CrossMark

ORIGINAL ARTICLE

Occupation-dependent loading increases bone strength in men

E. Biver [1] · G. Perréard Lopreno [2] · M. Hars [1] · B. van Rietbergen [3] · J. P. Vallée [4] ·
S. Ferrari [1] · M. Besse [2] · R. Rizzoli [1]

Abstract

Summary Ex vivo analyses of humeri and radii from an anthropological collection and in vivo analyses of the distal radius of retired men indicate that occupation-dependent loading positively influences bone strength by an increase of bone size when young followed by a slowdown of the age-related endocortical and trabecular bone alteration.

Introduction Skeleton responds to mechanical stimuli, but it is not established whether chronic loading in the context of occupational activities (OA) influences bone properties. We assessed the impact of occupation-dependent loading on upper limb bone strength.

Methods Individuals were classified according to the intensity of physical loading associated with their OA in two models. Ex vivo, computed tomography scans of the humeri and radii of 219 male skeletons (age of death, 20–93 years) from an anthropological collection of the 20th century (Simon collection) were used to determine estimates of bone strength and cross-sectional geometry. In vivo, distal radius were analysed in 180 men enrolled in the Geneva Retirees Cohort study using high-resolution peripheral quantitative computed tomography and finite element analysis.

Results Heavy-loading OA was associated with higher bone strength in both models. This benefit was associated with higher total area (Tt.Ar), medullary area (Me.Ar) and cortical area (Ct.Ar) in young adult skeletons, but the difference decreased in older age. In older men, the humerus supporting heavy loading had a lower Me.Ar. This effect resulted in greater asymmetries of the Me.Ar and the Ct.Ar/Tt.Ar ratio between the humeri of men with unilateral versus bilateral heavy-loading OA. In vivo, an additional benefit of heavy-loading OA was observed on the distal radius trabecular density and microstructure.

Conclusion Repeated occupation-dependent loading positively influences bone strength by an increase of bone size when young followed by a slowdown of the age-related endocortical and trabecular bone alteration. These data supports the necessity to promote bone health in the context of sedentary occupation.

✉ E. Biver
  Emmanuel.Biver@hcuge.ch

[1] Division of Bone Diseases, Department of Internal Medicine Specialties, Geneva University Hospitals and Faculty of Medicine, 4 Rue Gabrielle Perret-Gentil, 1211 Geneva 14, Switzerland

[2] Laboratory of Prehistoric Archaeology and Anthropology, F.-A. Forel Institut – Section of Earth and Environmental Sciences, University of Geneva. Uni Carl Vogt, 66 boulevard Carl Vogt, 1211 Geneva 4, Switzerland

[3] Department of Biomedical Engineering, Eindhoven University of Technology, PO Box 513, Eindhoven MB 5600, The Netherlands

[4] Division of Radiology, Geneva University Hospitals and Faculty of Medicine, 4 Rue Gabrielle Perret-Gentil, 1211 Geneva 14, Switzerland

Introduction

Occupational activity (OA) represents a high proportion of lifelong physical activity, particularly in manual workers, but it remains unknown whether chronic loading in the context of OA may have an impact on bone strength. Very few studies have investigated the influence of OA on bone properties and

fragility fracture risk in the general population. Only one study reported no clear and contradictory associations between physical workload on the hands and metacarpal cortical bone mass [1]. Conflicting results have been reported from cross-sectional studies about the association of bone mineral density (BMD) and OA. The association between bone and OA was classically reported in terms of epidemiologic associations with high-trauma fractures occurring during work time [2]. Epidemiological studies suggesting a possible protective influence of long-term exposure to heavy-loading OA on hip fragility fractures are biased by many confounding factors such as various nutritional, anthropometric and health-related patterns between groups [3–5]. These few heterogeneous data on the influence of OA and bone health reflect the methodological difficulties to consider the effects of lifelong OA and to distinguish leisure and home activities from OA [6].

Cortical bone is a major determinant of bone strength and fracture risk. It is influenced by genetic, physical, and nutritional factors [7, 8]. The increase in bone fragility with ageing results from reduced periosteal bone formation and increased endocortical resorption [9]. Exercise during growth increases bone size via periosteal apposition, whereas exercise at old age decreases endosteal bone loss in weight-bearing bone [10]. These positive effects of physical activity reflect the adaptation of bones to the loads they experience, as described by Wolff's law [11]. This is well illustrated in athletes, such as baseball players who develop load-adaptive changes of cortical bone in the humerus of the overloaded limbs, or olympic fencers in femurs [12–14]. However, this benefit may not be maintained throughout life. In a cross-sectional study, the high BMD observed in football players is no longer present in subjects aged over 60 years and retired for over 35 years, and fracture risk is not lower than predicted in older age [15]. Similarly, in professional baseball players, the benefits of loading on the humerus Ct.Ar and thickness decreases with ageing in former throwers, resulting in an increase of medullary expansion and cortex trabecularisation, with the maintenance of overall bone cross-sectional size [12].

Thus, the responsiveness of the skeleton to mechanical loading has been established in the frame of sports leisure activities [16, 17], in particular in elite athletes participating in unilateral dominant sports used as models for investigating skeletal responses to mechanical loading [12]. Whether mechanical stimuli generated by OA in manual workers of the general population are heavy enough to induce a skeletal response modulating bone strength has never been investigated. We used two approaches to test the influence of heavy-loading OA on bone with a focus on the non-weight-bearing skeleton to exclude the confounding effects of walking: (1) exvivo, by assessing an anthropologic bone collection with complete and reliable profession information and (2) in vivo, in a cohort of retired workers. Archaeological specimens from individuals who died in the first half of the 20th century can provide valuable information in addition to observational studies in living subjects [18, 19]. In our study, specimens represented a wide range of ages and were less subject to increased sedentary OA due to technological advances observed in our current societies. Thus, the benefit of heavy OA on cortical bone, which markedly contributes to bone strength, should be more perceptible. We hypothesised that chronic mechanical stresses induced by heavy-loading OA influence the geometry and mechanical properties of bones throughout life.

Methods

The anthropologic bone collection (ex vivo study)

The Simon collection is housed at the University of Geneva, Switzerland, and consists of 494 identified skeletons, including 477 adults (282 men; 195 women) aged 20 to 93 years who died between 1905 and 1968. The individuals in this collection were buried in 27 cemeteries in the Canton of Vaud, a rural area on the northern side of the Lake of Geneva. Gender, date of birth, age at death, geographical origins, kinship, and professions were recorded from district registries and death certificates [20, 21]. Due to its rural origin, this collection provides a unique opportunity to investigate a high proportion of subjects with heavy-loading OA. We analysed 206 paired humeri and 190 paired radii from 219 adult male skeletons with apparent adequate preservation and no fracture callus by computed tomography (CT) (Fig. 1a) [21].

Participants of the Geneva retirees cohort (in vivo study)

One hundred and eighty healthy men from the Geneva Retirees Cohort (GERICO) study recruited at time of retirement, i.e. 65 years, with bone microstructure data at distal radius were included in the in vivo study [22, 23]. Dietary calcium and protein intake were assessed by frequency questionnaires [24]. OA was recorded and physical loading related to lifelong OA and leisure time was separately quantified on a scale from 1 to 4 at various life periods (<9 years, 9–14 years, 15–25 years, 25–50 years and >50 years) using a face-to-face-administered questionnaire, as previously reported [25]. Grades of physical activity are defined as follows in this questionnaire: (1) grade light - eg sitting, office work; (2) grade moderate, e.g. light work involving standing; (3) grade heavy, e.g. moderately painful work, lifting heavy loads; (4) grade very heavy, e.g. very tedious work, agricultural or construction workers, professional sports. Lifelong quantitative loading activities (scale 1–4) represents the mean score of physical activity levels adjusted for the duration of each life period. The study protocol was approved by the ethics committee of the
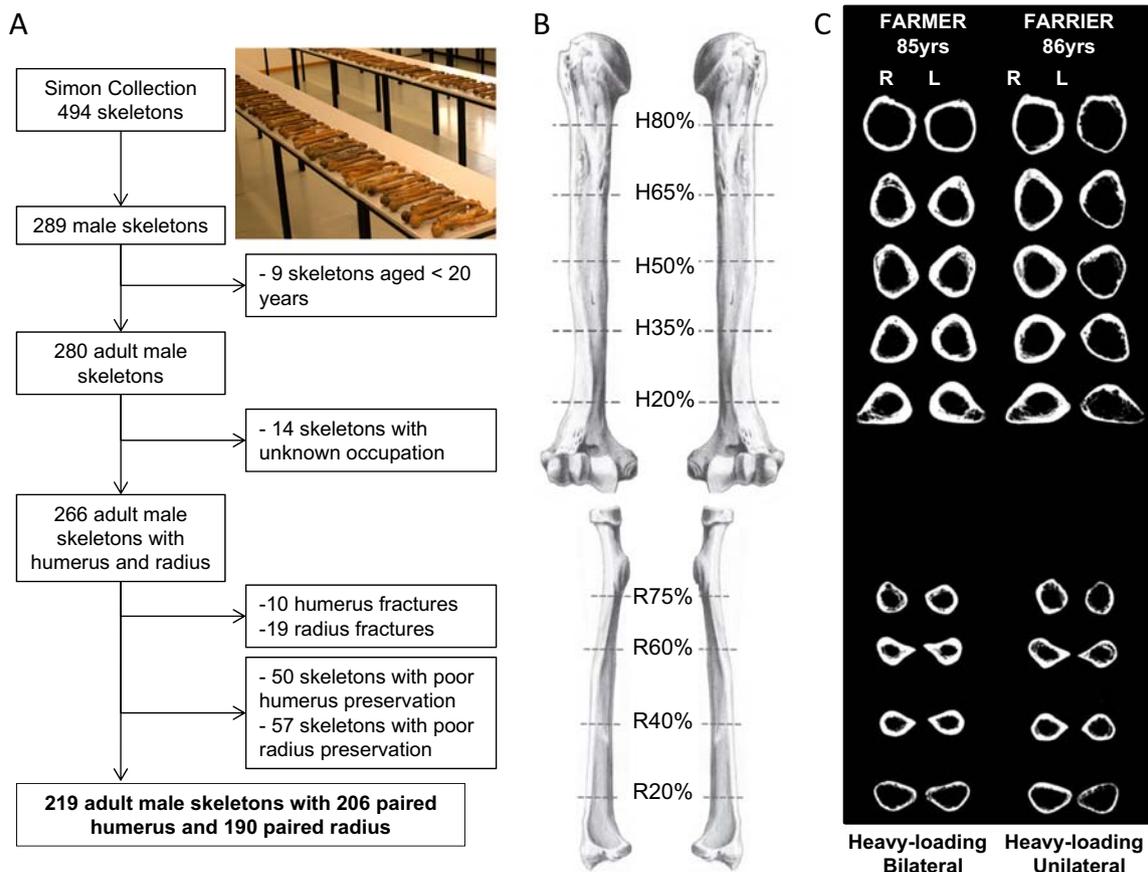
Fig. 1 a: Flowchart of the 219 selected skeletons for humeri and radii scans from the Simon anthropologic collection. **b** Cross sections at 80 %, 65 %, 50 %, 35 % and 20 % of humerus length and 75 %, 60 %, 40 % and 20 % of radius length where geometrical and mechanical properties were measured and calculated from CT scans. **c** Corresponding cross-sections of the humeri and radii of two brothers who died at the age of 85 and 86 years, respectively, illustrating the asymmetry of Ct.Ar and Me.Ar, according to the lateralization of heavy-loading OA. The asymmetry observed in a farrier (unilateral) is not observed in his brother of the same age, a farmer (bilateral). The age-related alteration of cortical bone is mainly observed at the non-dominant limb of the farrier (*R*, right; *L*, left)

Geneva University Hospitals and all subjects provided written informed consent.

Occupational activity classification

Identical criteria were used to categorise the OA intensity of subjects in the ex vivo and in vivo studies. Individuals were classified according to physical loading applied on the upper limbs associated with their OA. We used the criteria defined during a workshop "Musculoskeletal Stress Markers (MSM): limitations and achievements in the reconstruction of past activity patterns" (Coimbra University, 2009: http://www.uc.pt/en/cia/msm/) by an occupation working group of anthropologists [26]. Individuals were divided into light-loading and heavy-loading groups according to the intensity of physical loading associated with their OA (Tables 1 and 4). Intensity was considered heavy if the OA included the carrying of loads, the use of heavy tools requiring muscle strength, the practise of activities with repeated load bearing or repeated movement likely to induce shortness of breath (based on the biomechanical criteria "manual", "carrying of heavy loads", "intensity" and "hard work" of the group). In the ex vivo study, the heavy-loading OA group was subdivided into unilateral or bilateral groups according to the lateralisation of physical loading applied on the upper limbs (based on the biomechanical criteria "occupation specialisation" and "unilateral repetitive movement of the upper limbs" of the group).

Individuals included in the ex vivo study were classified into three categories of OA as follows (number of subjects in parentheses): *light-loading OA* accountant (2), attendant (1), architect (1), bank employee (1), car sales employee (2), cashier (1), cobbler (2), cook (1), dairy controller (1), driver (4), electrician (2), factory foreman (2), factory toolmaker (1), factory worker (9), fisherman (1), furnisher (1), gardener (1), glassmaker (2), hairdresser (2), hotel employee (1), industrialist (2), innkeeper (2), maintenance agent (1), merchant (6), no occupation (3), notary (1), office employee (5), painter (2), pensioner (1), plasterer (2), policeman (1), postman (1), post office employee (3), pork butcher (1), ranger (2), saddler (1), secretary (2) and train station employee (3); *bilateral heavy-*

Table 1 Characteristics of subjects of the Simon collection according to their occupational activity group

Occupational activity groups	Light-loading OA ($n=77$)	Heavy-loading OA ($n=142$)		P
		Bilateral ($n=94$)	Unilateral ($n=48$)	
	Non-manual and manual light specialised OA	Manual non-specialised OA	Manual heavy specialised OA	
Age at death (years)	55 [45–69]	60 [48–72]	57 [40–72]	0.559
Year of birth				
1838-1860	1 (1 %)	8 (9 %)	3 (6 %)	
1861-1890	32 (42 %)	49 (52 %)	19 (40 %)	0.110
1891-1920	40 (52 %)	32 (34 %)	21 (44 %)	
1921-1934	4 (5 %)	5 (5 %)	5 (10 %)	
Age group at death (years)				
20–45	21 (27 %)	22 (24 %)	15 (31 %)	
46–65	33 (43 %)	36 (38 %)	16 (33 %)	0.673
66–93	23 (30 %)	36 (38 %)	17 (36 %)	
Handedness (right-handed %)[a]	66 (86 %)	75 (80 %)	42 (87 %)	0.411
Humerus length (mm)	332 [323–344]	331[320–347]	329 [320–343]	0.749
Radius length (mm)	242 [234–252]	243 [235–251]	240 [235–248]	0.790

Data are median [interquartile range] or number (%). *OA* occupational activity

[a] determined according to the global directional asymmetry profile of linear geometrical properties of the humeri and radii

loading OA farmers/farm workers/labourers (94); *unilateral heavy-loading OA* baker (4), bricklayer (4), carpenter (1), cheese maker (2), cooper (1), farrier (4), locksmith (3), lumberjack (11), miller (2), roadman (2), sawyer (2), stonecutter (1), tinsmith (1), winemaker (9) and wheelwright (1).

Bone geometry and strength assessment

Ex vivo group

Bone geometry, including the maximum length (l, in mm) of the humerus and radius, the Tt.Ar (mm^2), Me.Ar (mm^2), Ct.Ar (mm^2) and the percentage of Ct.Ar (Ct.Ar/Tt.Ar), was assessed using a multi-detector row helical CT scanner (Philips Medical Systems MX8000 IDT 16, Hamburg, Germany, parameters of 16 slices, 120 kVp, 240 mAs, 16×0.75-mm collimation; pitch 2-mm and 1-mm slice thickness; voxel size 0.25 mm×0.25 mm×0.4 mm) on cross-sections at 80 %, 65 %, 50 %, 35 % and 20 % of the length of the two humeri and 75 %, 60 %, 40 % and 20 % of the length of the two radii (Fig. 1b and c). CT-derived measures enable to predict humeri and radii biomechanical properties [27, 28]. Estimates of bone strength were determined for each cross-section including the following: the cross-sectional moments of inertia (CSMI, mm^4) in the antero-posterior, medio-lateral, maximal and minimal diameter axis, representing the medio-lateral, antero-posterior, and minimal and maximal bending strength, respectively; the polar moment of inertia (J, mm^4) was obtained by adding the two maximum and minimum CSMI, reflecting torsional strength; the antero-posterior

and medio-lateral section modulus (Z, mm^3), as the ratio of bending strength to its maximally distributed distance on the bending axis, was calculated as the CSMI divided by the distance to the centre of the shaft. To take into account the variability of anthropometric parameters between individuals, the ratio of areas to length^2, CSMI to length^4, J to length^4 and Z to length^3 were calculated to adjust for the humeri or radii length [29]. All geometric and mechanical parameters were analysed at each cross-section and by averaging all cross-section values for the humeri and the radii separately.

In vivo group

Volumetric bone mineral density (vBMD) and microstructure variables were determined at the distal radius by high-resolution peripheral quantitative computed tomography (HR-pQCT) using an Xtreme CT instrument (Scanco Medical, Bassersdorf, Switzerland) as previously described [24]. In brief, the HR-pQCT images were filtered and the bone was segmented using the standard method recommended by the manufacturer. The periosteal and endosteal boundaries were defined using an automated contouring method [30]. Cortical thickness was then defined by applying a distance transformation function to the cortical compartment. Cortical porosity (percentage) was calculated as the number of void voxels in each binary cortex image divided by the total number of voxels. Determinations were performed on the non-dominant limb, unless a fracture was reported in the region of interest. Recorded variables were as follows: total, cortical, and trabecular vBMD, expressed as milligrammes per cubic centimetre of

calcium hydroxyapatite (mg/cm3); total area, cortical and trabecular areas (mm2); trabecular number (mm^{-1}), thickness and spacing (μm); trabecular spacing standard deviation (SD), an estimate of the heterogeneity of the trabecular structure (μm); and mean cortical thickness (μm). A finite element model of the radius was created directly from the segmented HR-pQCT images to calculate bone stiffness (kilo-Newton per millimetre=kN/mm), estimated failure load (N) using the criterion described by Pistoia and colleagues [31], and apparent modulus (N/mm2), an estimate of stiffness corrected for Tt.Ar. All finite element analyses were done using the finite element solver integrated in the IPL software version 1.15 (Scanco Medical AG), as previously described [24].

Skeleton asymmetry and handedness assessment

Handedness induces a natural asymmetry of linear geometrical properties with higher values in the dominant limb [32]. Handedness was determined for each skeleton according to the global directional asymmetry profile of linear geometrical properties of the humeri and radii, determined according to Mays and colleagues as asymmetry=[(right–left)/ ((right+left)/2)]×100, making it possible to take into account both its intensity and direction [33, 34]. For other analyses, absolute asymmetry of cross-section parameters were determined between the dominant and non-dominant limbs, as asymmetry=[(dominant–non-dominant)/(non dominant)]×100. For comparison between groups, asymmetry of geometric parameters was analyzed only at the humeri because the latter have larger bone areas than radii, providing thus data with lower variability.

Statistical analyses

Age at death of individuals from the anthropologic collection was divided into three categories: 20–45 years, 46–65 years, and 66–93 years. Data are reported as medians and interquartile ranges or numbers and percentages. As most variables were not normally distributed, nonparametric tests (Mann–Whitney and Kruskal–Wallis tests) were used to assess differences in continuous variables between groups. A chi-squared test was used for differences in frequency. Statistical analyses were performed using STATA software, version 12.1 (StataCorp LP, College Station, TX, USA).

Results

Heavy-loading occupational activity is associated with greater calculated strength and higher total and cortical areas in young men

The characteristics of individuals from the skeleton collection did not differ between OA groups (Table 1). One hundred eighty-three skeletons (84 %) were presumed right-handed men. Age was negatively associated with Ct.Ar and positively associated with Me.Ar (Fig. 2).
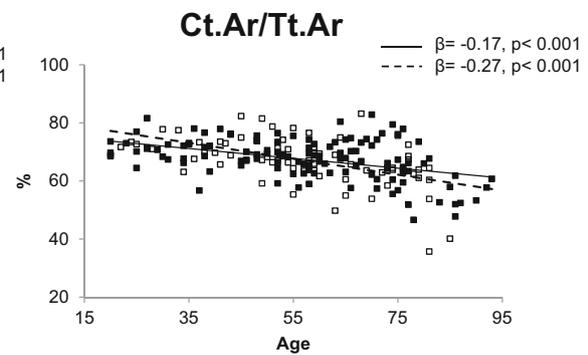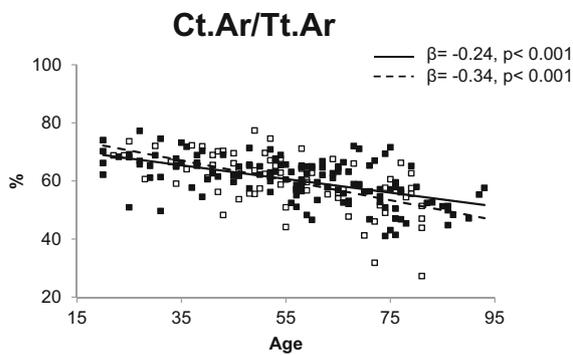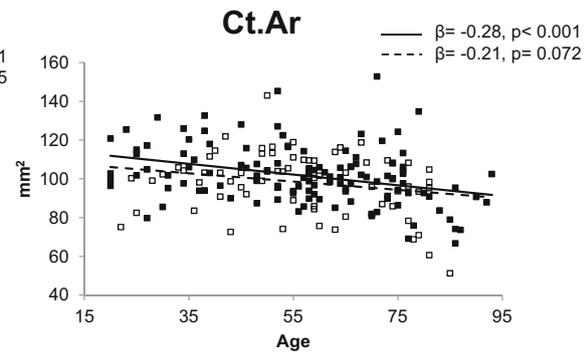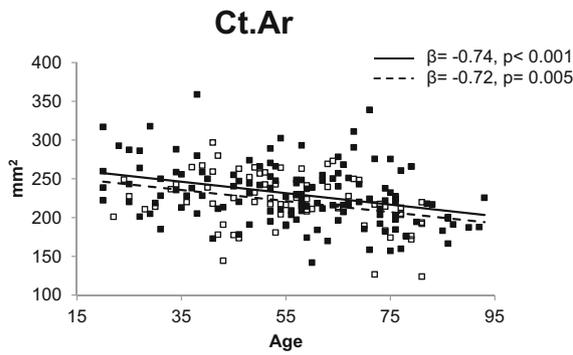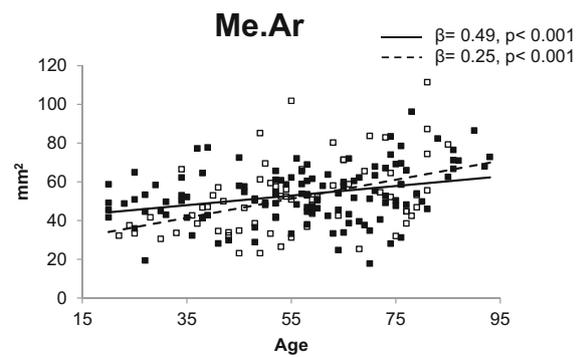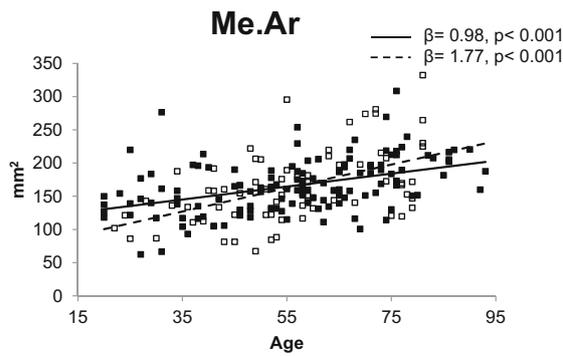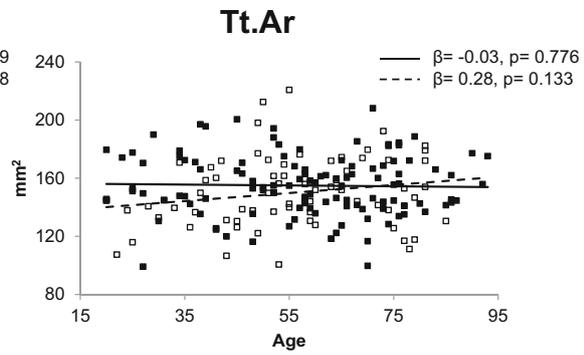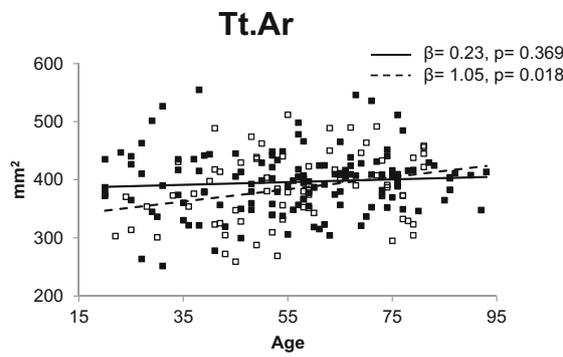
Table 2 shows the influence of heavy-loading OA on bone strength and geometry at the dominant upper limb. Men with heavy-loading OA had higher bending strength at the radius (antero-posterior and minimum CSMI +11.7 % and +10.3 %; $p=0.035$ and 0.037, respectively). Analyses according to age of death revealed that greater bone strength in the heavy-loading OA group was observed only in men who died between the age of 20 and 45 years. In this age class, all radii strength parameters were greater: higher bending strength (CSMI +14.4 to +27.2 %; $p=0.014-0.005$), torsional strength (J +23.8 %; $p=0.006$), and section modulus (+10.2 and + 19.7 %; $p=0.010–0.004$). At humeri, medio-lateral, minimum and maximum CSMI, and medio-lateral section modulus were higher (+27.6 %, +18.5 %, +35.3 %, and +18.3 %, respectively, all p values <0.05). The greater mechanical properties in men with heavy vs light-loading OA in the age group 20–45 were associated with larger Tt.Ar at the humerus and radius (+ 10.1 %, $p=0.027$ and +10.6 %, $p=0.004$, respectively) and larger Me.Ar and Ct.Ar at the radius (+31 %, $p=0.015$ and + 5.7 %, $p=0.045$, respectively). The Me.Ar increased in parallel with Tt.Ar, with no difference between groups in the Ct.Ar/ Tt.Ar ratio. These differences were not detected in men who were over 45 years at death, with values in the light-loading OA group gradually reaching those observed in the heavy-loading OA group, in which Tt.Ar at the humerus and radius did not significantly increase with age (Fig. 2). The differences in Tt.Ar and Ct.Ar between the heavy and light-loading OA groups at each of the nine cross-sections are shown in supplemental Table S1.

Heavy-loading occupational activity slows down the age-related endocortical expansion

Secondly, we focused on the heavy-loading OA group to investigate the asymmetry of geometrical parameters between the dominant and non-dominant limbs. We hypothesised that asymmetry should be higher in men with unilateral vs bilateral OA in a time-dependent manner. Asymmetry of humeri Tt.Ar, Me.Ar, and Ct.Ar/Tt.Ar ratio increased according to the age group, but this age-dependent increase of asymmetry was more marked in the unilateral group than the bilateral group (Table 3). Asymmetry was higher in the unilateral vs bilateral OA groups in men who died over the age of 65 years (Me.Ar asymmetry +15.2 % vs +9.1 %, $p=0.007$; Tt.Ar asymmetry + 7.8 % vs +5.0 %, $p=0.043$; Ct.Ar/Tt.Ar ratio asymmetry + 7.0 % vs +2.8 %, $p=0.002$). In this age group, values of geometric parameters at the dominant limb were similar in the unilateral and the bilateral heavy-loading OA groups. At the non-dominant distal humerus, Me.Ar was 18.4 % lower in the bilateral group ($p=0.033$) and associated with a 16.6 %

HUMERUS

RADIUS

Tt.Ar

— β= 0.23, p= 0.369
--- β= 1.05, p= 0.018

Tt.Ar

— β= -0.03, p= 0.776
--- β= 0.28, p= 0.133

Me.Ar

— β= 0.98, p< 0.001
--- β= 1.77, p< 0.001

Me.Ar

— β= 0.49, p< 0.001
--- β= 0.25, p< 0.001

Ct.Ar

— β= -0.74, p< 0.001
--- β= -0.72, p= 0.005

Ct.Ar

— β= -0.28, p< 0.001
--- β= -0.21, p= 0.072

Ct.Ar/Tt.Ar

— β= -0.24, p< 0.001
--- β= -0.34, p< 0.001

Ct.Ar/Tt.Ar

— β= -0.17, p< 0.001
--- β= -0.27, p< 0.001

◄ **Fig. 2** Effect of heavy-loading occupational activity on the cross-sectional geometry of humerus and radius of the dominant upper limb. Cross-sectional geometrical areas adjusted for length^2 at the dominant humerus and radius in the heavy-loading occupational activity group (—, black marker ■) and the light-loading occupational activity group (− − −, white marker □), according to age. For areas, each point represents for each subject the ratio of the average area at the five cross-sections of the humerus or four cross-sections of the radius to humerus or radius length^2, multiplied by the mean of average areas in all the subjects. The beta-coefficients of the linear regressions of the bone areas adjusted for length^2, with the corresponding p values, are indicated. Tt.Ar, total area; Me.Ar, medullary area; Ct.Ar, cortical area

higher Ct.Ar/Tt.Ar ratio ($p=0.020$) (supplemental Table S2). These data indicate that the increase of asymmetry with age is compatible with the hypothesis of an attenuation of age-related endocortical expansion by heavy-loading OA on the limb on which they are applied (most workers with heavy loading OA in the first part of the twentieth century continued to work hard after the current retirement age limit). This hypothesis is particularly well illustrated in Fig. 1c representing asymmetry of cross-sections of the humeri and radii of two elderly brothers with lateralized heavy-loading OA for one and non-lateralized heavy-loading OA for the other.

In vivo, men retired from heavy-loading occupational activity have higher estimated bone stiffness associated with lower bone microstructure alterations

We investigated in vivo cortical and trabecular (Tb) bone microstructure at the distal radius in 180 men of the GERICO cohort to confirm and better characterise the exvivo analyses, which suggested that mechanical stress induced by OA influenced bone strength by two of its determinants, Tt.Ar and endocortical expansion (which may be due to higher bone resorption, lower bone formation or both). We categorised the group into heavy-loading ($n=20$) and light-loading OA ($n=160$), using the same criteria applied to the ex vivo specimens (Table 4). There was no difference in age, anthropometric characteristics and tobacco and alcohol consumption between the two groups. The OA category was highly correlated with self-reported and time-adjusted cumulative quantitative OA loading ($p<0.001$), while there was no difference regarding leisure and sport time loading between the two groups ($p=0.580$). Protein intake was higher in men with heavy-loading OA ($p=0.003$). Bone stiffness and estimated failure load were higher in the heavy-loading OA group (+13.8 %, $p=0.015$ and +11.4 %, $p=0.017$, respectively) with similar Tt.Ar ($p=0.339$), thus confirming the ex vivo study; the Ct.Ar tended to be higher (+14.5 %; p=0.066). As there is no medullary cavity at the distal radius, we hypothesised that lower Tb bone alteration on HR-pQCT scans in vivo would be the parallel of the lower endocortical expansion observed on cross-sections of skeletal bones. This hypothesis was confirmed and the positive effect on bone stiffness and failure load was associated

with a lower Tb bone microstructure alteration in the heavy-loading OA group (Tb.BMD +12.7 %, $p=0.021$; Tb. spacing −7.1 %, $p=0.049$; Tb. number +7.4 %, $p=0.084$; Tb. thickness +7.2 %, $p=0.054$). Apart from this benefit on endocortical and Tb bone, we did not observe any benefit on intracortical compartment, as shown by the similar cortical density and the apparent higher cortical porosity ($p=0.037$) in the heavy-loading versus light-loading OA groups.

Discussion

These ex vivo and in vivo studies show that lifelong heavy-loading OA increase bone strength. This benefit is associated with two independent mechanisms influencing bone mass and strength: higher Tt.Ar and Me.Ar during early adulthood, and a slowdown of the age-related expansion in the Me.Ar and alteration of the Tb bone compartment.

The higher Tt.Ar observed in young manual workers suggests that OA-related mechanical stress promotes bone growth before peak bone size has been reached and during early adulthood. Heavy-loading OA, in particular farming, classically started early in youth in the twentieth century, a period during which the effect of OA on bone acquisition has been previously demonstrated [10]. In adults, Tt.Ar increases by periosteal apposition, which has been suggested to compensate endocortical bone loss observed with ageing and reduce the total net loss of bone [7, 35]. In the heavy-loading OA groups, the potential decrease of age-related bone resorption in elderly men, illustrated by the marked asymmetry of the medullary cavity and the lower alteration of Tb bone parameters, might explain the absence of Tt.Ar expansion. Manual OA (e.g. farmers) was usually maintained long after the age of 65 years in the twentieth century. In the light-loading OA group, no OA-related mechanical stress slowed bone loss and Tt.Ar continued to increase slowly until it caught up with the heavy-loading OA group, thus explaining why the early benefit on Tt.Ar attenuates with ageing. Thus, the benefit of heavy-loading OA on cortical bone results in the net difference between Tt.Ar and age-related endocortical expansion. In heavy-loading vs light-loading-OA, Tt.Ar and endocortical expansion are, respectively, higher and similar in young adult men, similar and lower in elderly men.

The impact of heavy OA on bone width observed in this study is consistent with previous anthropological studies in different ethnic groups. Differences in cross-sectional geometry parameters and structural adaptations according to physical activities were identified in long bones in these studies (humerus and femur mainly) [36–39], while this change has not been observed in metacarpal cortical bone [40].

We did not observe difference of asymmetry of areas between the bilateral and unilateral heavy-loading group in the age group 20–45, in contrast to previous reports in athletes

Table 2 Percent median difference (Δ) between the heavy- and light-loading occupational activity groups in mean values of geometric and mechanical properties of the five cross-sections of humeri and four cross-sections of radii at the dominant upper limb, according to age group

		HUMERUS								RADIUS							
Age group		All		20–45 years		46–65 years		66–93 years		All		20–45 years		46–65 years		66–93 years	
N		206		56		83		67		190		50		75		65	
		Δ (%)	P	Δ (%)	P	Δ (%)	P	Δ (%)	P	Δ (%)	P	Δ (%)	P	Δ (%)	P	Δ (%)	P
Bone strength																	
CSMI	Antero-posterior	+7.9	0.171	+23.2	0.083	+0.7	0.822	+13.5	0.339	+11.7	*0.035*	+26.8	*0.005*	+0.3	0.991	+5.3	0.265
	Medio-lateral	+5.1	0.113	+27.6	*0.026*	−0.7	0.859	+5.1	0.445	+0.5	0.496	+14.4	*0.014*	−5.9	0.372	−4.8	1.000
	Minimum	+5.8	0.189	+18.5	*0.026*	−3.1	0.600	+11.9	0.445	+10.3	*0.037*	+27.2	*0.005*	−2.4	0.923	+7.7	0.339
	Maximum	+3.4	0.105	+35.3	*0.046*	+2.2	0.978	+2.1	0.346	+2.5	0.459	+15.6	*0.010*	−5.5	0.366	−5.6	0.908
Polar moment of inertia (J)		+3.7	0.133	+27.7	0.056	−0.6	0.837	+6.3	0.339	+2.8	0.187	+23.8	*0.006*	−5.0	0.583	−3.2	0.696
Section modulus (Z)	Antero-posterior	+2.3	0.137	+15.3	0.066	−0.4	0.808	+6.4	0.171	+4.7	0.071	+19.7	*0.004*	−4.3	0.872	+1.6	0.401
	Medio-lateral	+3.2	0.147	+18.3	*0.030*	−0.9	0.655	+0.9	0.245	+1.3	0.379	+10.2	*0.010*	−4.1	0.471	−5.6	0.851
Geometric properties																	
Tt.Ar		+5.4	0.212	+10.1	*0.027*	+1.5	0.743	+0.3	0.939	+3.2	0.088	+10.6	*0.004*	−0.5	0.755	+3.9	0.622
Ct.Ar		+4.2	0.178	+6.2	0.141	+2.1	0.933	+6.7	0.112	−0.2	0.591	+5.7	*0.045*	−3.0	0.401	+0.9	0.685
Me.Ar		+4.0	0.391	+9.4	0.107	+0.5	0.670	−1.9	0.549	+4.9	0.175	+31.0	*0.015*	+0.6	0.906	+8.1	0.988
Ct.Ar /Tt.Ar		+1.4	0.974	−0.6	0.654	−0.9	0.933	+0.6	0.350	−0.2	0.852	−2.2	0.227	+1.8	0.780	+0.9	0.609

Items in italics are statistically significant *p*-values

Tt.Ar total area, *Ct.Ar* cortical area, *Me.Ar* medullary area, *CSMI* cross-sectional moments of inertia, *OA* occupational activity

[12, 13]. Differences of asymmetry were however observed in the oldest group in which loading was applied during a longer period of time. Physiological conditions in manual workers of the general population cannot be assimilated to those observed in athletes. Athletes provide an experimental model in which intensity of loading, muscle mass and strength surrounding the bones and nutritional intakes are amplified, leading to maximising the effects on bone geometry (Tt.Ar in this age class). These data suggest that a longer time is needed to observe the effect of loading in the physiological conditions of manual workers of the general population, as compared to specific models.

Several mechanisms may be involved in these processes. First, a direct effect of mechanical stimuli on bone cells might be mediated by osteocytes, which sense mechanical loading to produce signals, such as sclerostin or periostin [41, 42]. Second, the benefit of heavy-loading OA might be partly related to environmental confounding factors, such as nutritional or lifestyle factors, which may reflect the sociocultural influence of profession. Participants from the GERICO cohort with heavy-loading OA had higher protein intake, a well-known factor contributing to bone health [43]. However, in the Simon collection of skeletons, the higher asymmetries between the dominant and non-dominant limbs of men from the unilateral heavy-loading group suggest that the contribution of genetic and environmental factors is probably limited. Moreover, the Simon anthropologic collection is a remarkable homogeneous collection from a predominantly rural region in a well-defined area. In particular, calcium and protein intake were probably rich in local farm products, especially at the end of the nineteenth century and during the twentieth century. In addition, its genetic variability is reduced with little population migration and frequent kinships, obvious occupations may pass down through generations (sons of manual workers would tend to become manual workers themselves and marry daughters of manual workers).

A particular strength of our study is the use of unique datasets and methodologies to investigate the effects of lifelong OA on bone. Occupation classification categories were highly correlated with OA levels collected with a face-to-face-administered questionnaire in the GERICO cohort. By focusing on the humeri and radii, we eliminated the interference of OA-independent loading that may be observed in lower limb bones. Ex vivo data are in agreement with those observed in vivo at time of retirement in the GERICO cohort or specific conditions of various athletic sports [12, 13, 17]. Moreover, data from the GERICO cohort allowed determining which microstructural parameters were influenced by OA. Interestingly, an effect of loading on Tb bone was observed in addition to that one on cortical bone, the latter being mediated by an influence on endosteal rather than intracortical remodelling. The main limitations are the cross-sectional designs and the methodology that did not allow taking into account age-related changes in bone parameters, neither potential lifelong

Table 3 Asymmetry of mean values of geometric properties of the five cross-sections of humeri between the unilateral and bilateral heavy-loading occupational activity groups, according to age group

Age group	20–45 years				46–65 years				66–93 years				P age trend for bilateral	P age trend for unilateral
Heavy-loading OA	Asymmetry (%)		Δ (%pts)	P	Asymmetry (%)		Δ (%pts)	P	Asymmetry (%)		Δ (%pts)	P		
	Bilateral (n=19)	Unilateral (n=14)			Bilateral (n=32)	Unilateral (n=15)			Bilateral (n=29)	Unilateral (n=14)				
Tt.Ar	4.3 [2.3]	3.9 [2.2]	−0.3	0.799	4.8 [4.1]	3.9 [4·0]	−0.9	0.424	5.0 [3.3]	7.8 [5.6]	+2.9	*0.043*	0.579	*0.024*
Ct.Ar	3.7 [3.1]	2.8 [2.3]	−0.9	0.190	3.8 [3.5]	2.6 [3.6]	−1.1	0.632	2.7 [3.8]	4.3 [8.8]	+1.6	0.243	0.804	0.207
Me.Ar	5.6 [4.9]	5.5 [8.2]	−0.1	0.229	7.7 [7.2]	9.7 [10.3]	+2.0	0.819	9.1 [4.4]	15.2 [10.0]	+6.0	*0.007*	0.053	*0.026*
Ct.Ar/Tt.Ar	1.4 [1.6]	1.8 [2.8]	+0.5	0.489	2.7 [3.6]	2.6 [3.2]	−0.1	0.837	2.8 [3.1]	7.0 [5.9]	+4.1	*0.002*	*0.023*	*0.001*

Items in italics are statistically significant *p*-values. Data are median (interquartile range)

Tt.Ar total area, *Ct.Ar* cortical area, *Me.Ar* medullary area

changes in occupational and leisure time activities. Although probably less frequent in the first half of the twentieth century than nowadays, these changes may also be observed in a same professional group, a younger man tending to work harder than an older one because of different physical abilities and of workload changes (older workers with professional

Table 4 Characteristics of men included in the GERICO cohort and geometric and mechanical properties at distal radius according to occupational activity group

	Light-loading OA (N=160)	Heavy-loading OA (N=20)	P
Age (years)	65.1 [2.5]	66.0 [3.1]	0.287
Height (cm)	175 [9]	174 [9]	0.542
Weight (kg)	80.7 [17.2]	80.2 [18.4]	0.759
Body mass index (kg/m2)	26.2 [4.4]	26.3 [7.1]	0.387
Clinical fracture in adult age	76 (47 %)	11 (55 %)	0.527
Calcium intake (mg/day)	1218 [555]	1374 [627]	0.062
Protein intake (g/day)	81.4 [28.4]	101.4 [30.0]	*0.003*
Lifelong quantitative loading activities (scale 1–4)			
Occupational activity time	1.7 [1]	3.0 [1.3]	*<0.001*
Leisure and sport time	3.0 [0.7]	3.0 [0.7]	0.580
Biomechanical parameters			
Stiffness (kN/mm)	106.1 [29.3]	120.9 [36.3]	*0.015*
Estimated failure load (N)	3795 [933]	4226 [1161]	*0.017*
Apparent modulus (N/mm2)	1874 [580]	1931 [428]	0.178
Volumetric bone mineral density (mg HA/cm3)			
Total BMD	324 [76]	338 [88]	0.171
Trabecular BMD	169 [46]	190 [59]	*0.021*
Cortical BMD	874 [56]	877[62]	0.769
Tt.Ar (mm2)	360 [74]	361 [112]	0.339
Trabecular area (mm^2)	280 [86]	298 [126]	0.551
Cortical area (mm^2)	69.6 [18.7]	79.7 [18.4]	0.066
Cortical thickness (μm)	850 [220]	930 [270]	0.228
Cortical porosity (%)	2.8 [1.4]	3.3 [1.1]	*0.037*
Trabecular number (mm^{-1})	2.04 [0.37]	2.19 [0.26]	0.084
Trabecular thickness (μm)	69 [16]	74 [11]	0.054
Trabecular spacing (μm)	417 [96]	387 [65]	*0.049*
Trabecular spacing standard deviation (μm)	175 [55]	157 [35]	0.065

Items in italics are statistically significant *p*-values. Data are median (interquartile range) or number of subjects (%)

OA occupational activity, *BMD* bone mineral density, *Tt.Ar* total area

experience will tend to teach or supervise younger workers). Regarding the statistical analysis, we did not apply a Bonferroni correction to take into account multiple comparisons because this correction assumes that all the tests performed are independent. This type of correction would be too restrictive to be applied in this study with strongly correlated variables [44].

To our knowledge, this is the first report showing the benefit of OA-dependent repeated loading on bone strength based on ex vivo and in vivo data. Cortical bone appears to be modulated by heavy-loading OA by two mechanisms: promotion of Tt.Ar and Me.Ar in young adulthood followed by slowdown of the age-related bone loss at endocortical and trabecular surfaces. From a general and public health point of view, these data provide a rationale to suggest that sedentary OA due to technological advancement observed in our current society will contribute to lifelong higher bone fragility and fracture risk with ageing and support the necessity to promote lifelong load-bearing physical activities for bone health.

Compliance with ethical standards

Conflict of interest Dr. van Rietbergen reports personal fees from Scanco Medical AG, outside the submitted work; Emmanuel Biver, Geneviève Perréard Lopreno, Magaly Hars, Jean-Paul Vallée, Serge Ferrari, Marie Besse, and René Rizzoli declare that they have no conflict of interest.

References

1. Vehmas T, Solovieva S, Riihimaki H, Luoma K, Leino-Arjas P (2005) Hand workload and the metacarpal cortical index. A study of middle-aged teachers and dentists. Osteoporos Int 16:672–680

2. Islam SS, Biswas RS, Nambiar AM, Syamlal G, Velilla AM, Ducatman AM, Doyle EJ (2001) Incidence and risk of work-related fracture injuries: experience of a state-managed workers' compensation system. J Occup Environ Med 43:140–146

3. Cooper C, Wickham C, Coggon D (1990) Sedentary work in middle life and fracture of the proximal femur. Br J Ind Med 47:69–70

4. Jaglal SB, Kreiger N, Darlington GA (1995) Lifetime occupational physical activity and risk of hip fracture in women. Ann Epidemiol 5:321–324

5. Suen LK (1998) Occupation and risk of hip fracture. J Public Health Med 20:428–433

6. Moayyeri A, Besson H, Luben RN, Wareham NJ, Khaw KT (2010) The association between physical activity in different domains of life and risk of osteoporotic fractures. Bone 47:693–700

7. Seeman E (2002) Pathogenesis of bone fragility in women and men. Lancet 359:1841–1850

8. Dennison EM, Jameson KA, Edwards MH, Denison HJ, Aihie Sayer A, Cooper C (2014) Peripheral quantitative computed tomography measures are associated with adult fracture risk: the Hertfordshire cohort study. Bone 64:13–17

9. Szulc P, Seeman E, Duboeuf F, Sornay-Rendu E, Delmas PD (2006) Bone fragility: failure of periosteal apposition to compensate for increased endocortical resorption in postmenopausal women. J Bone Miner Res 21:1856–1863

10. Rizzoli R, Bianchi ML, Garabedian M, McKay HA, Moreno LA (2010) Maximizing bone mineral mass gain during growth for the prevention of fractures in the adolescents and the elderly. Bone 46:294–305

11. Wolff J (1892) The principle of transformation of bone. A Hirschwald, Berlin

12. Warden SJ, Mantila Roosa SM, Kersh ME, Hurd AL, Fleisig GS, Pandy MG, Fuchs RK (2014) Physical activity when young provides lifelong benefits to cortical bone size and strength in men. Proc Natl Acad Sci U S A 111:5337–5342

13. Chang G, Regatte RR, Schweitzer ME (2009) Olympic fencers: adaptations in cortical and trabecular bone determined by quantitative computed tomography. Osteoporos Int 20:779–785

14. Kannus P, Haapasalo H, Sankelo M, Sievanen H, Pasanen M, Heinonen A, Oja P, Vuori I (1995) Effect of starting age of physical activity on bone mass in the dominant arm of tennis and squash players. Ann Intern Med 123:27–31

15. Karlsson MK, Linden C, Karlsson C, Johnell O, Obrant K, Seeman E (2000) Exercise during growth and bone mineral density and fractures in old age. Lancet 355:469–470

16. Nilsson M, Ohlsson C, Mellstrom D, Lorentzon M (2013) Sport-specific association between exercise loading and the density, geometry, and microstructure of weight-bearing bone in young adult men. Osteoporos Int 24:1613–1622

17. Nilsson M, Sundh D, Ohlsson C, Karlsson M, Mellstrom D, Lorentzon M (2014) Exercise during growth and young adulthood is independently associated with cortical bone size and strength in old Swedish men. J Bone Miner Res 29:1795–1804

18. Ruff CB (2005) Mechanical determinants of bone form: insights from skeletal remains. J Musculoskelet Nueronal Interact 5:202–212

19. Perréard Lopreno GES (2003) Une démarche actualiste en paléoanthropologie: la collection de squelettes de référence. In: Besse M, Stahl Gretsch LI, Curdy P (eds) ConstellaSion: hommage à Alain Gallay, vol 95. Cahiers d'archéologie romande, Lausanne, pp 463–472

20. Gemmerich I (1999) Création d'une collection anthropologique de référence et application des caractères discrets dans le cas de généalogies connues. Geneva, p 277

21. Perréard Lopreno G (2007) Adaptation structurelle des os du membre supérieur et de la clavicule à l'activité : analyse de l'asymétrie des propriétés géométriques de sections transverses et de mesures linéaires dans une population identifiée (collection SIMON). Université de Genève (PhD, archives ouvertes)

22. Durosier C, van Lierop A, Ferrari S, Chevalley T, Papapoulos S, Rizzoli R (2013) Association of circulating sclerostin with bone mineral mass, microstructure, and turnover biochemical markers in healthy elderly men and women. J Clin Endocrinol Metab 98:3873–3883

23. Bonnet N, Biver E, Durosier C, Chevalley T, Rizzoli R, Ferrari S (2015) Additive genetic effects on circulating periostin contribute to the heritability of bone microstructure. J Clin Endocrinol Metab 100:E1014–E1021

24. Chevalley T, Bonjour JP, van Rietbergen B, Rizzoli R, Ferrari S (2012) Fractures in healthy females followed from childhood to early adulthood are associated with later menarcheal age and with impaired bone microstructure at peak bone mass. J Clin Endocrinol Metab 97:4174–4181

25. Silman AJ, O'Neill TW, Cooper C, Kanis J, Felsenberg D (1997) Influence of physical activity on vertebral deformity in men and women: results from the European vertebral osteoporosis study. J Bone Miner Res 12:813–819

26. Perréard Lopreno G, Alves Cardoso F, Assis S, Milella M, Speith N (2013) Categorization of occupation in documented skeletal collections: its relevance for the interpretation of activity-related osseous changes. Int J Osteoarchaeol 23:175–185

27. Kontulainen SA, Johnston JD, Liu D, Leung C, Oxland TR, McKay HA (2008) Strength indices from pQCT imaging predict up to 85% of variance in bone failure properties at tibial epiphysis and diaphysis. J Musculoskelet Nueronal Interact 8:401–409

28. Weatherholt AM, Avin KG, Hurd AL, Cox JL, Marberry ST, Santoni BG, Warden SJ (2014) Peripheral quantitative computed tomography predicts humeral diaphysis torsional mechanical properties with good short-term precision. J Clin Densitom. doi:10.1016/j.jocd.2014.10.002

29. Ruff CB (2000) Body size, body shape, and long bone strength in modern humans. J Hum Evol 38:269–290

30. Buie HR, Campbell GM, Klinck RJ, MacNeil JA, Boyd SK (2007) Automatic segmentation of cortical and trabecular compartments based on a dual threshold technique for in vivo micro-CT bone analysis. Bone 41:505–515

31. Pistoia W, van Rietbergen B, Lochmuller EM, Lill CA, Eckstein F, Ruegsegger P (2002) Estimation of distal radius failure load with micro-finite element analysis models based on three-dimensional peripheral quantitative computed tomography images. Bone 30:842–848

32. Shaw CN (2011) Is 'hand preference' coded in the hominin skeleton? an in-vivo study of bilateral morphological variation. J Hum Evol 61:480–487

33. Mays S, Steele J, Ford M (1999) Directional asymmetry in the human clavicle. Int J Osteoarchaeol 9:18–28

34. Steele J, Mays S (1995) Handedness and directional asymmetry in the long bones of the human upper limb. Int J Osteoarchaeol 5:39–49

35. Seeman E (2013) Age- and menopause-related bone loss compromise cortical and trabecular microstructure. J Gerontol A Biol Sci Med Sci 68:1218–1225

36. Burr DB, Ruff CB, Johnson C (1989) Structural adaptations of the femur and humerus to arboreal and terrestrial environments in three species of macaque. Am J Phys Anthropol 79:357–367

37. Maggiano IS, Schultz M, Kierdorf H, Sosa TS, Maggiano CM, Tiesler Blos V (2008) Cross-sectional analysis of long bones, occupational activities and long-distance trade of the classic Maya from Xcambo—archaeological and osteological evidence. Am J Phys Anthropol 136:470–477

38. Ogilvie MD, Hilton CE (2011) Cross-sectional geometry in the humeri of foragers and farmers from the prehispanic American Southwest: exploring patterns in the sexual division of labor. Am J Phys Anthropol 144:11–21

39. Rhodes JA, Knusel CJ (2005) Activity-related skeletal change in medieval humeri: cross-sectional and architectural alterations. Am J Phys Anthropol 128:536–546

40. Mays S (2001) Effects of age and occupation on cortical bone in a group of 18th-19th century British men. Am J Phys Anthropol 116:34–44

41. Schaffler MB, Kennedy OD (2012) Osteocyte signaling in bone. Curr Osteoporos Rep 10:118–125

42. Bonnet N, Standley KN, Bianchi EN, Stadelmann V, Foti M, Conway SJ, Ferrari SL (2009) The matricellular protein periostin is required for sost inhibition and the anabolic response to mechanical loading and physical activity. J Biol Chem 284:35939–35950

43. Rizzoli R, Stevenson JC, Bauer JM, van Loon LJ, Walrand S, Kanis JA, Cooper C, Brandi ML, Diez-Perez A, Reginster JY (2014) The role of dietary protein and vitamin D in maintaining musculoskeletal health in postmenopausal women: a consensus statement from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). Maturitas 79:122–132

44. Perneger TV (1998) What's wrong with Bonferroni adjustments. BMJ 316:1236–1238