Femoral cortical bone in a Portuguese reference skeletal collection

Massa óssea cortical do fémur numa coleção esquelética de referência portuguesa

Francisco Curate[1,2,3a], Eugénia Cunha[3,4b]

Abstract This study aims to investigate patterns of femoral cortical bone fragility with age (at death) and to evaluate its associations with sex and bone mineral density. Radiogrammetric parameters of the femur and bone mineral density at the proximal femur were assessed in an adult sample (N=98) from the Coimbra Identified Skeletal Collection (Portugal). Diaphysis total width (DTW), femoral cortical index (FEMCI) and bone mineral density (BMD) are significantly higher in males, while medullary width (MW) is not statistically different between sexes. Cortical bone parameters of

Resumo Neste trabalho, pretende-se investigar a fragilidade óssea cortical no fémur com a idade (à morte) e a sua associação ao sexo e à densidade mineral óssea. Os parâmetros radiogramétricos do fémur e a densidade mineral óssea no fémur proximal foram avaliados numa amostra de indivíduos adultos (N=98) da Coleção de Esqueletos Identificados da Universidade de Coimbra (Portugal). A largura total da diáfise (LTD), o índice cortical do fémur (FEMCI) e a densidade mineral óssea (DMO) são significativamente maiores nos homens, enquanto a largura medular (LM) não é estatisticamente di-

Francisco Curate, Eugénia Cunha

the femoral diaphysis are associated with age only in women, whereas BMD decreases with age in both sexes. The evaluation of femoral cortical bone reveals sex-specific trajectories of endosteal bone loss and periosteal apposition, stemming from sexual differences in the rate and pattern of bone loss, and in bone size. In females, endocortical bone loss rises with age, particularly in peri- and postmenopausal years, decelerating later in life. Concomitantly, accretion of bone in the subperiosteal surface persists throughout adulthood — partially offsetting bone fragility in women. Strength in the femoral mid-diaphysis appears to be preserved throughout most of the life course in both sexes.

ferente entre os sexos. Os parâmetros corticais da diáfise do fémur encontram-se associados à idade apenas nas mulheres; por seu lado, a DMO declina com a idade em ambos os sexos. A avaliação do osso cortical do fémur revela trajetórias sexuais específicas de perda óssea endosteal e aposição periosteal, que têm origem em diferenças sexuais no grau e padrão de perda de osso, bem como no tamanho ósseo. Nas mulheres, a perda endocortical de osso aumenta com a idade, particularmente nos anos peri- e pós-menopáusicos, desacelerando mais tarde. De forma concomitante, a acreção de osso na superfície subperiosteal persiste durante a vida adulta – equilibrando parcialmente a fragilidade óssea nas mulheres. A resistência óssea a meio da diáfise do fémur parece ser preservada durante grande parte da vida em ambos os sexos.

Keywords: Radiogrammetry; dual x-ray absorptiometry; periosteal apposition; endosteal resorption; Coimbra Identified Skeletal Collection.

Palavras-chave: Radiogrametria; absorciometria radiológica de dupla energia; aposição periosteal; absorção endosteal; Colecção de Esqueletos Identificados.

Introduction

Osteoporosis and bone fragility are major public health problems facing postmenopausal women and aging individuals from both sexes. The clinical impact of osteoporosis stems from the complications associated to it, namely hip, distal radius, proximal humerus and vertebral compression fractures (Sattui and Saag, 2014). A growing body of literature has detailed the long history of bone fragility in past groups, recounting the diachronic fluctuations in its epidemiological patterns, etiological agents and societal implications (Brickley and Ives, 2008; Curate, 2014a; 2014b).

Radiogrammetry and dual x-ray absorptiometry (DXA) are undoubtedly the most common methods to study bone loss in past populations (Brickley, 2002; Brickley and Agarwal, 2003; Curate, 2014a).

DXA scanning on the proximal femur measures the integral bone mass of the cortical and trabecular bone compartments (Bonnick, 2010). Conventional radiogrammetry reveals the alterations that occur in cortical bone (Ives and Brickley, 2004). As such, these techniques offer different – but not necessarily incompatible – views of bone remodeling and maintenance (Brickley and Agarwal, 2003).

Radiogrammetry quantifies the amplitude or geometry of cortical bone in tubular bones (Ives and Brickley, 2004). It is ineffective to evaluate osteoporosis at the individual level, but endures as a valuable tool to assess cortical bone loss in epidemiological settings (Shepherd et al., 2005; Yasaku et al., 2009). At the same time, radiogrammetry is still widely used in studies concerned with specific pathological conditions (Böttcher and Pfeil, 2008). Radiogrammetry of the second metacarpal has been favored in anthropological studies of cortical bone (e.g., Ekenman et al., 1995; Mays, 1996; Lazenby, 1998; Mays, 2000; 2001; Rewekant, 2001; Mays, 2006; Ives, 2007; Beauchesne and Agarwal, 2014; Curate, 2011; Glencross and Agarwal, 2011; Robb et al., 2012; Curate et al., 2015; Umbelino et al., 2016). Less often, the humerus, femur and tibia have also been used to evaluate cortical bone loss in skeletal samples (e.g., van Gerven et al., 1969; Bergot and Bocquet, 1976; Bloom et al., 1984; DeRousseau, 1985; González--Reimers et al., 1998; Mays et al., 1998).

The perception of osteoporosis as a disease of trabecular bone loss is fundamentally incorrect (Seeman, 2013). Trabecular bone exposure to faster remodeling and bone loss relates to its higher surface area; conversely, trabecular bone represents just 20% of the overall bone matrix volume. Therefore, the originally slower loss of cortical bone (~80% of the skeleton) causes a comparable amount of bone loss throughout the first years after menopause, being responsible for greater bone loss after 60 years of age (Seeman, 2013; Zebaze et al., 2010). Also, cortical bone is especially important to bone stability and strength – influencing resistance to external loads and the occurrence of fractures (Holzer et al., 2009).

This study focuses on the assessment of cortical bone at the femoral diaphysis in an adult sample from the Coimbra Identified Skeletal Collection (CISC). Radiogrammetry at the femur mid-diaphysis allows for comparisons with the second metacarpal, accounting for differences in functional stress – e.g., weight bearing and tension – associated with each bone. Also, given the relative size of the bones, femoral measurement error is lower. Finally, it conveys a valuable contrast with the proximal femur, rich in trabecular bone and a classic site for osteoporotic fractures. This paper aims to evaluate and interpret patterns of cortical bone fragility – with a particular emphasis on endosteal bone loss and periosteal apposition – with aging, and to explore its

associations with sex and bone mineral density (BMD) at the proximal femur. Scientific advancement can be significantly supported by sharing both methods and raw data resources. As such, another objective is to divulge a database of femoral radiogrammetric parameters based in a reference skeletal population.

Materials and Methods

The CISC comprises 505 skeletons from the *Cemitério Municipal da Conchada* (cemetery at Coimbra, Portugal). All individuals died between 1904 and 1936, i.e., before the massive introduction of medical therapies against bone loss. Biographical information for each individual is available, including sex and age at death (Cunha and Wasterlain, 2007). The observed sample includes 98 Portuguese nationals from both sexes, born between 1831 and 1914, and that died between 1910 and 1936. Recorded ages at death range from 21 to 89 years old. Individuals were predominantly non-specialized manual workers with low socioeconomic status. A purposive sampling strategy was adopted, with equal numbers of females and males. Also, only individuals without macroscopical post-depositional alterations and/or blatant pathological conditions were included in the sample. Anteroposterior radiographs of the midshaft area of the left femur of each individual were taken using a mammogram film with an exposure time of mAseg 80-50,

exposure of Kv 30-35 and focal distance of 1.0 m. Maximum length of the femur, as defined by Martin and Saller (1957), was determined. Measurements of diaphysis total width (DTW) and medullary width (MW) were taken following a standardized guide (Ives and Brickley, 2004; raw data available in Data S1). Radiogrammetry was used to establish cortical index (FEMCI) in the femoral mid-shaft (Mays et al., 1998). The revised femoral cortical thicknesses index (RFCI) and adjusted medullary width index (AMWI) were also computed (Glencross and Agarwal, 2011). Indexes were obtained from the raw measurements (in mm) as follows:

$$FEMCI = \frac{\text{diaphysis total width} - \text{medullary width}}{\text{diaphysis total width}} \times 100$$

$$RFCI = \frac{\text{diaphysis total width} - \text{medullary width}}{\text{maximum length of the femur}} \times 100$$

$$AMWI = \frac{\text{medullary width}}{\text{maximum length of the femur}} \times 100$$

Bone mineral density was evaluated in the femoral neck through DXA. The femora were scanned using a Hologic QDR-4500A densitometer. Each femur was placed in standard anteroposterior position, with the diaphysis parallel to the central axis of the scanner, in a low--density container with dehydrated rice (10 cm depth). The absence of soft tissues and bone marrow in historical skeletal remains hampers DXA measurements; as such, a water bath or rice are usually used as soft-tissue proxies (Brickley and Agarwal, 2003; Curate, 2014a).

Descriptive statistics, viz. group means, standard deviation (SD) and 95% confidence intervals (95% CI) for the mean were estimated for each continuous variable. Normality was assessed through the skewness and kurtosis of the distributions (Kline, 2010). Homoscedasticity was evaluated with the Levene's test. A student's t-test (independent samples) was applied to evaluate the null hypothesis that the means of two groups were equal. Linear Pearson correlation was used to evaluate a possible linear relationship between the cortical parameters of the femur with recorded age at death and bone mineral density at the neck of the femur. Local polynomial regression fitting smoothing (LOESS) was employed to explore nonlinear empirical relationships between variables. LOESS offers a graphical summary of the relationship between variables by fitting a function of the independent variables locally (Cleveland, 1979). Twenty femora were measured in different days to check repeatability of the cortical measurements (DTW and MW). Measurement error was evaluated with the technical error of measurement (TEM), the relative technical error of measurement (rTEM) (Ulijaszek and Kerr, 1999) and the reliability coefficient (R_c) (Ward and Jamison, 1991). All statistical and graphical analyses were performed with R programming language (R Development Core Team, 2016; Chang and Wickham, 2016).

Results

The detection of the endosteal margin is sometimes complex rendering radiogrammetric measurements challenging (Schäfer et al., 2008). Notwithstanding, the results suggest that cortical measurements (DTW and MW) were performed within adequate levels of measurement error (Table 1).

Mean age (at death) is not statistically different between sexes (Student's t: -0.442; df=96; p=0.660). Maximum length of the femur (MLF), DTW, FEMCI, higher in men (MLF, Student's t: 6.307; df=96; p<0.001 / DTW, Student's t: 4.141; df=96; p<0.001 / FEMCI, Student's t: 2.140; df=96; p=0.035). Revised femoral cortical thickness index and adjusted medullary width

Table 1. Intraobserver error for the DTW and MW measurements.

Measurement	TEM	rTEM	R_c	N
DTW	0.0044	0.0170	0.99	20
MW	0.0036	0.0320	0.99	20

index differences between sexes are close to significance but fail to reject the null hypothesis (RFCI, Student's t: 1.958; df=96; p=0.053 / AMWI, Student's t: -1.851; df=96; p=0.067). MW is slightly lesser in women but the difference is not significant (MW, Student's t: 0.109; df=96; p=0.913). BMD is significantly lower in women (BMD$_{neck}$, Student's t: 2.010; df=96; p=0.047). Descriptive statistics are summarized in table 2.

Table 2. Descriptive statistics for both sexes.

	Females				Males				Student's t test	
	Mean	SD	95% CI	N	Mean	SD	95% CI	N	t	sig.
Age at Death	51.88	19.03	46.41–57.34	49	50.27	17.04	45.3-55.16	49	0.442	0.660
MLF	421.69	25.66	414.33-429.06	49	455.24	26.99	447.49-63.00	49	6.307	<0.001
DTW	24.81	2.34	24.14 – 25.49	49	26.81	2.44	26.11-27.52	49	4.141	<0.001
MW	11.23	2.00	10.65 -11.80	49	11.28	2.00	10.56-12.00	49	0.109	0.913
FEMCI	54.69	7.05	52.66 -56.71	49	57.99	8.19	55.64-60.34	49	2.140	0.035
RFCI	3.22	0.47	3.08 –3.35	49	3.42	0.55	3.26 -3.58	49	1.958	0.053
AMWI	2.67	0.50	2.53 –2.81	49	2.48	0.53	2.33-2.63	49	-1.851	0.067
BMDneck	0.696	0.15	0.652 -0.740	49	0.758	0.15	0.714-0.802	49	2.010	0.047

Cortical bone parameters are linearly correlated with age in women (Pearson's DTW*age: 0.413; p=0.003 / Pearson's MW*age: 0.495; p<0.001/Pearson's FEMCI*age: -0.291; p=0.043 / Pearson's AMWI*age: 0.480; p<0.001), except the revised femoral cortical thickness index (Pearson's RFCI*age: 0.004; p=0.979). MW, DTW and AMWI exhibit a moderate positive bivariate relationship with age. FEMCI displays a weak, although significant, correlation with age. The net loss of cortical bone between the first years of adulthood (20-29 years) and the seventh decade (70+ years) is 13.6%, with an average loss of 2.3% per decade. Periosteal apposition (DTW as surrogate) increases by 12.4%, while endocortical loss (MW as surrogate) increases by 26.0%. Notwithstanding, the pattern of net loss is not constant, with minor variation in the first decades of adulthood and an impressive net cortical loss of 19.8% between the fifth and sixth decades. Local polynomial regression fitting smooth-

ing shows that MW increases faster after the fifth decade (Figures 1-3). BMD_{neck} is negatively associated with age (Pearson's BMD_{neck}*age: -0.659; p<0.001). FEMCI, MW and AMWI are moderately associated with BMD_{neck} (Pearson's FEMCI*BMD_{neck}: 0.478; p<0.001; Pearson's MW*BMD_{neck}: -0.472; p<0.001; Pearson's AMWI*BMDneck: -0.499; p<0.001), while RFCI is weakly correlated with BMD at the ROI "neck" (Pearson's RFCI*BMD_{neck}: -0.318; p=0.026). DTW is not linearly correlated with BMD_{neck} (Pearson's DTW*BMD_{neck}: -0.079; p=0.588).

Amongst men, none of the cortical bone parameters is significantly correlated with age at death (Pearson's DTW*age: 0.139; p=0.340 / Pearson's MW*age: 0.069; p=0.639 / Pearson's FEMCI*age: -0.016; p=0.911 / Pearson's RFCI*age: 0.120; p=0.413 / Pearson's AMWI*age: 0.123; p=0.398). Cortical bone net loss between the first adult decade (20–29 years) and old age (70+ years) is 5.4%. DTW increased by 7.2%, and MW increased by 12.6%. The pattern of cortical loss is very irregular, with decennial discrepancies in the cortical bone net balance (Figures 4–6). Bone mineral density at the femoral neck is negatively associated with age (Pearson's BMDneck*age: -0.541; p<0.001). None of the femoral cortical bone parameters is associated with BMD_{neck} (Pearson's DTW*BMD_{neck}: 0.047; p=0.747 / Pearson's MW*BMD_{neck}: -0.186; p=0.201 / Pearson's FEMCI*BMD_{neck}: 0.243; p=0.092 / Pearson's RFCI*BMD_{neck}: 0.196; p=0.176 / Pearson's AMWI*BMD_{neck}: -0.230; p=0.112).

Discussion

Sexual dissimilarity in femoral cortical parameters, particularly DTW and FEMCI, but also femoral length, revised femoral cortical thickness index and adjusted medullary width index, stems from sex-specific variations in bone size, and rate and pattern of bone loss (Samuel et al., 2009). Generally, males have larger bones, with puberty enacting a major role in skeletal size determination (Seeman, 2003; Samuel et al., 2009). In women, post-pubertal estrogen production supposedly inhibits periosteal bone formation and, consequently, bounds bone diameter; while pubertal androgen in men intensifies periosteal bone formation and bone diameter. Also, during growth men undergo a long-standing period of bone gain, resulting in the increase of bone cortical thickness (Seeman, 2003). On the other hand, bone loss accelerates in peri- and post-menopausal women as estrogen withdrawal increases the rate of bone remodeling, and more bone is resorbed and less is formed at each basic multicellular unit (Seeman, 2008). The differences between the sexes in cortical bone loss have been detailed both in modern (e.g., Virtamä and Helelä, 1969; Maggio et al., 1995; Ginsburg et al., 2001) and historical populations (e.g., Carlson et al., 1976; Mays et al., 1998; Drusini et al., 2000; Ives, 2007; Glencross and Agarwal, 2011; Umbelino et al., 2016). In the same skeletal collection but with a different sample, radiogram-
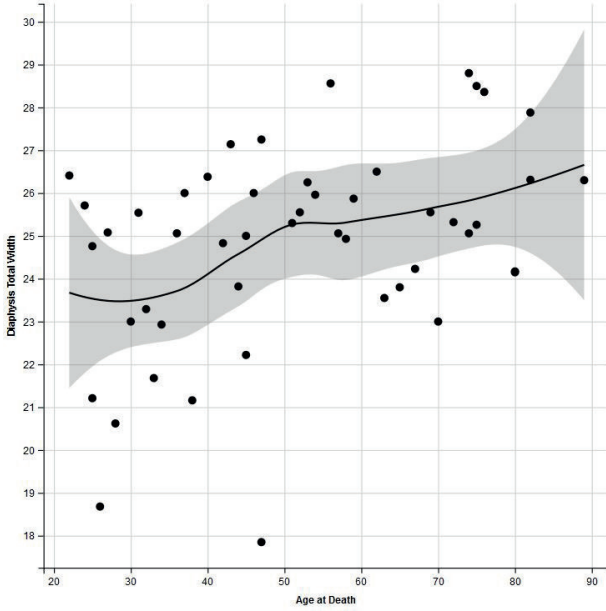
Figure 1. Local polynomial regression fitting smoothing for DTW (mm) and age at death in females from the CISC sample.
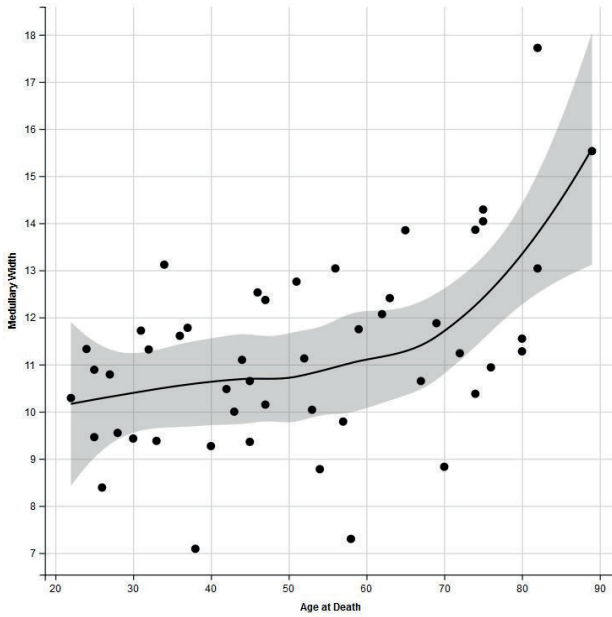

Figure 2. LOESS smoothing for medullary width (mm) and age at death (females, CISC sample).
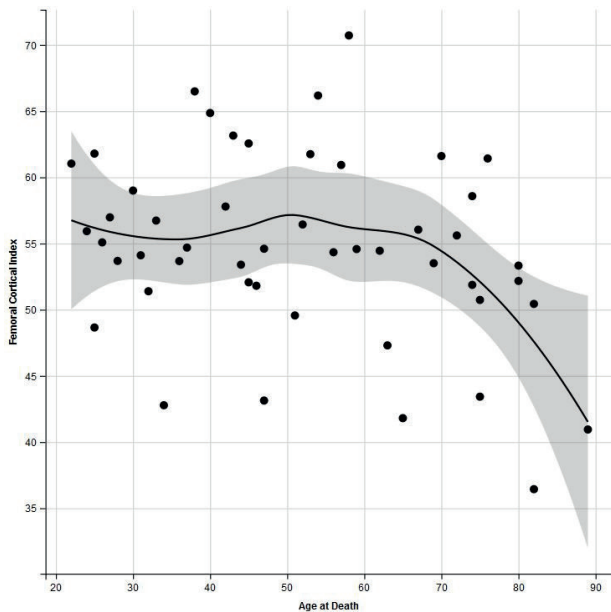
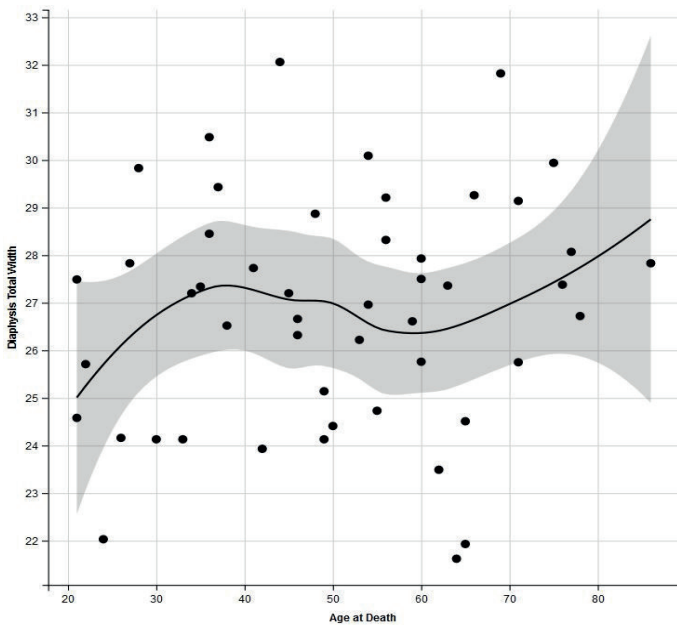**Figure 3.** LOESS smoothing for FEMCI and age at death (females, CISC sample).

Figure 4. LOESS smoothing for diaphysis total width (mm) and age at death (males, CISC sample).
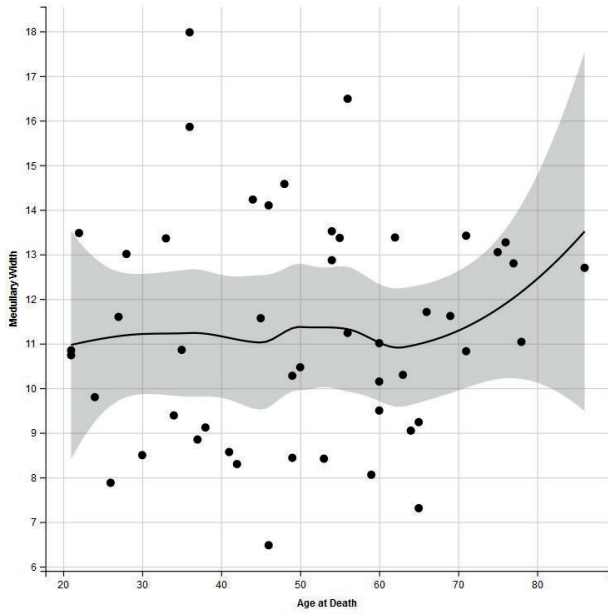
Figure 5. Local polynomial regression fitting smoothing for MW (mm) and age at death in males from the CISC sample.
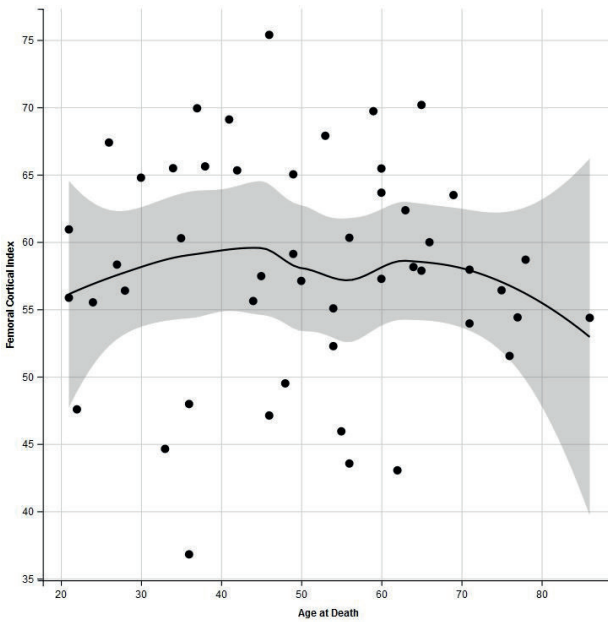

Figure 6. LOESS smoothing for femoral cortical index and age at death (males, CISC sample).

metry of the second metacarpal also exposed significant differences between sexes (Curate et al., 2015).

Cortical bone changes were significantly related with age only in females, with results showing signs of gendered trajectories of age-related cortical bone loss. In the second metacarpal, cortical index and medullary width were significantly associated with age in both sexes (Curate et al., 2015). Femoral medullary cavity enlarges in the course of aging as a result of imbalance of endosteal bone formation and resorption that leads to endocortical bone loss (Jergas, 2008). Although bone remodeling at the endosteal envelope is thought to increase mildly in aging men, it drastically increases in perimenopausal and early postmenopausal women, slowing with further aging (Clarke, 2008). As such, the "rate" of endosteal cortical bone loss is faster in women when compared to men – considering both MW and AMWI. Medullary width in women generally shows a slow and gradual increase with age, but the LOESS regression curve suggests an acceleration of endosteal bone loss starting around 50 years of age – it is important to note that the mean age of menopause in historical populations most likely ranged from 45 to 50 years (Pavelka and Fedigan, 1991). Remarkably, MW increases 15.1% between the fifth and sixth decades, and only 4.5% between the sixth and the seventh decades of life. Bone loss decelerates in the three to five years ensuing

menopause, although it endures at a faster rate than before menopause (Seeman, 2008). Amongst men, medullary expansion is virtually absent until much later in life, with an apparent MW increase only after the middle of the sixth decade.

Age-continuous apposition of bone on the periosteal surface was originally validated by Smith and Walker (1964) and has been considered as an adaptive response to preserve resistance to bending (Lazenby, 1990; Allen et al., 2004; Szulc et al., 2006; Seeman, 2008; Peck and Stout, 2009). Diaphysis total width at the mediolateral axis — which can be regarded as a surrogate of periosteal apposition — increases moderately with age in women. In contradiction with some cross-sectional studies, in men DTW did not increase significantly with age (Virtamä and Helelä, 1969; Lazenby, 1990; Feik et al., 2000; Mays, 2001; Peck and Stout, 2009), and periosteal apposition (as a decennial percentage) was greater in women. Nevertheless, other epidemiological studies describe a greater percentage increase in periosteal apposition in women (Garn et al., 1967; 1972; Kaptoge et al., 2003). In a prehistoric Mississippian sample, van Gerven et al. (1969) reported female gains and male losses in periosteal diameter; while Wallace et al. (2014) observed (in a sample of Inuit foragers) that periosteal area did not increase with age in either sex.

Dynamics of periosteal apposition in the femoral and second metacarpal diaphyses are apparently different: the

external dimensions of the second metacarpal do not increase with age in males or females (Curate et al., 2015). The femur is a weight-bearing bone, subjected to increased biomechanical loading, which can explain some of the observed dissimilarities.

The underlying causes of periosteal apposition are intricate to delimit but it is probable that the extent of mechanical compensation depends on initial bone size, with smaller bones – women in the studied sample are generally smaller than men – showing more periosteal apposition. Sex-specific disparities in periosteal apposition have been partially attributed to sexual bone size differences, with slender diaphyses requiring greater rates of periosteal bone gain over time (Jepsen and Andarawis-Puri, 2012). Also, loading differences possibly contribute to individual dissimilarities in periosteal apposition at the lower limbs; e.g., long-term immobilization seems to inhibit periosteal bone formation (Schäfer et al., 2008). Mechanical stimulation is usually much greater in men than women (Vanderschueren et al., 2006). Certainly, most men in the CISC sample were manual workers engaged in highly demanding physical occupations – but, as a rule, women also experienced a physically active lifestyle, involving strenuous workloads (Cunha and Umbelino, 1995).

Cortical bone resorption at the endosteal and periosteal sites react differently to distinct metabolic stimuli (Grampp et al., 1997). The endosteal surface exhibits a higher remodeling activity, probably as a consequence of greater biomechanical strains or cytokine exposure from the contiguous bone marrow (Clarke, 2008). Also, periosteal cells appear to differ from endosteal cells; each cell population responds differently both qualitatively and quantitatively to a wide variety of hormones and growth factors (Allen et al., 2004). The femoral cortical index refers to a dimensionless parameter that is the ratio of medullary cavity width to bone diameter (Shepherd et al., 2005), and tentatively reflects the conjoint endosteal and periosteal remodeling activity. FEMCI declines slightly with age in females (but not in males) as a result of the uncoupling in bone deposition and resorption that occurs throughout aging – a small increase in periosteal bone formation in women is exceeded by a greater intensification in endosteal resorption with subsequent cortical thickness reduction. LOESS regression indicates that FEMCI decline in females occurs only after the seventh decade, suggesting that the femur maintains its strength until later in life. In males, strength seems preserved throughout the life course. Cortical index – as observed in the second metacarpal – usually declines from younger to older age groups in both females and males (Rewekant, 2001; Ives, 2007; Beauchesne and Agarwal, 2014; Mays, 2015) or just in females (Mays, 1996) from archeological samples. Cortical bone in the femur seems to decrease only in females (Erick-

sen, 1982; Mays et al., 1998), but a negative association of relative cortical area of the femur with age in both sexes has also been observed (Doyle et al., 2011). Interestingly, the revised femoral cortical thickness index (a ratio adjustment intended to remove size information) (Glencross and Agarwal, 2011) does not show an association with age in any of the sexual groups.

For females, correlations between cortical parameters at the femoral diaphysis and BMD measured at the ROI "neck" are significant (except for DTW with BMD_{neck}), but the association is moderate. In males, cortical bone in the femur is not associated with BMD_{neck}. Female results are similar to the associations between cortical bone and BMD stated by Mays et al. (1998), with a weaker association in males. Ives and Brickley (2005) reported a non-significant association between BMD_{neck} and metacarpal cortical index in a pooled sample from both sexes. The results support the concept that bone loss and mass are not homogeneous within and among skeletal elements of the same individual, both because biomechanical factors and differences in macroscopical bone composition (Bonnick, 2010).

Conclusions

Femoral cortical bone loss during aging does not follow a linear course, with sex-specific patterns of endosteal bone loss and periosteal apposition. In women, endocortical bone loss increases with age, especially in presumed perimenopausal and early postmenopausal women, slowing later in life. Concurrently, accretion of bone in the femoral outer diameter throughout adult life continues – helping to preserve bone strength until the sixth decade. In men, medullary expansion and periosteal apposition are fundamentally nonexistent during adult life. Strength in the femoral diaphysis seems to be preserved throughout life. The observed correlations between femoral cortical bone and BMD at the femoral neck are suggestive of skeletal heterogeneity in bone loss and mass both between bones and within the same bone.

Radiogrammetry of the femur offers additional viewpoints to the study of bone loss in historical populations, and this study reiterates that different methods offer unique insights about bone remodeling and maintenance (Brickley and Agarwal, 2003). Notwithstanding, this study presents some limitations, including the cross-sectional nature of the data, reliance on mediolateral axis measurements only and sample size.

Acknowledgements

References

Allen, M. R.; Hock, J. M.; Burr, D. B. 2004. Periosteum: biology, regulation, and response to osteoporosis therapies. *Bone*, 35(5): 1003–1012. DOI: 10.1016/j.bone.2004.07.014.

Beauchesne, P.; Agarwal, S. 2014. Age-Related cortical bone maintenance and loss in an Imperial Roman Population. *International Journal of Osteoarchaeology*, 24(1): 15-30. DOI: 10.1002/oa.1303.

Bergot, C.; Bocquet, J-P. 1976. Étude systématique en function de l'âge, de l'os spongieux et de l'os cortical de l'humérus et du fémur. *Bulletins et Mémoires de la Société d'Anthropologie de Paris*, 3(3): 215-242. DOI : 10.3406/bmsap.1976.1852.

Bloom, R. A.; Smith, P.; Dujovney, L. 1984. Singh index and cortical thickness in an early Arab population. *Collegium Anthropologicum*, 8: 67-72.

Bonnick, S. L. 2010. *Bone densitometry in clinical practice — Application and interpretation*. (3rd edition). Totowa, NJ, Humana Press. DOI: 10.1007/978-1-60327-499-9.

Böttcher, J.; Pfeil, A. 2008. Diagnosis of periarticular osteoporosis in rheumatoid arthritis using digital X-ray radiogrammetry. *Arthritis Research and Therapy*, 10: 103-106. DOI: 10.1186/ar2352.

Brickley, M. 2002. An investigation of historical and archaeological evidence for age-related bone loss and osteoporosis. *International Journal of Osteoarchaeology*, 12(5): 364-371. DOI: 10.1002/oa.635.

Brickley. M.; Agarwal, S. C. 2003. Techniques for the investigation of age-related bone loss and osteoporosis in archaeological bone. *In*: Agarwal, S. C.; Stout, S. D. (eds.) *Bone loss and osteoporosis: an anthropological perspective*. New York, Kluwer Plenum Academic Press: 157-172. DOI: 10.1007/978-1-4419-8891-1_10.

Brickley, M.; Ives, R. 2008. *The bioarchaeology of metabolic bone disease*. Oxford, Academic Press.

Carlson, D.; Armelagos, G.; van Gerven, D. 1976. Patterns of age-related cortical bone loss (osteoporosis) within the femoral diaphysis. *Human Biology*, 48: 295-314.

Chang, W.; Wickham, H. 2016. *ggvis: Interactive Grammar of Graphics. R package version 0.4.2*. http://CRAN.R-project.org/package=ggvis.

Clarke, B. 2008. Normal bone anatomy and physiology. *Clinical Journal of the American Society of Nephrology,* 3: S131-S139. DOI: 10.2215/CJN.04151206.

Cleveland, W. S. 1979. Robust locally weighted regression and smoothing scatterplots. *Journal of the American Statistical Association*, 74: 829-836. 10.1080/01621459.1979.10481038.

Cunha, E.; Umbelino, C. 1995. What can bones tell about labour and occupation: the analysis of skeletal markers of occupational stress in the Identified Skeletal Collection of the Anthropological Museum of the University of Coimbra (preliminary results). *Antropologia Portuguesa*, 13: 49-68.

Cunha, E.; Wasterlain, R. S. 2007. The Coimbra identified skeletal collections. *In*: Grupe, G.; Peters, J. (eds.) *Skeletal series and their*

socio-economic context. Rahden/Westf, Verlag Marie Leidorf: 23-33.

Curate, F. 2011. *O perímetro do declínio. Osteoporose e fracturas de fragilidade em três amostras osteológicas identificadas Portuguesas — sécs. XIX & XX*. Tese de Doutoramento em Antropologia Biológica, Departamento de Ciências da Vida da Faculdade de Ciências e Tecnologia, Universidade de Coimbra.

Curate, F. 2014a. Osteoporosis and paleopathology: a review. *Journal of Anthropological Sciences*, 92: 119-146.

Curate, F. 2014b. Osteoporosis and nutrition: a paleopathological insight. *Antropologia Portuguesa*, 31: 29-51. DOI: 10.14195/2182-7982_31_2.

Curate, F.; Cunha, E.; Matos, V.; Pedroso de Lima, J.; Navega, D. 2015. Cortical bone loss and osteoporotic fractures in the Coimbra Identified Skeletal Collection. *American Journal of Physical Anthropology*, 156: 114.

DeRousseau, C. J. 1985. Aging in the musculoskeletal system of rhesus monkeys: III. Bone loss. *American Journal of Physical Anthropology*, 68(2): 157-167. DOI: 10.1002/ajpa.1330680203.

Doyle, L. E.; Lazenby, R. A.; Pfeiffer, S. 2011. Cortical bone mass and geometry: age, sex, and intraskeletal variation in nineteenth-century Euro-Canadians. *American Journal of Human Biology*, 23(4): 534-545. DOI: 10.1002/ajhb.21185.

Drusini, A.; Bredariol, S.; Carrara, N.; Bonati, M. 2000. Cortical bone dynamics and age-related osteopenia in a Longobard archaeological sample from three graveyards of the Veneto Region (Northeast Italy). *International Journal of Osteoarchaeology,* 10(4): 268-279. DOI: 10.1002/1099-1212(200007/08)10:4<268:AID-OA529>3.0.CO;2-Q.

Ekenman, I.; Eriksson, S.; Lindgren, J. 1995. Bone density in medieval skeletons. *Calcified Tissue International*, 56(5): 355-358. DOI: 10.1007/BF00301601.

Ericksen, M. F. 1982. Aging changes in thickness of the proximal femoral cortex. *American Journal of Physical Anthropology*, 59(2): 121-130. 10.1002/ajpa.1330590202.

Feik, S. A.; Thomas, C. D. L.; Bruns, R.; Clement, J. G. 2000. Regional variations in cortical modeling in the femoral mid-shaft: Sex and age differences. *American Journal of Physical Anthropology*, 112(2): 191-205. DOI: 10.1002/(SICI)1096-8644(2000)112:2<191:AID-AJPA6>3.0.CO;2-3.

Garn, S. M., Rohmann, C. G.; Wagner, B.; Ascoli, W. 1967. Continuing bone growth throughout life: a general phenomenon. *American Journal of Physical Anthropology*, 26(3): 313-317. DOI: 10.1002/ajpa.1330260306.

Garn, S. M.; Frisancho, A. R.; Sandusky, S. T.; McCann, M. B. 1972. Confirmation of the sex difference in continuing subperiosteal apposition. *American Journal of Physical Anthropology*, 36(3): 377-380. DOI: 10.1002/ajpa.1330360308.

Ginsburg, E.; Skaric-Juric, T.; Kobyliansky, E.; Malkin, I.; Rudan, P. 2001. Evidence on major gene control of cortical index in pedi-

Francisco Curate, Eugénia Cunha

gree data from Middle Dalmatia, Croatia. *American Journal of Human Biology*, 13(3): 398-408. DOI: 10.1002/ajhb.1064.

Glencross, B.; Agarwal, S. 2011. An investigation of cortical bone loss and fracture patterns in the Neolithic community of Çatalhöÿük, Turkey using metacarpal radiogrammetry. *Journal of Archaeological Science*, 38: 513-521. DOI: 10.1002/(SICI)1520-6300(1998)10:1<37:AID-AJHB5>3.0.CO;2-9.

González-Reimers, E.; Velasco-Vazquez, J.; Barros-Lopez, N.; Arnay-de-la-Rosa, M.; Santolaria-Fernandez, F.; Castilla-Garcia, A. 1998. Corticomedular index of the right tibia in the diagnosis of osteopenia in prehistoric skeletal remains. *American Journal of Human Biology*, 10(1): 37-44. DOI: 10.1002/(SICI)1520-6300(1998)10:1<37:AID-AJHB5>3.0.CO;2-9.

Grampp, S.; Steiner, E.; Imhof, H. 1997. Radiological diagnosis of osteoporosis. *European Radiology*, 7(S2): S11-S19. DOI: 10.1007/PL00006859.

Holzer, G.; von Skrbensky, G.; Holzer, L.A.; Pichl, W. 2009. Hip fractures and the contribution of cortical versus trabecular bone to femoral neck strength. *Journal of Bone and Mineral Research*, 24(3): 468-474. DOI: 10.1359/jbmr.081108.

Ives, R. 2007. *An investigation of vitamin D deficiency, osteomalacia and age-related osteoporosis in six post-medieval urban collections*. Unpublished PhD Thesis. Birmingham, University of Birmingham.

Ives, R.; Brickley, M. 2004. A procedural guide to metacarpal radiogrammetry in archaeology. *International Journal of Osteoarchaeology*, 14(1): 7-17. DOI: 10.1002/oa.709.

Ives, R.; Brickley, M. 2005. Metacarpal radiogrammetry: a useful indicator of bone loss throughout the skeleton? *Journal of Archaeological Science*, 32(10): 1552-1559. DOI: 10.1016/j.jas.2005.04.008.

Jepsen, K. J.; Andarawis-Puri, N. 2012. The amount of periosteal apposition required to maintain bone strength during aging depends on adult bone morphology and tissue-modulus degrading rate. *Journal of Bone and Mineral Research*, 27(9): 1916-1926. DOI: 10.1002/jbmr.1643.

Jergas, M. 2008. Radiology of osteoporosis. *In*: Grampp, S. (ed.) *Radiology of osteoporosis*. Berlin, Springer: 77-103. DOI: 10.1007/978-3-540-68604-0_6.

Kaptoge, S.; Dalzell, N.; Loveridge, N.; Beck, T. J.; Khaw, K-T.; Reeve, J. 2003. Effects of gender, anthropometric variables, and aging on the evolution of hip strength in men and women aged over 65. *Bone*, 32(5): 561-570. DOI: 10.1016/S8756-3282(03)00055-3.

Kline, R. B. 2010. *Principles and practice of structural equation modeling*. New York, The Guilford Press.

Lazenby, R. A. 1990. Continuing periosteal apposition I: documentation, hypotheses, and interpretation. *American Journal of Physical Anthropology*, 82(4): 451-472. DOI: 10.1002/ajpa.1330820407.

Lazenby, R. A. 1998. Second metacarpal mid-shaft geometry in an historic cemetery sample. *American Journal of Physical An-*

thropology, 106(2): 157-167. DOI: 10.1002/(SICI)1096-8644(199806)106:2<157:AID-AJPA4>3.0.CO;2-N.

Maggio, D.; Pacifici, R.; Cherubini, A.; Aisa, M. C.; Santucci, C.; Cucinotta, D.; Senin, U. 1995. Appendicular cortical bone loss after age 65: Sex-dependent event? *Calcified Tissue International*, 56(5): 410-414. DOI: 10.1007/BF00301612.

Martin, R.; Saller, K. 1957. *Lerbuch der Anthropologie in systematischer Darstellung mit besonderer Berucksichtigung der anthropologischen Methoden*. Stuttgart, Gustav Fisher.

Mays, S. A. 1996. Age-dependent bone loss in a medieval population. *International Journal of Osteoarchaeology*, 6(2): 144-154. DOI: 10.1002/(SICI)1099-1212(199603)6:2<144:AID-OA261>3.0.CO;2-G.

Mays, S. A. 2000. Age-dependent cortical bone loss in women from 18th and early 19th century London. American Journal of Physical Anthropology, 112(3): 349-361. DOI: 10.1002/1096-8644(200007)112:3<349:   :AID-AJPA6> 3.0.CO;2-

Mays, S. A. 2001. Effects of age and occupation on cortical bone in a group of 18th-19th century British men. *American Journal of Physical Anthropology*, 116(1): 34-44. DOI: 10.1002/ajpa.1099.

Mays, S. A. 2006. Age-related cortical bone loss in women from a 3rd–4th century AD population from England. *American Journal of Physical Anthropology*, 129(4): 518-528. DOI: 10.1002/ajpa.20365.

Mays, S. A. 2015. Age-Associated Reduction in Cortical Bone in Males, Trends from the Third Century AD to the Present Day. *Calcified Tissue International*, 96(4): 370-371. DOI: 10.1007/s00223-015-9958-8.

Mays, S. A.; Lees, B.; Stevenson, J. C. 1998. Age-dependent bone loss in the femur in a medieval population. *International Journal of Osteoarchaeology*, 8(2): 97-106. DOI: 10.1002/(SICI)1099-1212(199803/04)8:2<97:AID-OA412>3.0.CO;2-U.

Pavelka, M.; Fedigan, L. 1991. Menopause: A comparative life history perspective. *Yearbook of Physical Anthropology*, 34(S13): 13-38. DOI: 10.1002/ajpa.1330340604.

Peck. J.; Stout, S.D. 2009. The effects of total hip arthroplasty on the structural and biomechanical properties of adult bone. *American Journal of Physical Anthropology*, 138(2): 221-230. DOI: 10.1002/ajpa.20921.

R Development Core Team. 2016. *R: A language and environment for statistical computing*. Vienna, Austria, R Foundation for Statistical Computing. URL http://www.R-project.org/.

Rewekant, A. 2001. Do environmental disturbances of an individual's growth and development influence the later bone involution processes? A study of two Mediaeval populations. *International Journal of Osteoarchaeology*, 11(6): 433-443. DOI: 10.1002/oa.584.

Robb, K. F.; Buckley, H. R.; Spriggs, M.; Bedford, S. 2012. Cortical index of three prehistoric human Pacific Island samples. *Interna-*

tional Journal of Osteoarchaeology, 22(3): 284-293. DOI: 10.1002/oa.1205.

Samuel, S. P.; Baran, G. R.; Wei, Y.; Davis, B. L. 2009. Biomechanics — Part II. *In*: Khurana, Jasvir S. (ed.) *Bone Pathology*. Totowa, NJ, Humana Press, 69-77. DOI: 10.1007/978-1-59745-347-9_4.

Sattui, S. E.; Saag, K. G. 2014. Fracture mortality: associations with epidemiology and osteoporosis treatment. *Nature Reviews Endocrinology*, 10: 592-602. DOI: 10.1038/nrendo.2014.125.

Schäfer, M-L.; Pfeil, A.; Renz, D. M.; Lehmann, G.; Schmidt, M.; Hansch, A.; Hein, G.; Wolf, G.; Kaiser, W. A.; Böttcher, J. 2008. Effects of long-term immobilisation on cortical bone mass after traumatic amputation of the phalanges estimated by digital X-ray radiogrammetry. *Osteoporosis International*, 19(9): 1291-1299. DOI: 10.1007/s00198-008-0570-x.

Seeman, E. 2003. Invited Review: Pathogenesis of osteoporosis. *Journal of Applied Physiology*, 95: 2142-2151. DOI: 10.1152/japplphysiol.00564.2003.

Seeman, E. 2008. Bone quality: the material and structural basis of bone strength. *Journal of Bone and Mineral Metabolism*, 26(1): 1-8. DOI: 10.1007/s00774-007-0793-5.

Seeman, E. 2013. Age - and menopause - related bone loss compromise cortical and trabecular microstructure. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 68(10): 1218-1225. DOI: 10.1093/gerona/glt071.

Shepherd, J. A.; Meta, M.; Landau, J.; Sherrer, Y.; Goddard, D. H.; Ovalle, M. I.; Rosholm, A.; Genant, H. K. 2005. Metacarpal index and bone mineral density in healthy African-American women. *Osteoporosis International*, 16(12): 1621-1626. DOI: 10.1007/s00198-005-1885-5.

Smith, R. W. Jr.; Walker, R. R. 1964. Femoral expansion in aging women: implications for osteoporosis and fractures. *Science*, 145: 156-157. DOI: 10.1126/science.145.3628.156.

Szulc, P.; Munoz, F.; Duboeuf, F.; Marchand, F.; Delmas, P. D. 2006. Low width of tubular bones is associated with increased risk of fragility fracture in elderly men—the MINOS study. *Bone*, 38(4): 595-602. DOI: 10.1016/j.bone.2005.09.004.

Ulijaszek, S.; Kerr, D. 1999. Anthropometric measurement error and the assessment of nutritional status. *British Journal of Nutrition*, 82(3): 165-177. DOI: 10.1017/S0007114599001348.

Umbelino, C.; Curate, F.; Perinha, A.; Ferreira, T.; Cunha, E.; Bicho, N. 2016. Cortical bone loss in a sample of human skeletons from the Muge Shell middens. *Archaeological and Anthropological Sciences*. Published online: 13 October 2016. DOI: 10.1007/s12520-016-0402-4.

van Gerven, D.; Armelagos, G.; Bartley, M. 1969. Roentgenographic and direct measurement of femoral cortical involution in a prehistoric Mississippian -population. *American Journal of Physical Anthropology*, 31(1): 23–38. DOI: 10.1002/ajpa.1330310105.

Vanderschueren, D.; Venken, K.; Ophoff, J.; Bouillon, R.; Boonen, S. 2006. Clinical review: Sex steroids and the periosteum–

reconsidering the roles of androgens and estrogens in periosteal expansion. *The Journal of Clinical Endocrinology and Metabolism*, 91(2): 378-382. DOI: 10.1210/jc.2005-1766.

Virtamä, P.; Helelä, T. 1969. Radiographic measurements of cortical bone. Variation in a normal population between 1 and 90 years of age. *Acta Radiologica*, S293: 7-268.

Wallace, I. J.; Nesbitt, A.; Mongle, C.; Gould, E. S.; Grine, F. E. 2014. Age-related variation in limb bone diaphyseal structure among Inuit foragers from Point Hope, northern Alaska. *Archives of Osteoporosis*, 9: 202. DOI: 10.1007/s11657-014-0202-3.

Ward, R.; Jamison, P. 1991. Measurement precision and reliability in craniofacial anthropometry: implications and suggestions for clinical applications. *Journal of Craniofacial Genetics and Developmental Biology*, 11: 156-164.

Yasaku, K.; Ishikawa-Takata, K.; Koitaya, N.; Yoshimoto, K.; Ohta, T. 2009. One-year change in the second metacarpal bone mass associated with menopause nutrition and physical activity. *The Journal of Nutrition Health and Aging*, 13(6): 545-549. DOI: 10.1007/s12603-009-0105-y.

Zebaze, R. M.; Ghasem-Zadeh, A.; Bohte, A.; Iuliano-Burns, S.; Mirams, M.; Price, R. I., Mackie, E. J.; Seeman, E. 2010. Intracortical remodeling and porosity in the distal radius and post-mortem femurs of women: a cross-sectional study. *Lancet*, 375: 1729-1736. DOI: 10.1016/S0140-6736(10)60320-0.