The extinct osteoarthritic lagomorphs (*Prolagus sardus*) from Sardinia (Italy) reveal further evidence of life history evolution in insular domains

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Abstract

The study of past pathologies by means of quantitative reports is an underexplored approach to deal with the biology and ecology of extinct taxa. In the present study, we assessed the prevalence rate of primary osteoarthritis in a large sample of *Prolagus sardus* (Mammalia, Lagomorpha) from Medusa Cave (also known as Grotta Dragonara, Sardinia, Italy; Late Pleistocene) to shed light on the evolutionary history of small mammals under isolation regimes. The hip and knee joints of 246 femora were examined grossly, microscopically, and using advanced radiology, recording essential biological features such as age or weight. We noted that 27.7% of skeletally mature sample had degenerative disorder of the joints, with higher frequency in adults (p-value < 0.05), regardless of their body mass (p-value > 0.05). Histologically, affected joints displayed changes in subchondral plate potentially reflecting adaptive modeling. Our analysis revealed ageing (the extended lifespan) as the main driver of this prevalence rate, whereas mechanical factors (caused by a particular lifestyle) were considered of significantly lesser importance. Our results provide additional empirical support to the analytical framework of life history theory from a new perspective, according to which, under low extrinsic mortality regimes, selection should favor slow-strategies (extended lifespan) in small-sized mammals.
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1. Introduction

The study of diseases in the deep time, through the accurate and comprehensive review of fossil remains, may discern novel biological details about extinct taxa, including relevant data on immunology, physiology, life history, behavior, and intra- and interspecific relationships (Rothschild and Martin, 2006; Waldron, 2009, 2012). For a long time, palaeopathological findings were reported as merely "curiosities", and they have been described as unusual abnormalities in particular specimens (Rothschild and Martin, 1993; Upex and Dobney, 2012 and references therein). In recent years, however, the study of palaeopathologies has sparked a trajectory of scientific

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interest, emphasizing the relevance of quantitative reports at population level to understand the impact of illnesses on the species' biology and ecology (Upex and Dobney, 2012). Until now, only a few investigations have addressed palaeopathological disorders in small mammals (Luna et al., 2017; Zoboli et al., 2018; Moncunill-Solé et al., 2019), likely because of a complex set of issues (e.g., small dimensions, poor skeletal preservation, etc.) (Moncunill-Solé et al., 2019), and none of them have targeted the quantitative records.

One of the most frequently detected and reported pathological conditions in the fossil record is osteoarthritis (OA) (Baker and Brothwell, 1980; Rothschild, 1990; Rothschild and Martin, 1993, 2006; Waldron, 2009, 2012; Grauer, 2012; Rothschild et al., 2012 and references therein) and, indeed, OA was one of the first skeletal disorders documented in an archaeological non-human vertebrate (Harcourt, 1967). This chronic, progressive and debilitating degenerative disease is characterized by degradation of the hyaline articular cartilage (fibrillation, thinning and erosion) of diarthrodial joints. Progressive degradation of the articular cartilage results in variable secondary changes, including osseous formation at the joint margins (osteophytes) and bone modeling of joint-associated bone, entailing pain, joint deformation, and, ultimately, loss of joint function (Colombo et al., 1983; Swieszkowski et al., 2007; Suckow et al., 2012). OA also affects subchondral bone, synovial tissue, articular capsule, and periarticular soft tissues (López-Armada et al., 2004). Fortunately, the major pathological features of bones affected by OA have not changed over time and we can recognized them in fossils (Waldron, 2009), meaning that vertebrates have been affected by this disorder from the very earliest times (at least from the Early Cretaceous; Rothschild et al., 2012).

Idiopathic OA, i.e., primary OA (pOA), is triggered by the long-term use ("wear-and-tear") of the articulation combined with aging (Oglesbee, 2012). This complex multifactorial disease is linked to a set of well-known risk factors (e.g., age, sex, obesity, or movement), albeit older age is the most prominent one. It is probable that changes in the musculoskeletal system entailed by aging, together to other factors (e.g., obesity, genetics, etc.), are the main contributors to pOA development. In non-human animals, pOA is generally limited to captive specimens, as a direct consequence of the artificial environment (e.g., not exposed to predators) regardless of their conditions (diet, weight or activity), and it is rarely observed in wild-caught individuals (Rothschild, 2003). In other cases, OA derives from trauma, infection, autoimmune disorders or other preexisting conditions (i.e., secondary OA, sOA) (Waldron, 2009, 2012).

Considering this background, the present study aimed to describe the prevalence of pOA in the skeletally mature sample of *Prolagus sardus* (Wagner, 1829) (Mammalia, Lagomorpha) retrieved from the Late Pleistocene deposit of Medusa Cave (Grotta della Medusa, at Cala Dragunara, Porto Conte bay – Capo Caccia area, Alghero, northwest Sardinia, Italy; Fig. 1). This fossil site has been coined historically as Grotta Dragonara in the palaeontological literature (Malatesta, 1970; Palombo et al., 2017; Moncunill-Solé et al., 2021). This species and locality have been considered suitable for cutting-edge palaeopathological approach for several reasons. *Prolagus sardus* is an endemic insular species that inhabited Corsica and Sardinia from about 800 kyr (Moncunill-Solé et al., 2016a) to historical times (Vigne and Valladas, 1996; Valenzuela et al., 2022). It was the last representative of the genus *Prolagus*, which appeared in central Europe about 20 Myr, and was widely
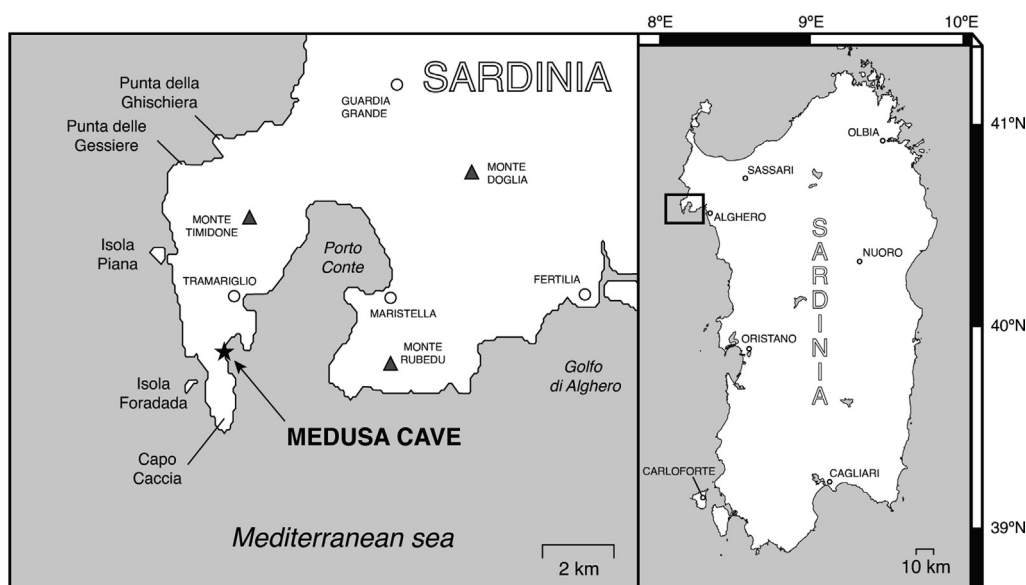

Fig. 1. Map of study area, Sardinia (Italy), and the location of Medusa Cave (black star). The main cities (white dots) and geographic features (grey triangles) are marked. Data from Palombo et al. (2017) and mapping with GMT 6.4.0. (Wessel et al., 2019).

distributed in Europe throughout the Neogene (Angelone et al., 2020 and references therein). The taxonomical position of the genus is a matter of debate. Although *Prolagus* has traditionally been considered an ochotonid (Family Ochotonidae), some authors prefer to assign it to the Family Prolagidae based on its particular morphology. The preliminary analyses of mitochondrial DNA of *Prolagus sardus* are promising for solving this issue (Bover et al., 2022). In addition, *Prolagus sardus* has been the focus of recent studies aimed to unravel the palaeobiology of insular endemic fossil lagomorphs, particularly body mass reconstructions (Moncunill-Solé et al., 2016a, 2021), and pathological conditions had already been described in their long bones, vertebrae and ribs (Zoboli et al., 2018).

Medusa Cave housed one of the richest collection of *P. sardus* remains (Boldrini, 2009; Moncunill-Solé et al., 2021). It is a northeast aligned small karst cavity of about 30 m of extension, perpendicularly oriented to a Mesozoic calcareous cliff, partially flooded by the sea (for stratigraphic details, see Malatesta, 1970; Boldrini, 2009; Palombo and Rozzi, 2014; Palombo et al., 2017; Fig. 1). Fossil remains were recovered in a red clay level dated back to the Late Pleistocene (22.390–21.910 ka cal BP; data obtained from a tooth of the deer *Praemegaceros cazioti* (Depéret, 1898) recovered in the so-called "level 5", see Palombo et al., 2017: fig. 5). Under a biochronological point of view, they pertain to the Dragonara faunal subcomplex of the *Microtus* (*Tyrrhenicola*) faunal complex (ranging from the Middle Pleistocene to the Holocene) (for a complete faunal list, see Palombo, 2009; Palombo et al., 2017).

The results presented in this study will contribute to a more detailed understanding of the life history and eco-evolutionary adaptations of *P. sardus* (see also Moncunill-Solé, 2021) and will extend the ongoing research focused on the ecology and evolution of fossil lagomorphs in insular regimes.

2. Material and methods

2.1. Material, measurements, and body mass estimation

The study focused on femur (distal and proximal epiphyses) because it is the bone most extensively affected by pOA in extant lagomorphs (Arzi et al., 2012). We recognized 861 femora (411 right, R; and 450 left, L) of *Prolagus sardus* among the remains of the Medusa Cave (Fig. 1), curated in the collection of the Laboratorio di Paleontologia dei Vertebrati (Dipartimento di Scienze, Università degli Studi Roma Tre, Italy). Among those remains, 246 femora were regarded as suitable for the research purpose: 97 specimens had closed growth plates (49 R and 48 L) and 149 had at least one epiphysis fused (49 R proximal, 18 R distal, 63 L proximal, and 19 L distal), suggesting skeletal maturation (see Table S1). The epiphyses were categorized into 4 distinct grades according to their condition: 1) broken (**B**), 2) fused (**F**), 3) fused with suture line (**Fsl**), and 4) unfused (**U**). Thereafter, considering the intact epiphyses, the specimens were grouped into 3 age categories: 1) Juveniles (**J**), with at least one fused epiphyses though with visible suture lines; 2) Young Adults (**Y**), with fused epiphyses, some of them may still show suture line visible; and 3) Adults (**A**), with both epiphyses fused and suture lines not distinguishable (Kauhala and Soveri, 2001).

The following measurements (mm) were taken with a digital caliper (error $\pm$ 0.02 mm) following standardized procedures (for details, see Moncunill-Solé et al., 2015: fig. 1): **FL**, femoral length; **FTDm**, femoral transversal diameter at the midshaft; **FAPDm**, femoral anteroposterior diameter at the midshaft; **FTDp**, proximal femoral transversal diameter; **FTDd**, distal femoral transversal diameter; and **FAPDd**, distal femoral anteroposterior diameter. The body mass (**BM**) of each specimen was estimated using weight predictive equations described in current lagomorphs based on epiphyseal dimensions (Moncunill-Solé et al., 2015). Sexual dimorphism was not considered because it is minimal in extant lagomorphs (Lu et al., 2014; Ferreira et al., 2015), and sex is not found to be a risk factor of pOA disorder (Arzi et al., 2012; Oglesbee, 2012).

2.2. Specimen assessment and image pOA evaluation

High-resolution images were acquired of each specimen using a digital camera (Leica DFC290 mounted on a Leica MZ6 modular stereomicroscope). In intact specimens, 11 images were taken, covering the proximal (anterior, cranial, medial, and posterior views) and distal aspect of the femur (anterior (2 images), cranial, caudal, lateral, medial, and posterior views) (Fig. S1). In broken, damaged, or juvenile specimens, the intact portion was photographed for partial assessment. The photographs of each individual were merged into one high resolution photograph, which was displayed on a medical grade screen. All images were reviewed simultaneously until consensus was reached by two reviewers (BA and BF). Three regions of the femur, the femoral head and neck (**FH**), the trochlea (**FT**), and the distal femoral articular surface (**FD**), were assessed for the presence and severity of pOA, and semi-quantitively scored using a scale from 0 to 3 (Fig. S2; Arzi et al., 2012, 2013). A score of 0 was given if no evidence of pOA was present. A score of 1 was given to indicate mild pOA when any evidence of mild new bone formation was present along any joint surface. A score of 2 was given to indicate moderate pOA, i.e., when the previously described changes were more pronounced. A score of 3 was given to indicate marked pOA if the previously described changes were even more pronounced. The specimen was scored "unreadable" for a specific region if a large portion ($>$ ca. 50%), or the entirety, of the articular surface was missing (see further details in Arzi et al., 2012, 2013). In all cases, reviewers ensured that the observed changes did not derive from other pre-existing conditions (sOA).

2.3. Statistical methods

A descriptive analysis of the variables was conducted to obtain basic information of the dataset: frequency tables (counts and %) in categorical variables (laterality, age class, pOA occurrence and severity); and descriptive statistics, normality test (Shapiro-Wilk test) and equality of variances test (Levene's test) in continuous ones (BM, FTDm, FAPDm) (Appendix S1).

The association of occurrence and severity of pOA among the different femoral epiphyses (FH, FT, and DF) was evaluated using McNemar test, Cochran's Q test and $\chi2$ test. We applied $\chi2$ test to determine the association of pOA (occurrence and severity) with laterality, and Cochran-Armitage test and Jonckheere-Terpstra test with age. The BM and midshaft diameters differences among groups were examined using a T-test/Mann–Whitney U test (pOA occurrence) and ANOVA/Kruskal-Wallis test (pOA severity). The association among pOA and size variables was evaluated by binary and multinominal logistic regressions. The contribution of size to the models was examined using Wald test, whereas odds ratio (OR) indicated if the increase in size could be related to an increase or decrease probability of pOA occurrence or severity. All these inferential tests were performed on two datasets: (i) including all sample specimens and (ii) excluding those specimens with at least one broken epiphysis. When assessing age, only the second dataset (unbroken specimens) was considered (Appendix S1).

The significance level (p-value) of all statistical tests was fixed at 5%. The statistical assessment was carried out in the software Jamovi 0.9.2.3 (The Jamovi Project, 2019), IBM SPSS Statistics Version 22.0.0.0 (Property of IBM Corporation) and R 4.0.4 (packages *ReadR* and *DescTools*) (R Core Team, 2021).

2.4. MicroCT scan and histology

MicroCT scanning and histological procedures were carried out in specimens A003, A045, A055 and R46 (Table S1), whose pOA scores ranged from 0 to 2, to identify microanatomical and infrastructural osseous modifications. The scans were performed at UC Davis Veterinary Orthopedic Research Laboratory (Davis, USA). Femora were scanned with Scanco Medical μCT 35 (Bassersdorf, Switzerland). The scanning parameters were 55 kVp 145 μA, integration 400 msec, averages of four exposures per projection, 1000 projections per 180° with a 0.5 mm aluminum filter and 15 μm voxel size. Image noise was reduced using a low-pass Gaussian filter ($\sigma = 1$, support = 2). Digital images were reconstructed to maintain the anatomical planes of the femora with FIJI software (Open source ImageJ2 core), and assessed by a veterinary anatomic pathologist and osteologist (RZ). Specifically, using the mineralized bone morphology depicted in the images the following components

of the bone were assessed: trabeculae conformation, orientation, and interconnection; overall bone contours; osteocyte lacunae distribution and morphology; vascular and osteonal channels presence, frequency and distribution; mineralized cartilage and subchondral bone thickness and architecture. The quantitative data from the microCT analysis was not included in this study due to small sample size, but the general trend such as trabecular thickness and interconnectivity and trabecular density followed the morphological observations described in the results.

For the histological examinations, hard tissue embedding and processing was performed with EXAKT instruments (Norderstedt, Germany) at UC Davis Veterinary Orthopedic Research Laboratory (Davis, USA). Femora were embedded in 2-hydroxyethyl methacrylate, isobornyl methacrylate (Technovit 7200 VLC) and sectioned to 500 μm with EXAKT diamond belt bandsaw. The 500 μm sections were subsequently manually polished down to 100 μm thin sections. The slides were then reviewed, interpreted and described by two board-certified veterinary pathologists (NV and RZ). The images were captured with Olympus BX46 microscope attached to an Olympus DP27 camera via CellSens software.

3. Results

3.1. Descriptive analysis

Most of the specimens were adults (76.8%), though young adults (14.2%) and juveniles (8.9%) were also recognized (Fig. 2A, Table 1). Midshaft diameters (FAPDm and FTDm) and BM were gained successfully in almost all the specimens (99.6%, Table S1). The average BM of the sample was 723 g (450–1113 g, N = 222) (Fig. 2B), and values of FTDm were slightly larger (also with higher SD) than those of FAPDm ($\bar{x} = 4.98$ and 4.08; SD = 0.441 and 0.299 respectively). The distribution of FTDm and BM significantly deviated from normality, so the chosen statistical tests for these variables were non-parametric (Appendix S1).

The pOA assessment was conducted on 91.5% of the samples (since 21 individuals were identified as "unreadable"), noting a higher preservation state of proximal epiphysis (86.2%) than distal epiphysis (60.0%) (Table 1). Thus, a larger number of scores were obtained in FH (75.6%) than FT or FD (47.6% and 44.3% respectively) (Fig. 2D–F, Table 1). One specimen in four (24.9%) showed at least one epiphysis with pOA signs (R = 24.3% and L = 25.42%; J = 17.6%, Y = 16.7% and A = 27.7%). The 27.4% of FH showed signs of pOA disease (J = 30.8%, Y = 20.7% and A = 28.5%) (Fig. 2D, Table 1). On the other hand, FT and FD were less affected. A single specimen scored 1 examining FT, whereas only the 8.3% of FD showed evidence of pOA (J = 0%, Y = 0% and A = 11.1%) (Fig. 2E, F, Table 1).
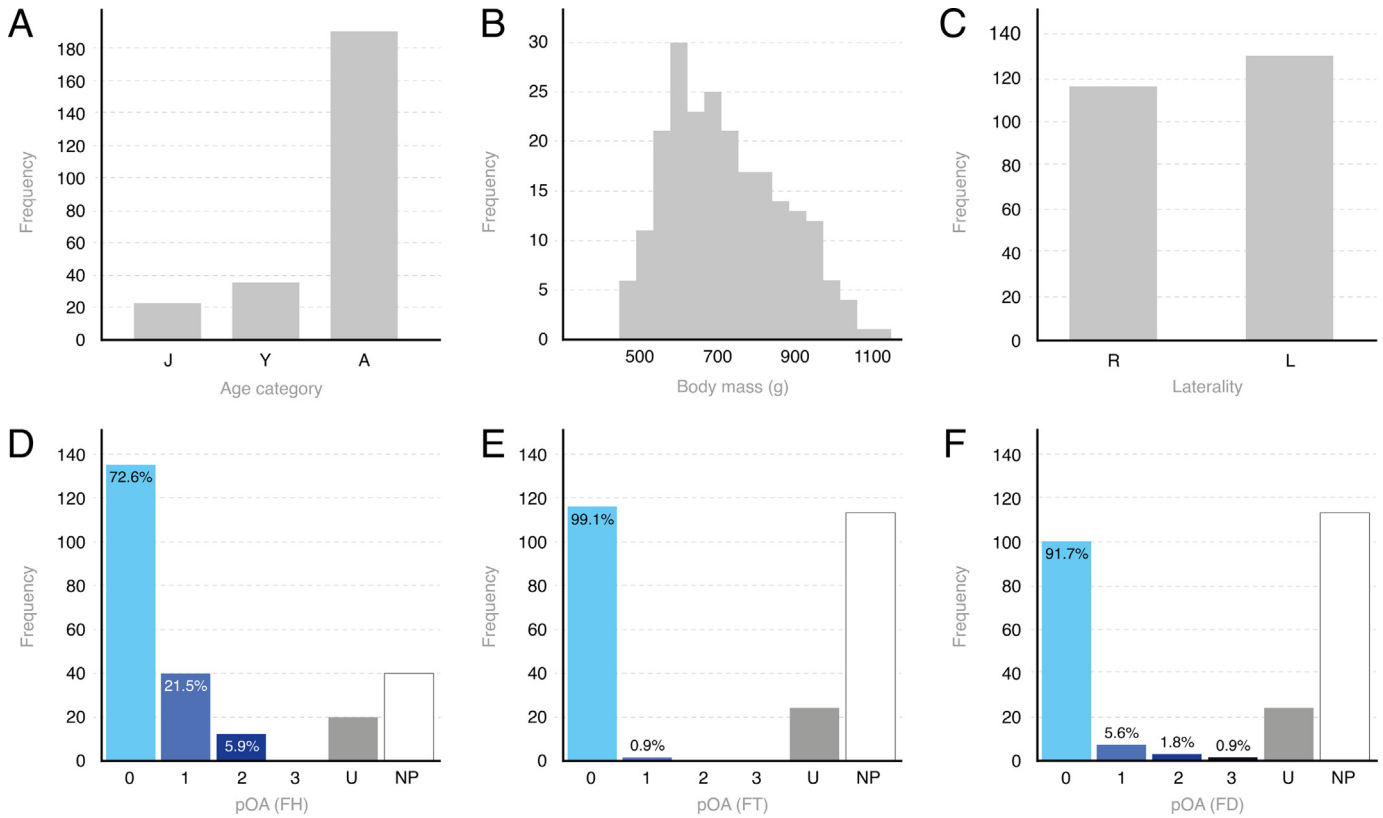
Fig. 2. Histograms of femora by age category (A), body mass (B) and laterality (C), and bar graphs of severity of pOA in FH (D), FT (E), and FD (F). Abbreviations: 0, absence of pOA; 1, mild pOA; 2, moderate pOA; 3, severe pOA; A, adult; FD, distal femur articular surface; FH, femoral head and neck; FT, femoral trochlea; J, juvenile; L, left; NP, not preserved; pOA, primary osteoarthritis; R, right; U, unfused; Y, young adult. See the text for descriptions of the scores.

Table 1
Results of the pOA examination in each femoral region (femoral head, trochlea, and distal epiphysis), considering severity, laterality, age class and body mass. Abbreviations: N, number of specimens. For details, see the main text.

Femoral region	pOA severity	N	Laterality		Age class			BM (in g)	
			right	left	juvenile	young adult	adult	$\bar{X}$	SD
Femoral Head	0	135	67	68	9	23	103	717.8	148.95
(FH)	1	40	16	24	4	5	31	751.37	140.11
	2	11	5	6	0	1	10	728.4	157.54
	3	0	0	0	0	0	0	-	-
	Total	**186**	**88 (47.3%)**	**98 (52.7%)**	**13 (7.0%)**	**29 (15.6%)**	**144 (77.4%)**		
Trochlea	0	116	60	56	7	23	86	707.95	138.75
(FT)	1	1	0	1	0	0	1	674.31	-
	2	0	0	0	0	0	0	-	-
	3	0	0	0	0	0	0	-	-
	Total	**117**	**60 (51.3%)**	**57 (48.7%)**	**7 (6.0%)**	**23 (19.6%)**	**87 (74.4%)**		
Distal epiphysis	0	100	49	51	6	22	72	714.86	142.60
(FD)	1	6	5	1	0	0	6	677.88	98.63
	2	2	2	0	0	0	2	575.82	74.58
	3	1	1	0	0	0	1	770.58	-
	Total	**109**	**57 (52.3%)**	**52 (47.7%)**	**6 (5.5%)**	**22 (20.2%)**	**81 (74.3%)**		

3.2. Inferential statistics

The proportion of individuals with evidence of pOA in FH, FT and FD was statistically significantly different in the two datasets (p-value < 0.05), noting a strong association among occurrence in the three regions (Cochran's Q = 14.00; p-value = 0.001). That is to say, it is far more likely to have femora only affected by pOA in FH, than femora with pathological signs also in FT and FD (Fig. 3A). Considering intact femora, results also showed strong dependency between FH and FD scores ($\chi^2_4 = 35.4$, p-value = 0.001; Fig. 3B, C).
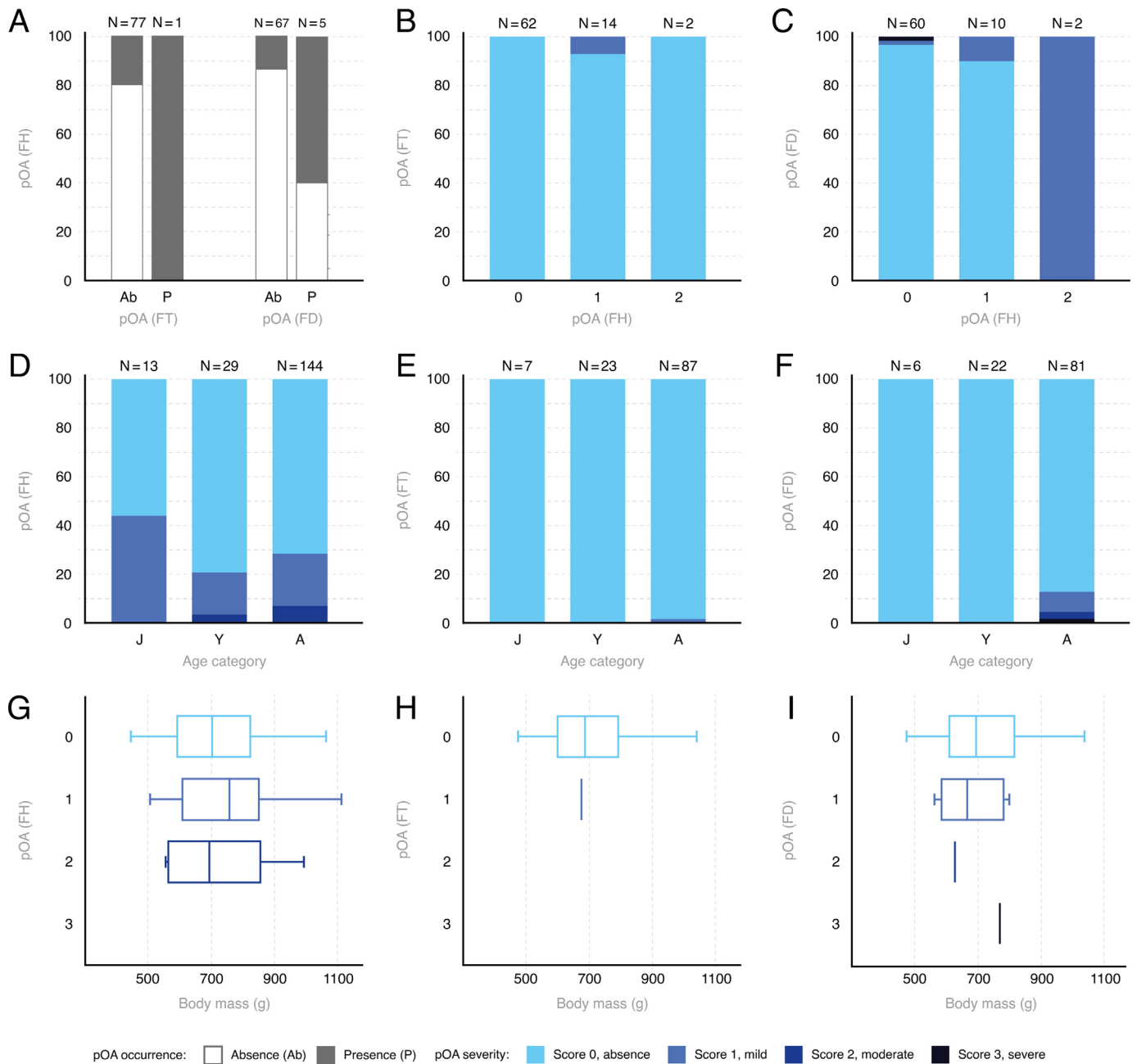
Fig. 3. Stacked bar plots of occurrence (A) and severity (B, C) of pOA in FH, FT, and FD; of pOA severity by age group in FH (D), FT (E), and FD (F); and boxplots of body mass (BM) by each severity group type in FH (G), FT (H), and FD (I). Abbreviations: 0, absence of pOA; 1, mild pOA; 2, moderate pOA; 3, severe pOA; A, adult; Ab, absence; FD, distal femur articular surface; FH, femoral head and neck; FT, femoral trochlea; J, juvenile; N, sample size; P, presence; pOA, primary osteoarthritis; Y, young adult. See the text for descriptions of the scores.

Occurrence and severity of pOA were independent of laterality in both datasets (p-value > 0.05) (Fig. 2C, Table S1). On the other hand, an increasing trend was evident between pOA occurrence and age, albeit only statistically significant in FD (Cochran-Armitage Z = -1.6772; p-value < 0.05). By contrast, the distribution of pOA scores was not different among ages categories, and no trend could be statistically established (Jonckheere-Terpstra; p-value > 0.05) (Fig. 3D–F, Table S1).

The specimens affected by pOA did not show size differences from healthy ones in both datasets (Mann-Whitney U and T-test, p-value > 0.05), just as there were no differences among individuals considering the severity of the pOA (Kruskal-Wallis and ANOVA, p-value > 0.05) (Fig. 3G–I, Table S1). Variation explained by binary logistic models (pOA occurrence) was very low (Nagelkerke's R^2 ranges from 0.002 to 0.043 considering all sample, and from 0.000 to 0.015 assessing only intact specimens,

Appendix S1), without a significant contribution of size variables (p-value > 0.05). In this regard, the size increment was not related to an increased chance of developing pOA (OR intervals of confidence include value 1). Multinominal logistic regressions (pOA severity) were also unsuccessful in both datasets (Appendix S1). BM, FTDm and FAPDm did not contribute significantly to these models (p-value > 0.05), and Nagelkerke's R^2 were very low (from 0.003 to 0.064 in all sample, and from 0.008 to 0.067 assessing intact bones). In this regard, larger sizes were not associated with worsening pOA (OR = 1) (Appendix S1).

3.3. MicroCT and hard tissue histology

The examination of femoral head specimens with gross pOA scores of 0 (Fig. 4A) and 2 (Fig. 4B) with microCT and histology revealed macro and micro-architectural differences. Many histological features of the bone tissue were discernible including mineralized cartilage layer in subchondral bone plate, vascular channels and osteocyte lacunae, that allowed for both qualitative and quantitative analysis of the selected specimens. Histologically, the femoral head of a specimen with a pOA score of zero
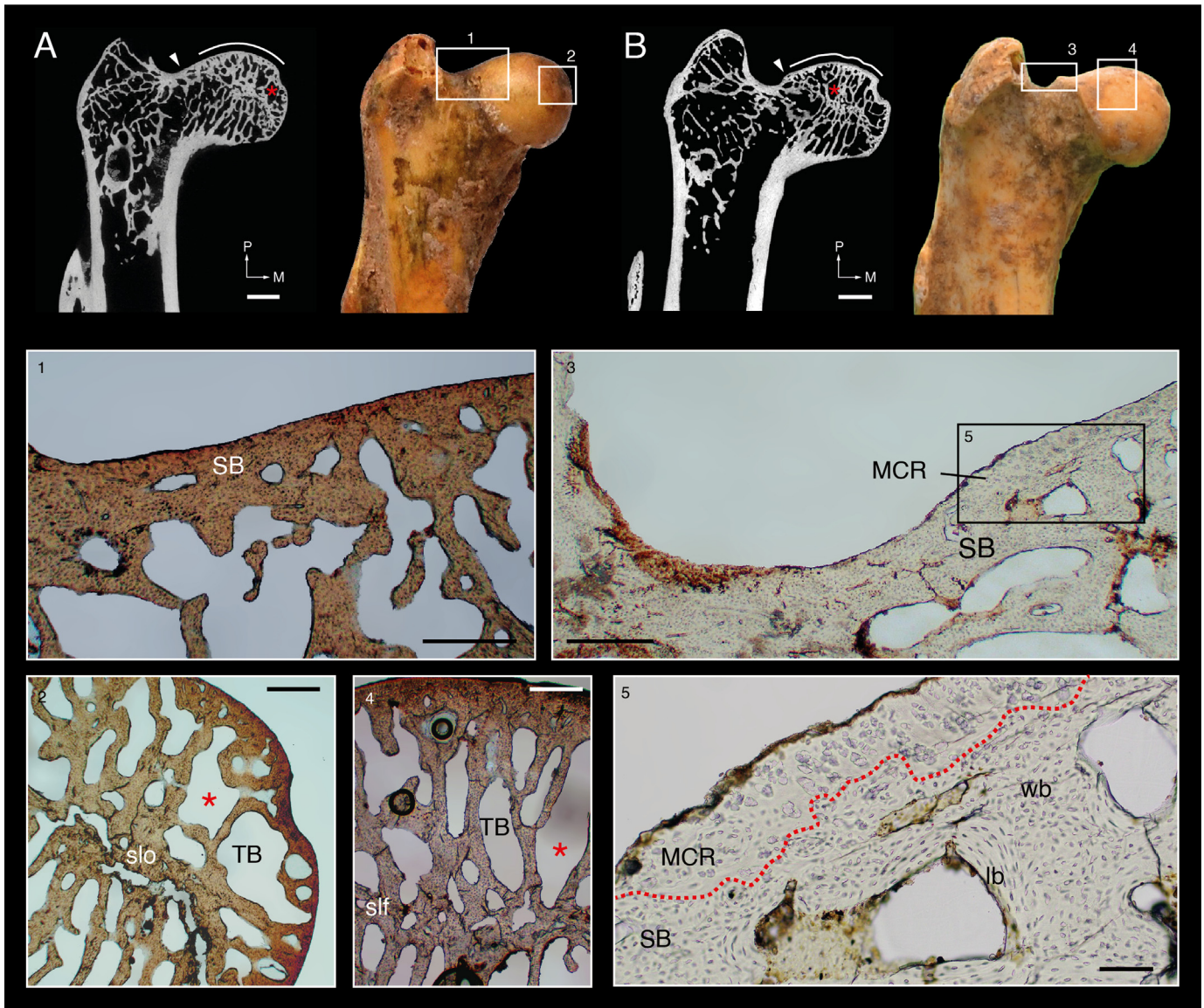

Fig. 4. MicroCT and bone histology images of *P. sardus* femoral heads: (A) healthy specimen (grade 0, A045), and (B) osteoarthritic one (grade 2, A003). Note the differences in the amount of trabecular bone (red asterisk), the physis contour and collapse of femoral neck (white line), and bump area (white arrowhead) formed by MCR (red dotted line). Abbreviations: lb, lamellar bone; M, medial; MCR, mineralized cartilage region; P, proximal; SB, subchondral bone; slf, fused suture line; slo, open suture line; TB, trabecular bone; wb, woven bone. Scale bar means 2 mm in microCT, 500 μm in histological sections excepting the last one which equals 100 μm.

had a uniform and regular distribution of the trabecular bone and osteocyte lacunae with smooth contour and uniform thickness of the subchondral bone. Vascular channels were regularly distributed. Segmental, undulating separation of the epiphyseal and metaphyseal trabeculae in the region of femoral head physis was detected in the specimen was suggestive of "partially open" physis suggesting it belonged to a younger individual (Fig. 4A). The specimen with higher pOA score had quantitative reduction in the trabecular plate interconnectivity density (reduction in the amount of trabecular bone) with concurrent mild femoral neck collapse (Fig. 4B). The subchondral bone in the femoral head with score of 2 had scalloped surface contour and the mineralized cartilage layer appeared thicker than in a specimen with a score of 0. An elevated area (nick-named the "bump") was detected on the femoral neck of the individual with pOA score of 2. This structure formed by a mixture of mature, lamellar and immature, woven bone could be an osteophyte that formed as a result of a modeling process (microarchitectural bony adaptation to injury) (Fig. 4B).

The microCTs of femoral condyles of the specimen with pOA score of 1 demonstrated segmental thickening of the cortical bone at the abaxial aspect of the lateral condyle. Histological correlate of the site illustrated mildly irregular cortical thickening at the same site (Fig. 5). In specimen with a pOA score of 2, the microCT scans of the femoral condyles showed increased thickness of the cortical bone with scalloped contours. The articulating aspect of the medial condyle had markedly thickened subchondral bone (Fig. 5B). Histologically, these observations correlated with irregular increased mineralized cartilage layer and thickened subjacent bone (Fig. 5B.3, 5B.4). The contour of the trochlear cortical bone was scalloped with notable variation in bone density (Fig. 5C).

4. Discussion

4.1. Causes and risk factors of pOA in P. sardus

Extant lagomorphs have a high predisposition to develop a large variety of musculoskeletal and joint disorders (Harcourt-Brown and Langley-Hobbs, 2014). Our study reveals that joint abnormalities were significant and widely detectable in the skeletally mature *Prolagus* sample from Medusa Cave with 27.7% of examined specimens affected by pOA.

Aging is considered the main risk factor of this degenerative disorder in lagomorphs (Arzi et al., 2012; Harcourt-Brown and Langley-Hobbs, 2014). Recently, a significant increase of pOA incidence and prevalence have been described in domestic rabbits (Harcourt-Brown and Langley-Hobbs, 2014), and has been related to their increased lifespan (consequence of the nourishment and caring in private homes) (Quesenberry and Carpenter, 2004; Arzi et al, 2012; Oglesbee, 2012; Harcourt-Brown and Langley-Hobbs, 2014). Pursuant to that, observational studies in Old World primates have revealed that artificially-restricted populations exhibit a larger prevalence of pOA than free-ranging ones (5% and < 1% respectively), as they benefit from a longer lifespan in protected environment (Rothschild and Woods, 1992; Jurmain, 2000). Similarly, it is noted that zoo or colony-raised animals show roughly a 10-fold increase in pOA prevalence (Rothschild, 2003). Our palaeopathological study has also revealed a relationship among age and pOA occurrence in the *P. sardus* femora, albeit only statistically significant when considering FD. This result may be a consequence of the age determination method used, which prevents establishing the precise age of individuals (Kauhala and Soveri, 2001). More accurate approaches of age determination could not be applied due to their destructive nature (Moncunill-Solé et al., 2016b).

Our study did not detect significant correlations between body mass and pOA, agreeing with previous investigations where body weight is highlighted as a relevant risk factor only when specimens are heavier than 5 kg (Arzi et al., 2012). The largest rabbit breeds (e.g., British giant rabbit, weighting up to 7 kg) had higher prevalence of pOA than rabbits lighter than 5 kg (e.g., the Netherland dwarf, weighting ca. 0.5–1.1 kg, thus similar in size to *P. sardus*) (Arzi et al., 2012; Harcourt-Brown and Langley-Hobbs, 2014). Our results also revealed a lesser severity of pOA in *P. sardus* than domestic rabbits, potentially in part attributable to its smaller size (Marshall et al., 2009; Muehleman et al., 2010). Furthermore, high pOA grades (grade 2 and 3) could have a profound impact on the lives of individuals of extinct species (e.g., decreased mobility or impaired grooming abilities) (Quesenberry and Carpenter, 2004; Oglesbee, 2012; Harcourt-Brown and Langley-Hobbs, 2014), predisposing to other severe disorders (e.g., ulcerative pododermatitis, spinal fractures or deformities, osteoporosis, pressure sores or urine sludge) (Varga, 2014). Such specimens were

Fig. 5. MicroCT and bone histology images of *P. sardus* femoral condyles and patellar region: (A) mild-affected specimen (grade 1, A055), and (B, C) moderate-affected one (grade 2, R46; white dotted line indicates the parafrontal plane of cutting at trochlear region). Note the denser cortical bone (white and black arrow) and important MCR in the distal area of individual grade 1 (red dotted line). In the specimen grade 2, it is observed scalloped contour in patellar region (white arrow) and notable cortical bone in distal region (black arrow and white bracket) formed by a dense subchondral bone (red double-arrow line) and the deep extension of MCR (red dotted line). Abbreviations: A, anterior; D, distal; L, lateral; M, medial; MCR, mineralized cartilage region; po, primary osteon; SB, subchondral bone; TB, trabecular bone; wb, woven bone. Scale bar means 2 mm in micro CT, 500 μm in histological sections excepting the magnifications in which scale equals 100 μm.
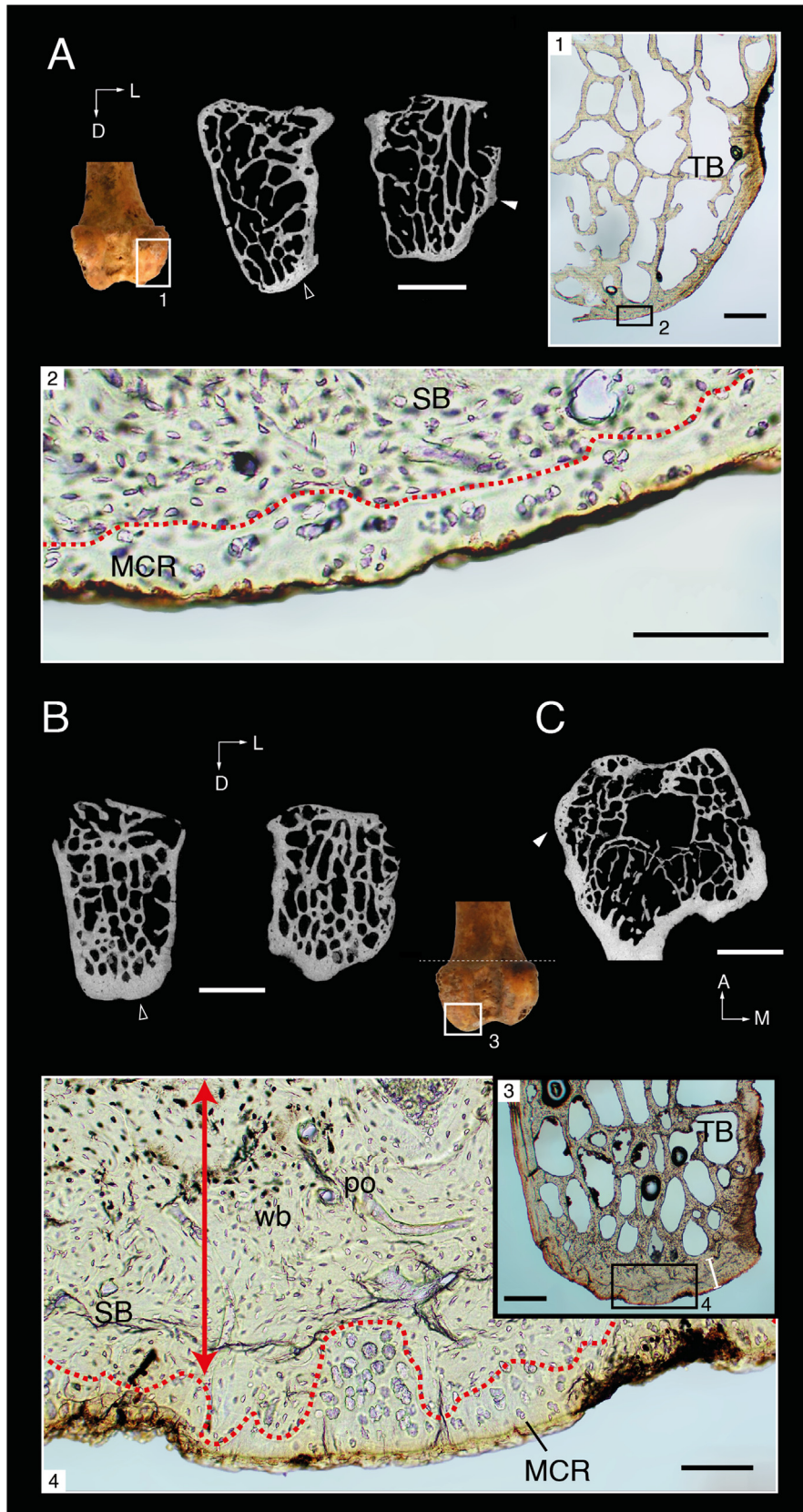
certainly easier targets for predators (Varga, 2014), albeit neither the typology of the vertebrate assemblage nor the material status points to predation as the cause of death (Palombo et al., 2017).

In the light of foregoing, the prevalence of pOA (27.7% in skeletal mature portion of the sample) reported in the wild small-sized *P. sardus* from Medusa Cave is relatively high and remarkable, especially when comparing with natural prevalence in domestic rabbits (20.9% in knee and 26.1%, in hip; > 1 year of age) (Arzi et al., 2012), dogs (20%; > 1 year of age) (Clements et al., 2006), and cats (22%; > 1 year of age) (Godfrey, 2005); as well as with pOA prevalence of wild taxa (e.g., lions, elephants, etc.; of adult age) (Nganvongpanit et al., 2017). Noting the nature of pOA in lagomorphs (Arzi et al., 2012), an increased longevity of *Prolagus sardus* should be the main ecological driver of the observed results (Rothschild and Woods, 1992; Quesenberry and Carpenter, 2004; Oglesbee, 2012; Harcourt-Brown and Langley-Hobbs, 2014), agreeing with previous studies (Angelone et al., 2017; Moncunill-Solé et al., 2021; Fernández-Bejarano et al., 2022).

Some authors, however, account the role of particular lifestyles (mechanical factors, repetitive movements carried out during life) for the development of pOA (Waldron and Cox, 1989; Hunter and Felson, 2006; Rothschild and Martin, 2006). For instance, the high frequency of pOA observed in the Late Pleistocene lions from Natural Trap Cave (Wyoming, USA) has been associated with the habitat differences in modern lions, since their hunting took place on uneven grounds (rocky environments) (von Koenigswald and Schmitt, 1987; Rothschild and Martin, 2006). Conversely, Dawson (1969), who described the skeleton of *P. sardus*, did not detect extreme deviations in the postcranial bones of this taxon. In the femur, a low position of a strong third trochanter is present, and, considering the ilium morphology, it was suggested that the different parts of the gluteal group (maximus, medius and minimus) had more independent actions and the range of movements was greater than in recent leporids (specialized in fast running). According to this, Dawson (1969) described *P. sardus* as a species not tailored for running but with skills to dig, climb and scramble the rough terrain (rocky) of Sardinia and Corsica. This fits with the range of skills and habitats observed in some extant lagomorphs, specifically those of the rock-dweller ochotonids (Smith et al., 2018; Moncunill-Solé, 2021), for which specific pOA problems have not been described in wildlife populations. In general, mechanical factors play a major role in human development of pOA, while in non-human vertebrates, pOAs are more related to inflammatory processes (Rothschild and Martin, 2006).

In view of this, the differences in the habitat or lifestyle of the extinct *P. sardus* alone are not enough to explain the high pOA prevalence observed in this extinct taxon, and the increased longevity hypothesis seems more likely.

4.2. Life history approach

Extension of the longevity (in comparison to mainland relatives) should be the main evolutionary driver of the high pOA prevalence observed in *P. sardus*. Considering the *P. sardus* body mass from Medusa Cave (BM ca. 700–750 g), we expect allometrically that this species had a lifespan of 5.3 years (4.87–5.69 y) (using regression models of extant relatives; Blueweiss et al., 1978; Peters, 1983; Moncunill-Solé et al., 2021). Nevertheless, a decoupling between life history and BM has been noted in congeneric insular endemic species of the Gargano palaeoarchipelago (*P. apricenicus* Mazza, 1987; latest Miocene, Italy), which lived longer than expected by its size (extended by ca. 1.5–2.5 y; Moncunill-Solé et al., 2016b). This species and *P. sardus* inhabited insular environments, characterized by reduced resource levels and a lower extrinsic mortality than mainland regimes (Sondaar, 1977). These different selective pressures may alter life history traits (e.g., age at maturity, age specific birth, etc.), to which adult body size is sensitive (Palkovacs, 2003). The fitness of small mammals living in isolation is increased by maturing later and at a larger size than their mainland forerunners, so selection pushes a change in the life history strategy. Insular small-sized animals are generally characterized by an extended age at maturity and longevity, and an enlarged adult body size, as well as an increased fecundity (likely in the size of offspring, as they reproduce at larger sizes) and population density (Promislow and Harvey, 1990; Stearns, 1992; Palkovacs, 2003; Mappes et al., 2008; Rotger et al., 2023). In other words, they shift towards the slow-end of the life history continuum (Orlandi-Oliveras et al., 2016; Angelone et al., 2017; Miszkiewicz et al., 2020). An increased lifespan is also recorded in large species or mainland small-sized species exposed to low extrinsic mortality levels (Wilkinson and South, 2002; Jordana et al., 2012; Smith et al., 2018).

Our results confirm and reinforce complementary studies in the *P. sardus* life history (Angelone et al., 2017; Moncunill-Solé et al., 2021; Fernández-Bejarano et al., 2022), providing empirical evidence of the shift towards the slow end in small-sized insular mammals. Generally, osteopathologies (fractures, infections, tumors, metabolic diseases, etc.) are fairly common in insular taxa (Maempel, 1993; Dermitzakis et al., 2006; Jordana et al., 2011; Palombo and Zedda, 2016, 2022; Lyras et al., 2016, 2019; Zoboli et al., 2018). Overall, they were healed, stating that individuals survived for a quite a long time after the wound (Mariani-Costantini et al., 1996). This trend is related to an extended longevity and the absence of interspecific pressures (Jordana et al., 2011; Moncunill-Solé et al., 2019).

5. Conclusions

The current study is the first to describe the natural occurrence of pOA in an extinct small mammal. The

macro- and micro-assessment of the femora of *Prolagus sardus* from Late Pleistocene Medusa Cave revealed that 27.7% of the skeletally mature portion of the sample was affected by pOA, with an anatomical manifestations similar to what is observed in extant relatives. An extended lifespan was considered the main evolutionary driver of this high prevalence, whereas mechanical factors (e.g., changes in the lifestyle) are of lesser significance. Our results reinforce the preliminary findings on *P. sardus* life history, which suggest that this species showed a slower life history strategy than mainland species (which certainly lived under higher extrinsic mortality regimes); and provide additional empirical support to the analytical framework proposed by the theory of life history from a new perspective. The results obtained here agree with the eco-evolutionary responses described to date in extinct insular lagomorphs, and provide new data of the evolutionary process in insular regimes by means of cutting-edge approaches (quantitative reports or microanatomical techniques).

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Supplementary data

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