepwise model, only body mass emerged as statistically significant in nonphylogenetic tests ($F_{1,19} = 13.6$, $P < 0.01$). In phylogenetic tests using the stepwise model, both body mass and substrate use were statistically significant, with larger bodied primates and those that make greater use of the ground for locomotion exhibiting higher prevalence of spondyloarthropathy (body mass: $b = 8.69$, $F_{1,18} = 4.07$, $P < 0.05$; substrate: $b = 4.62$, $F_{1,18} = 3.71$, $P < 0.05$). Results here differ from Table 1, with a smaller number of contrasts available for the stepwise model because information was unavailable for some variables in some species. Thus, results for substrate use in primates are inconsistent across analyses, when compared with a more consistent pattern found with body mass in all analyses.

Table 2 Analysis of discrete variables in primates using the Brunch algorithm.

Variable	Number of contrasts	Mean contrast	*t*-statistic
Mating partner number	8	−0.04	−0.07
Diet (fruit vs. leaves)	6	0.42	0.57
Substrate	6	0.98	1.71†
Sexual swellings	3	−1.00	−0.74
Threat categories	5	0.52	0.48

†$P < 0.10$ in directed test. No result is statistically significant at $P < 0.05$.

Spondyloarthropathy in carnivores

In focused tests using carnivore species values, body mass again emerged as the most significant predictor of the prevalence of spondyloanthropathy (Fig. 2). As with results obtained in primates, other variables were statistically significant when body mass was not included as a covariate, including life-history traits, home range size and day range length (Table 3). Spondyloarthropathy was negatively associated with population density and also overall population size, again reaching significance in a directed test. Substrate use was nonsignificant (Table 3), even when aquatic species were lumped with terrestrial ones ($F_{2,97} = 0.14$, $P = 0.87$) and when aquatic species were excluded from the analysis ($F_{2,86} = 0.17$, $P = 0.85$). After controlling for body mass, all of these significant results disappeared. Body mass again explained a high proportion of the variance in prevalence of spondyloarthropathy ($r^2 = 0.42$), and body mass remained significant in a nonparametric test ($r_s = 0.62$, $P < 0.0001$).

In phylogenetic tests using independent contrasts, body mass was significant in 50% of the tests in which

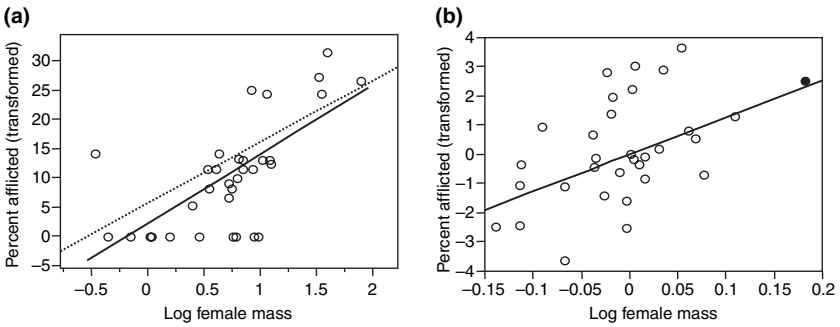

Fig. 1 Body mass and prevalence of spondyloarthropathy in primates. Plots show results for (a) species values and (b) independent contrasts. Prevalence values were transformed by taking the arc-sin square root of the percentage of animals showing signs of spondyloarthropathy. The dashed line in (a) shows results after excluding species for which spondyloarthropathy was not documented. Results remained significant ($t_{21} = 4.13$, $P = 0.0003$). The filled circle in (b) represents an outlier identified by mahalanobis distance in JMP (vers. 5.0.1). The line excludes this data point and remains significant ($t_{30} = 2.65$, $P = 0.008$).

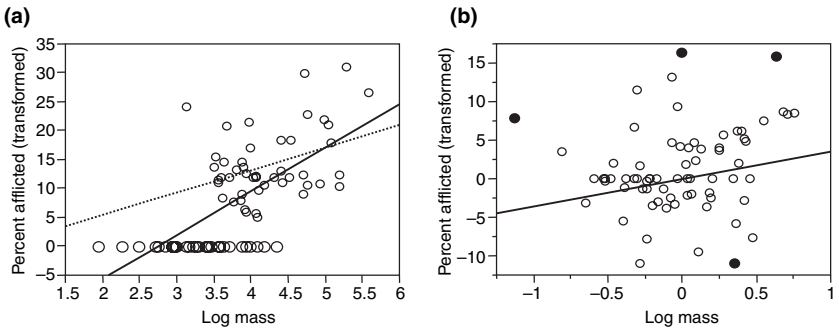

Fig. 2 Body mass and prevalence of spondyloarthropathy in carnivores. Plots show results for (a) species values and (b) independent contrasts. Prevalence values were transformed by taking the arc-sin square root of the percentage of animals showing signs of spondyloarthropathy. The dashed line in (a) shows results after excluding species for which spondyloarthropathy was not documented. Results remained significant ($t_{45} = 2.63$, $P = 0.007$). The filled circles in (b) represent four outliers identified by mahalanobis distance in JMP (vers. 5.0.1). Results were significant when these outliers are excluded ($t_{65} = 2.16$, $P = 0.02$), but the variance explained is low ($r^2 = 0.06$).

Table 3 Focused results for carnivores in nonphylogenetic and phylogenetic tests.

	Nonphylogenetic				Phylogenetic (independent contrasts)			
	n	Bivariate test	Include mass	Mass significant?	*n*	Bivariate test	Include mass	Mass significant?
Body mass (female)‡	80	7.59***	n/a	n/a	70	1.48	n/a	n/a
Longevity‡	76	4.08***	−0.19	Yes	67	2.56**	2.12*	No
Sexual maturity (female)	72	4.50***	−0.12	Yes	64	3.20**	2.78**	No
Interbirth interval	72	3.90***	−0.67	Yes	62	1.16	−0.61	Yes
Population density‡	59	−3.65**	0.78	Yes	53	−1.58	−0.21	No
Population size‡	58	−3.68**	0.34	Yes	52	−2.48*	−1.54	No
Home range‡	34	4.94***	0.61	Yes	31	−0.07	−1.17	Yes
Day range	22	2.19*	−0.44	Yes	21	1.68	1.06	No
Diet (per cent meat)‡	66	−0.90	−1.69	Yes	60	−0.38	−0.89	Yes
Mating system‡,§	46	−0.46	−1.55	Yes	41	0.53	−0.09	Yes
Substrate use‡,§	100	0.27	0.72	Yes	87	−1.30	−2.39*	Yes
Threat status§	97	3.45***	0.91	Yes	84	0.72	0.51	Yes

†For most cells, table shows *t*-statistics, with the direction of the effect indicated by the sign of the statistic. Significance levels: *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, in all cases (except threat status) using directed tests (see text). For substrate use in nonphylogenetic tests, table shows *F*-statistics.

‡Variable included in multivariate (stepwise) model.

§Treated as continuously varying in phylogenetic results presented in this table. See Table 4 for analyses that used the brunch algorithm for phylogenetic analysis of discrete traits. Mating system was treated as a dichotomous variable that compared monogamous and nonmonogamous species of carnivores.

Table 4 Analysis of discrete variables in carnivores using the Brunch algorithm†.

Variable	Number of contrasts	Mean contrast	*t*-statistic
Mating system	2	2.70	1.39
Substrate	18	0.43	0.22
Diet codes	13	1.17	0.88
Threat categories	17	1.46	1.56

†No result is statistically significant at $P < 0.05$.

it was included as a covariate. However, body mass on its own emerged as a significant predictor of spondyloarthropathy only when four outliers were excluded ($F_{1,65} = 4.68$, $P < 0.05$, directed test, Fig. 2). Body mass was also significant in a nonparametric test with all contrasts included ($r_s = 0.22$, $P < 0.05$). Two life-history variables remained significant even when body mass was included as a covariate (longevity and sexual maturity). Substrate use was also statistically significant when body mass was included in the test, but in a direction opposite to predictions (i.e. higher prevalence in more arboreal species). As with nonphylogenetic tests, classification of aquatic species in different ways had little effect on results involving substrate use, and Brunch tests involving transitions in discrete traits (Purvis & Rambaut, 1995) were also nonsignificant (Table 4).

In the stepwise multiple regression model that analysed species values, body mass emerged as the only

variable entered in the model when all variables were removed ($F_{1,24} = 28.6$, $P < 0.0001$), although percentage of meat (a negative association) and substrate were included in the final model when all variables were initially entered in the stepwise regression. As noted in the Materials and Methods, however, VIFs indicated the potential for collinearity in this full model for nonphylogenetic tests. A model that included only these three variables produced significant effects for all variables, although percentage of meat in the diet was opposite to predictions (mass: $t_{59} = 8.17$, $P < 0.0001$; per cent meat: $t_{59} = -2.59$, $P < 0.05$; substrate codes including aquatic species: $t_{59} = 2.08$, $P < 0.05$). To make the analysis more comparable with the analysis of primates, we excluded species listed as fully or partly aquatic, and this produced similar results. In the stepwise regression analysis of independent contrasts, longevity was found to be a better predictor of spondyloarthropathy than body mass (longevity: $F_{1,22} = 5.31$, $P < 0.05$; mass: $F_{1,22} = 1.65$, $P = 0.13$; mass was forced into the stepwise model). Results were again unstable, however, with population density and home range area included (but not significant) when initiating the multiple regression model with all variables included.

Spondyloarthropathy and host threat status

In a final set of tests, we investigated whether spondyloarthropathy correlates with threat levels in primates and carnivores. In a nonphylogenetic analysis of the primate data using ANOVA, more threatened primates exhibited higher prevalence of spondyloarthropathy (Fig. 3), but this pattern disappeared after controlling for body mass and/or phylogeny (Tables 1 and 3). We also found a positive association between body mass and threat level (Crunch test: $t_{32} = 2.18$, $P < 0.05$, two-tailed; nonsignificant in Brunch, but with four of five transitions in threat status associated with increased body mass). These results suggest that the significant results in nonphylogenetic analysis of threat level were driven by the confounding effect of body mass. A nearly identical effect was seen in carnivores, with threat status significant in the bivariate test (Fig. 3), but not after controlling for body mass and/or phylogeny (Table 3 and 4). Threat status was again associated with body mass, with body mass increasing in 11 of 15 transitions to higher threat status (Brunch test: $t_{14} = 2.23$, $P < 0.05$, two-tailed).

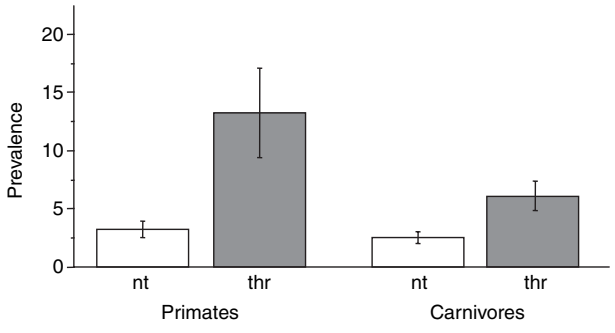

Fig. 3 Host threat status and prevalence of spondyloarthropathy. Bars represent prevalence of spondyloarthropathy in primates and carnivores in relation to dichotomous classifications of threat status. nt = not threatened, thr = threatened (vulnerable, endangered or critically endangered).

Discussion

The analyses presented here reveal a strong association between body mass and inflammatory arthritic bone lesions in primates and carnivores. Results involving body mass generally remained significant in phylogenetic comparative tests, and when controlling for other variables that are correlated with body mass. Previous comparative studies have also identified body mass as a predictor of parasite prevalence more generally in mammals (Moore & Wilson, 2002). These results are consistent with the hypothesis that larger bodied mammals are exposed to a greater number of infectious agents, possibly through greater consumption of resources, including organisms that have been implicated in causing spondyloarthropathy. The results are also consistent with a 'biomechanical' hypothesis that spondyloarthropathy in large-bodied mammals is driven by the stresses of locomotion in these species (e.g. if physical stress on the joints increase more rapidly than cross-sectional joint area in these species). For example, stress-related joint damage could lead to more inflammatory responses in larger bodied mammals, which could then interact with local infections to negatively impact the healing process. Indeed, pathogens associated with spondyloarthropathy have been demonstrated in synovial fluid in humans (Pacheco-Tena *et al.*, 2001), and given that the pathology involves inflammatory, erosive processes that are more typical of infectious organisms, it is unlikely that biomechanical stresses alone could cause spondyloarthropathy.

A remarkable outcome of our study is the simple finding that, on average, over 5% of primates and 3% of carnivores exhibit symptoms that are consistent with spondyloarthropathy, with prevalence greater than 15% in some species. Animals afflicted by spondyloarthropathy exhibit symptoms similar to humans, including limited movement, eye inflammation and retarded growth. Thus, it seems likely that spondyloarthropathy causes substantial fitness costs in wild mammals, and it could be a concern for conservation of threatened species. Indeed, we found that more threatened primates and carnivores exhibit higher prevalence of spondyloarthropathy in nonphylogenetic tests, with this pattern likely to be driven by generally higher threat levels in larger bodied primates and carnivores. Indications of this disease in wild animals could be

determined through physical assessment during routine capture or through noninvasive samples; at present, however, standardized tests are not available. Our results therefore highlight the importance of developing diagnostic tests, such as assessment of joint range, for application in the field, especially for large-bodied animals.

Our results add to the apparent onslaught of extinction risks faced by large mammals. Primates and carnivores of large body size are significantly more prone to extinction, especially when combined with other intrinsic biological characteristics that relate to slow reproduction, low population numbers and a high trophic level (Purvis *et al*., 2000; Gittleman & Gompper, 2005). Indeed, although anthropogenic effects from high human population densities, habitat destruction and climate change are generally considered the most important explanatory factors for predicting impending extinction, these effects are only salient within particular species' biology (Cardillo *et al*., 2004). Of relevance here is that a recent model predicting extinction risk across all mammals shows that among both biological and human-related effects, small-sized mammals (< 3 kg) are mainly influenced by high human population numbers, whereas species of larger size are significantly impacted by both biology and human-related factors (Cardillo *et al*., 2005). If natural populations of large-bodied mammals have elevated levels of inflammatory arthritic conditions, as suggested by our comparative findings across primates and carnivores, then the multitude of factors associated with environmental and biological stresses are even greater in threatened species.

In conclusion, the results presented here show how fundamental questions in animal health and conservation can be addressed using phylogenetic comparative methods. A substantial number of animals in our database exhibit symptoms of disease that are likely to have fitness-related costs, and these impacts increase with body mass. Future research in the field, laboratory and through additional mammalian comparisons will help to identify the underlying causes of spondyloarthropathy and its consequences for wild mammals. A variety of other ailments show up on bone in readily accessible skeletal collections, including osteoarthritis, infectious arthritis, tumours and metabolic diseases, such as osteomalacia. These diseases could be investigated in future comparative studies.

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Appendix

Museums visited to compile the comparative data set

American Museum of Natural History, New York City (AMNH)
Philadelphia Academy of Sciences (ANSP)
Carnegie Museum (CM)
Cleveland Museum of Natural History (CMNH)
Field Museum of Natural History, Chicago (FMNH)
Museum of Comparative Zoology, Harvard University, Boston (MCZ)
Museum of Vertebrate Zoology, University of California, Berkeley (MVZ)
US National Museum of Natural History, Washington, DC (NMNH)
University of British Columbia (UBC)
Los Angeles County Museum (LACM)
Royal Ontario Museum, Torongo (ROM)
Arizona State University, Tempe (GP)
University of Florida, Gainesville (UF)
Irish Royal Natural History Museum, Dublin (IRSNB)
Michigan State University, East Lansing (MSU)
National Museum of Canada, Hull (NMC)
Reiksmuseum Natural History, Leiden (RMNH)
University of Nebraska, Lincoln (UNSM)
University of Oklahoma (OK)
Texas Wildlife Center, Collage Station (TCWC)
Museo Nationale de Ciences Naturale, Madrid (MNCM)
Zoological Museum of Amsterdam (ZMA)
Texas Tech University, Lubbuck (TTU)
Illinois State Museum (ISM)
Idaho Museum of Natural History, Pocatello (IMNH)
University of Wisconsin Zoological Museum, Madison (UWCS)
California Academy of Sciences, San Francisco (CAL)
University of Naples Museum of Zoology (UNMZ)
Musee et Service d'archeologie de Neuchatel Laboratoire d'Archeozoologie, Neuchatel, Switzerland (SAN-FA)
Natural History of Berne, Switzerland (NHMBE)
Marcel Guentert; Hebrew University, Jerusalem (HUJ)
Musee Royal de l'Afrique Centrale, Tervuren, Belgium (MRAC)
Mario Pavia Osteologic Collection, Universita Degli Studi di Torino, Dipartimento Di Scienze della Terra, Torino, Italy (MPOC)
Museo Cinco di Storio Naturale di Carmagnola, Italy (MCCI).
University of Kansas Museum of Natural History (KU) Lawrence KS

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