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Smaller long bone cross-sectional size in people who died of tuberculosis: Insights on frailty factors from a 19th and early 20th century Finnish population

Liina Mansukoski[a,b,*], Vitale Stefano Sparacello[c]

[a] Department of Anthropology, Durham University, Dawson Building South Road, Durham, DH1 3LE, United Kingdom
[b] School of Sport, Exercise and Health Sciences, Loughborough University, Ashby Road, Loughborough, Leicestershire, LE11 3TU, United Kingdom
[c] UMR5199 PACEA, Univ. Bordeaux, Batiment B8, Avenue Geoffroy Saint Hilaire, CS 50023, 33615 Pessac Cedex, France

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ABSTRACT

There is little research on how individuals suffering from tuberculosis may differ from those not infected in terms of overall skeletal morphology. Tuberculosis was endemic in 19th and early 20th century Finland making documented skeletal collections of Finns ideal to study effects of the disease on bone. The present study compares long bone cross-sectional total area between individuals who died of tuberculosis and those with another recorded cause of death in a Finnish sample. Adult male individuals (N = 105) were selected for analysis. Complete humeri (N = 56), femora (N = 66) and tibiae (N = 64) were 3D scanned using a laser scanner and total cross-sectional areas calculated with AsciiSection software. Individuals who died of tuberculosis (N = 24, 15 humeri, 14 femora, 13 tibiae) had, when standardized for body size, significantly smaller total cross-sectional femoral and humeral, but not tibial, areas. The mechanisms behind the observed relationship may reflect a combination of biological 'frailty' in terms of susceptibility to infection, reduced childhood activity and/or vitamin D deficiency, which possibly influenced both subperiosteal development during adolescence and, later, susceptibility to contracting and dying of TB. Due to the relatively small sample future studies are needed to further investigate the relationship between TB and bone cross-sectional size.

1. Introduction

In the recent past, tuberculosis (TB) was one of the leading causes of death (Roberts and Buikstra, 2003) and, despite the availability of antibiotic treatment, tuberculosis is currently a re-emerging disease that still causes millions of deaths every year (WHO, 2016). Tuberculosis was endemic in 19th and early 20th century Finland, and it was the main identified cause of death in 16% of the population (Harjula, 2007). Documented collections of the Finns are therefore ideal for investigating the effects of TB on bones, as well as the possible indicators of susceptibility to TB recorded in the skeleton.

Changes to the skeleton due to tuberculosis are usually due to the infection spreading from its primary focus (Roberts and Buikstra, 2003). Tuberculosis leaves traces in the skeleton in approximately 3–5% of cases, with lesions occurring particularly in the vertebrae (Holloway et al., 2011; Resnick and Niwayama 1995), although rates appear to be higher, up to 30%, for extrapulmonary tuberculosis (Jaffe, 1972). In children, TB may hinder bone growth through osteomyelitis of the growth plates (Aufderheide and Rodriguez Martin, 1998), and in adults, radiography has revealed marked demineralisation of long bones (Tuli, 2016). Direct metabolic effects on the bone occur when infection reaches skeletal sites via vascular channels (Tuli, 2016). Indirect effects may occur due to the link between the body's inflammatory response and hypothalamic–pituitary–adrenal (HPA) axis function, because as a bacterial disease TB causes an immune response and thus promotes the release of cytokines (Bozza et al., 2007; Etna et al., 2014). These in turn could lead to reduced bone growth due to cortisol secretion (Walsh, 2015). In addition, TB leads to malnutrition (i.e. "consumption"), especially involving problems in protein absorption (Macallan, 1999; Schwenk and Macallan, 2000), which may affect bone growth and their normal turnover in adult life.

Despite the above, there is little research on how individuals suffering from TB may differ from those who are not infected in terms of overall skeletal morphology, that is, in traits other than TB related lesions. In particular, it would be relevant for bioarchaeological studies to understand how this disease may alter the mechanical competence of long bones, which is usually assessed through the study of their diaphyseal cross-sections. In developing individuals, long-term metabolic

* Corresponding author at: School of Sport, Exercise and Health Sciences, Loughborough University, Ashby Road, Loughborough, Leicestershire, LE11 3TU, United Kingdom.
E-mail address: l.mansukoski@lboro.ac.uk (L. Mansukoski).

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insults significantly alter bone development by slowing down subperiosteal apposition and accelerating medullary expansion (Garn et al., 1964, 1969; Himes et al., 1975). In adults, long-term severe malnutrition and inactivity can lead to significant decreases in bone mass (Bourrin et al., 2000; Garn et al., 1964, 1969; Tuli, 2013). This decrease is mainly due to variations in bone mineral density and trabecular bone density rather than cortical bone area (Nordström and Nordström, 2011; Tervo et al., 2009), and cortical thinning is generally due to an expansion in the medullary area (Bass et al., 2002; Garn et al., 1964, 1969; Himes et al., 1975; Hummert, 1983; Huss-Ashmore, 1981).

The relationship of TB and bone mechanical competence through the study of cross-sectional geometry properties (CSG) was investigated by Sparacello et al. (2016). The study found that one adolescent individual from the Neolithic of Italy (Liguria region) who died of TB was relatively gracile in comparison to his peers, suggesting a period of compromised periosteal apposition during growth. In contrast, an adult individual with Pott's spine did not show any apparent changes in upper and lower limb structure. This would suggest that, while significantly disrupting bone development, TB does may not have a major impact on adult long bones, or at least not enough to be detectable via CSG in a bioarchaeological setting.

However, in palaeopathological studies sufficient sample sizes are difficult to obtain and the diagnosis of the disease from bony changes remains uncertain as conditions other than TB may cause very similar lesions (Holloway et al., 2011). The present study expands on these findings by using a larger sample size of individuals whose cause of death was recorded as TB by a medical examiner in a post-mortem examination, termed here "TB sample". The relationship between skeletal robusticity and tuberculosis was investigated by comparing late 19th and early 20th century Finnish adult males who died of TB with those with another recorded cause of death ("non-TB sample"). The aim was to assess whether there is a difference in robusticity – measured as size-standardized bone cross-sectional total area (TA) – between the TB and non-TB Finnish samples. We expected no differences, after controlling for body dimensions and age, especially considering that subperiosteal area should be the bone property that would be the least affected by the long-term consequences of the disease in adult life.

2. Materials and methods

2.1. Study sample

Throughout the study, the ethical guidelines of the British Association for Biological Anthropology and Osteoarchaeology were followed (BABAO, 2015). The sample belongs to a skeletal collection of identified individuals, housed at the Finnish Museum of Natural History in Helsinki. The individuals in the sample were born between 1850 and 1914, and died between 1915 and 1937. Written post-mortem records accompanying the individuals include information on names, years of birth, occupations, recorded living statures and causes of death (Söderholm, 2002; Telkkä, 1950). The collection consists principally of low and medium social status individuals whose remains were sent to the University of Helsinki by local medical examiners (Söderholm, 2002).

Any bones showing signs of healed fractures or other clear alterations were excluded from analysis. In total 105 male individuals were included (N = 56 humeri, N = 66 femora and N = 64 tibiae). No data were collected on female individuals; there are only four females in the collection with TB listed as cause of death, an insufficient sample size. The name of each individual in the collection is known and was used to assign sex; there were no individuals for whom the recorded name was ambiguous. The name data indicate all individuals were ethnic Finns, but this is not conclusive evidence, as the accompanying records make no reference to ethnicity. Only adult individuals were included in this study with ages at death ranging from 18 to 81. Biological maturity was estimated using the recorded age at death of the individuals together with assessing epiphyseal fusion of present limb long bones. Sample sizes and mean ages at death by bone and by cause of death category are detailed in Table 1.

Table 1
Study sample sizes, mean ages, age ranges and standard deviations by bone and cause of death category (TB or not TB).

	Cause of death TB	Cause of death not TB
Humerus		
Sample size	15	41
Mean age at death	44.73	43.95
Age range (years)	23–77	22–81
SD (years)	14.41	16.83
Femur		
Sample size	14	52
Mean age at death	36.07	44.75*
Age range (years)	21–77	18–81
SD (years)	14.02	17.07
Tibia		
Sample size	13	51
Mean age at death	32.92	44.76**
Age range (years)	21–45	18–81
SD (years)	7.91	17.24

* Mann-Whitney *U* Test: difference with the "cause of death TB" sample significant at the p = 0.1 level.

** Mann-Whitney *U* Test: difference with the "cause of death TB" sample significant at the p = 0.05 level.

Though well preserved, the collection does not comprise complete skeletons and for most individuals only a few long bones are present (often either upper or lower limbs, but not both), with the humerus sample consisting of largely different individuals than the samples for femur and tibia. For each individual with a present tibia (N = 64) there is also a femur, and for 15 of those, there is also a humerus. If different bones were present for the same individual (humerus, femur and/or tibia) all were included in their respective samples. Individuals were assigned to two categories for each bone (humerus, femur, tibia): (1) cause of death TB (15 humeri, 14 femora, 13 tibiae), and (2) cause of death not TB (41 humeri, 52 femora, 51 tibiae). The early 20th century medical examiners did not use modern disease classifications to assign a diagnostic code for cause of death, and those classified as having died of TB (N = 24) either had a cause of death "tuberculosis" or "keuhkotauti" (a historically used Finnish name for the disease; see supplementary materials for a summary of other causes of death in this sample). For most individuals, bones from the left side of the body were chosen, except in the few cases when they were absent (N = 2 humeri, N = 4 femora, N = 3 tibiae), where the right side was analysed instead.

2.2. Measurement protocol

The maximum lengths of humeri, femora and tibiae were measured manually using an osteometric board following White et al. (2011). Vertical femoral head diameter (M18; Bräuer, 1988) measurements were taken using a Sylvac digital sliding caliper following Ruff and Scott (1991).

Total cross-sectional area (TA, in mm^2) was calculated from 3D models in AsciiSection (instructions for acquiring the program are available from the PAVE research group http://www.pave.arch.cam.ac.uk/index.html) following the method by Davies et al. (2012). Using 3D models increases accuracy in reconstructing cross sections by requiring fewer passages compared to periosteal silicon moulds, and 3D models make data collection faster especially when multiple sections are extracted (Davies et al., 2012). For femur and tibia, TA was calculated at midshaft (50% of bone length), while for the humerus, the mid-distal section was considered (35% of bone length) following the standard practice in the field of CSG (Ruff, 2002). Body mass was estimated using the vertical femoral head diameter measurements and the formula by

Grine et al. (1995). This formula was chosen because it was assumed to be particularly suited for estimating the body mass of Finns, as they are considered a large-bodied population (Auerbach and Ruff 2004; Ruff et al., 2005). For femora and tibiae, TA was size standardized by dividing TA by estimated body mass and multiplying by 100, after Sparacello and Marchi (2008). For most of the humeral sample no lower limb bones were present and size standardization was performed by $\frac{TA}{bone\ length^3}$, after Ruff (2008).

The procedure by which the 3D models were oriented prior to running them in AsciiSection is subjective, even following the guidelines given in Ruff (2002). A sensitivity analysis was conducted with a subsample of 10 femur scans. The orientation of each bone was altered slightly on two axes and the new models were saved. The TA at midshaft of these altered models were then compared with the originals. To assess the reliability of the orientation, both the technical error of measurement and the coefficient of reliability were calculated following Lewis (1999), whereby the variance in the TA introduced by the researcher was compared to the variance that already existed (standard deviation). The results gave a reliability coefficient of 0.97 for this sample, which corresponds to an error of less than 5% and was concluded to be acceptable.

2.3. Statistical analysis

Each bone (humerus, femur, tibia) was analysed separately. As data were normally distributed (Shapiro Wilk $p > 0.05$) independent sample *t*-tests were used in SPSS (version 20) to assess whether a significant difference in TA existed between individuals with cause of death TB and the ones with other causes of death. For each bone, independent sample *t*-tests were also used to check for differences in mean maximum bone length (mm). For the individuals for whom there is a body mass estimation from the femoral head measurements, an independent sample *t*-test was used to compare body mass (kg) between the two groups.

Age at death is a significant determinant of bone total area during development up to the age of peak bone mass (Lazenby, 1990; Ruff, 2005). It continues to be significant later in life due to continued periosteal apposition to mechanically compensate for medullary expansion, especially in males (Martin and Atkinson, 1977; Ruff and Hayes, 1988). In addition, metabolic disturbances due to TB during growth can hinder periosteal apposition, resulting in smaller total area (Sparacello et al., 2016). We therefore tested our subsamples (humerus, femur and tibia in the two categories by cause of death) for differences in age using a Mann-Whitney *U* test, and we used Pearson's correlations to investigate whether variation in TA might be explained by differences in age.

3. Results

The TB sample had significantly smaller mean total cross-sectional area (TA) in the humerus and femur when compared to the non-TB sample (Table 2; Fig. 1). For tibia, the trend was in the same direction, but the difference in mean TA did not reach statistical significance. Fig. 2 shows the scatterplot by cause of death of non-standardized TA on bone length (for the humerus) and body mass (for femur and tibia). Individuals who died of TB appear to fall at the lower end of TA's distribution, given similar bone length or body mass. There were no significant differences in group means in maximum bone lengths (mm), or in estimated body mass (kg).

Differences in mean age were significant at the $p = 0.05$ for the tibia subsample and at the $p = 0.1$ level for the femur subsample (Table 1). There was no significant correlation between age at death and TA for any bone (humerus, femur, tibia) in either the TB or non-TB sample for the femur or tibia (Table 3). For the humerus, the TB sample showed a significant positive correlation ($R = 0.403$ $p < 0.05$) between age at death and TA.

Table 2
Results of independent samples *t*-tests for the variables considered in this study between groups based on cause of death category (TB or not TB). Bolding denotes statistical significance in a *T*-Test ($p < 0.05$).

Variable	% difference[a]	t	Degrees of freedom	p
TA mid-distal humerus	9.79	−2.341	54	**< 0.05**
TA midshaft femur	6.18	−2.195	64	**< 0.05**
TA midshaft tibia	4.63	−1.626	62	0.109
Humerus maximum length	−0.61	1.48	55	0.145
Femur maximum length	1.96	0.431	64	0.668
Tibia maximum length	2.05	−0.999	62	0.322
Estimated body mass	2.36	0.994	64	0.324

[a] Difference of the mean between the "cause of death not TB" and the "cause of death TB" groups, divided by the average between the two groups, and multiplied by 100.

4. Discussion

Using a documented collection from 19th and early 20th century Finland, this study compared bone robusticity, measured as size standardized bone cross-sectional total subperiosteal area (TA) for the TB and non-TB samples. We expected (our null hypothesis) to find no differences between the two samples. Although there is a scarcity of clinical evidence about bone cross-sectional changes due to adult-onset infectious disease, loss in bone cortices due to severe metabolic disturbances or immobilization should mainly be the result of endosteal expansion, with minor changes to subperiosteal area (Bourrin et al., 2000; Eser et al., 2004; Gross and Rubin, 1995; Garn et al., 1969; Nordström and Nordström, 2011). Contrary to our expectations, results show that the TB sample had significantly smaller size-standardized TA at the femur midshaft and mid-distal humerus than the non-TB individuals, although there is considerable overlap between the two groups.

Gracilization of long bones due to smaller TA was previously found in one adolescent Neolithic individual who died with TB, which was explained in terms of arrested periosteal apposition during development (Sparacello et al., 2016). However, the single adult individual with TB in the same study sample did not show cross-sectional changes, making it unclear whether the same mechanism behind the relationship between bone size and TB proposed by Sparacello et al. (2016) can explain our result. In this scenario the lower TA in our TB sample would be due to a long-term infection that had its onset during development, before the attainment of peak bone mass in adolescence (Pearson and Lieberman, 2004; Sparacello and Pearson, 2010). Those individuals would most likely have died young considering that the first antibiotics and vaccines against TB were widely employed only in the second half of the 20th century (WHO, 1955; Zumla et al., 2015). The survival period for untreated pulmonary TB averages 2–3 years based on a recent meta-analysis (Tiemersma et al., 2011), although it can be longer (Matos and Santos, 2015). In the present study no correlation between age at death and TA was found in the TB sample. Additionally, the two categories based on cause of death have non-significantly different mean age at death for the humerus and femur (Table 1), which are the bones for which significant differences in TA are present (Table 2). This suggests that lower TA in the TB sample may have not been driven by the presence of individuals who died young and suffered of adolescent-onset halted periosteal apposition due to TB. However, one possible explanation is that some individuals may have had TB during adolescence – enough to suffer of impaired development – and then their immune system was able to contain the pathogen until a fatal reactivation of the disease occurred later in life.

Another possibility is that those who died of TB in this Finnish sample were more biologically 'frail', as Wood et al. (1992) have

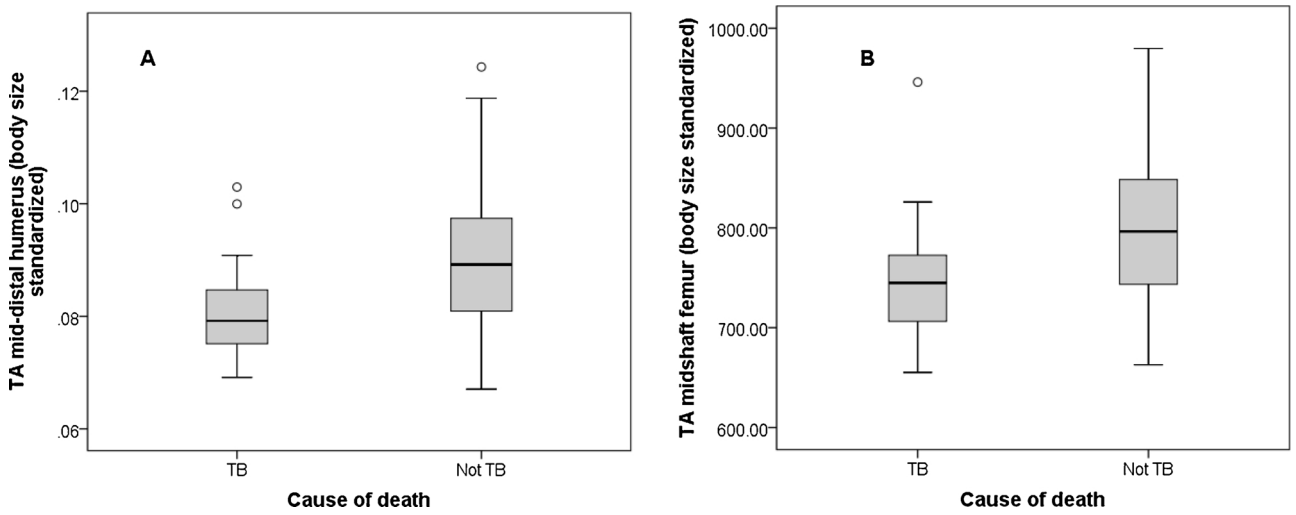

Fig. 1. A) Boxplots (median, quartiles, minimum and maximum) of total area (TA) at mid-distal humerus and B) midshaft femur comparing groups based on cause of death (TB or not TB).

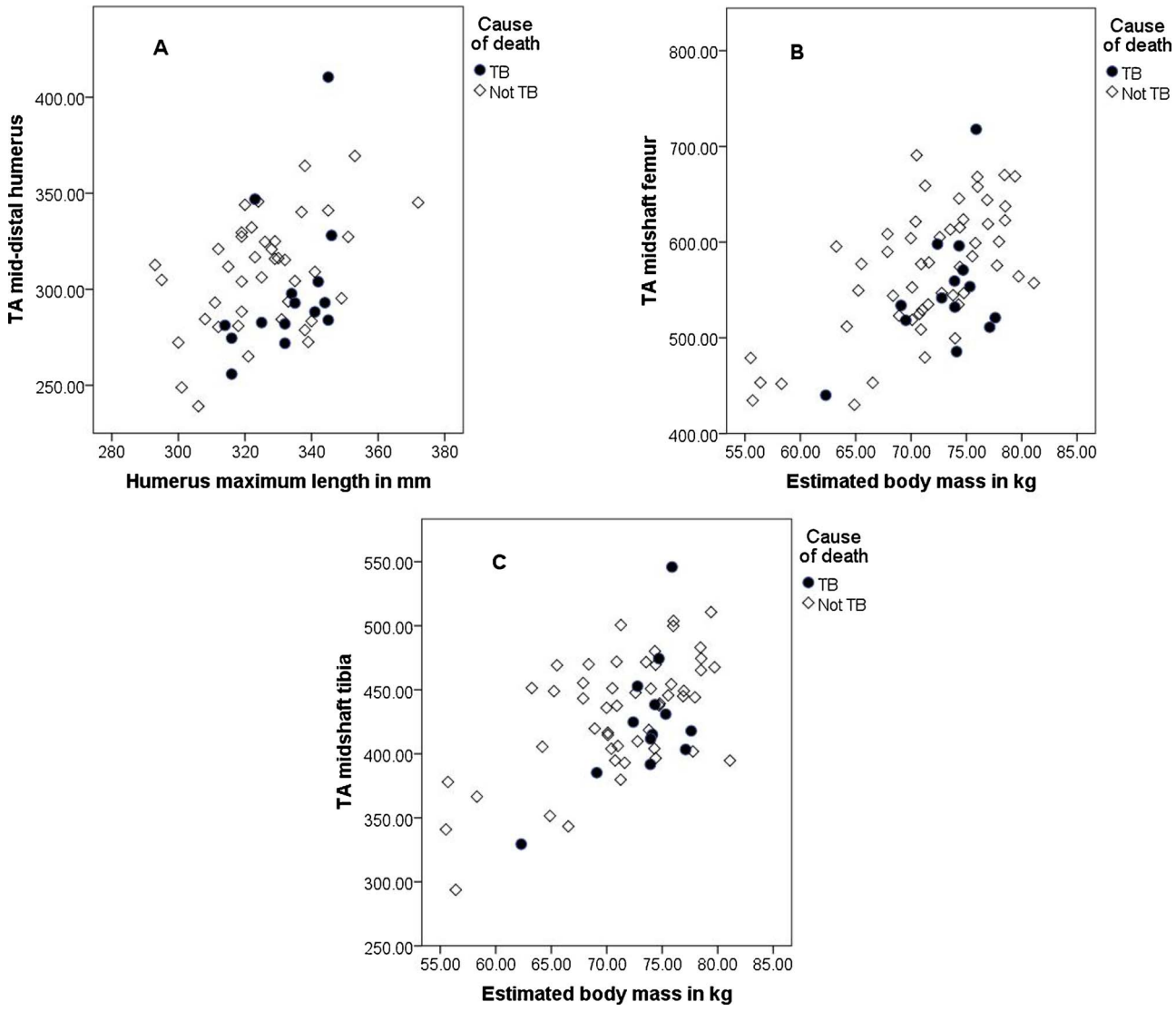

Fig. 2. Scatterplots categorized by cause of death (TB or not TB) of A) humeral mid-distal non-standardized total area (TA) on humeral maximum length; B) femoral midshaft non-standardized TA on estimated body mass, and C) tibial midshaft non-standardized TA on estimated body mass.

Table 3
Results of Pearson's correlations between age at death and long bone total area (TA) by groups based on cause of death category (TB or not TB). Bolding denotes statistical significance in a *T*-Test ($p < 0.05$).

Age at death		
	R	*p*
Cause of death TB		
TA mid-distal humerus	−0.101	0.721
TA midshaft femur	0.111	0.705
TA midshaft tibia	−0.135	0.660
Cause of death not TB		
TA mid-distal humerus	0.403	**< 0.05**
TA midshaft femur	0.121	0.392
TA midshaft tibia	0.102	0.478

discussed in relation to the osteological paradox, and that smaller TA is an indicator of such frailty and susceptibility to infectious disease. It is well known that malnutrition has an adverse effect on the immune system (Hughes and Kelly, 2006) and increases the susceptibility for TB infection (Cegielski and McMurray, 2004; Oursler et al., 2002). For example, malnutrition and/or frequent debilitating infections may have made the individuals who died of TB less physically active as children. In fact, the total area of a long bone section is highly influenced by physical activity during the pre- and peri-pubertal periods (Lazenby, 1990; Pearson and Lieberman, 2004). However, most studies indicate low socioeconomic status and malnutrition lead to thinner cortical bone but mainly through endosteal expansion in a fashion similar as described above for immobilized adults (Garn et al., 1969; Himes et al., 1975; Hummert, 1983; Mays et al., 2009).

We propose another mechanism that could explain how malnutrition, particularly vitamin D deficiency, may have halted subperiosteal apposition and increased susceptibility for TB in this specific setting. Due to reduced sunlight exposure in northern Europe most vitamin D intake derives from the consumption of fish and eggs, as well as dietary supplements (Lamberg-Allardt et al., 1984; Spiro and Buttriss, 2014). Consequently, in modern times vitamin D deficiency and poor nutrition are linked to low socioeconomic status (Galobardes et al., 2001; Laitinen et al., 1995; Räsänen et al., 2006). Extreme deprivation of vitamin D leads to rickets and growth retardation (Holick, 2006), but even less severe deficiencies in vitamin D status have a negative effect on serum sex hormone levels (Kinuta et al., 2000; Wehr et al., 2010). In developing males this causes decreased subperiosteal apposition and results in smaller cross-sections (Seeman, 2002). Strikingly, vitamin D deficiency has also been linked to a higher susceptibility to TB infection and to a more negative outcome (Chandra et al., 2004; Coussens et al., 2012; Liu et al., 2006).

Evidence of malnutrition and famine in Finland during the period under consideration here is well documented (Grada, 2001; Häkkinen, 2004; Heikkinen, 1986; Kannisto et al., 1999; Vihola, 1994). It is therefore possible that the individuals with TB in this sample belonged to a lower socioeconomic status, which put them at the lower end of a spectrum of vitamin D deficiency that presumably included most of the population, given the environmental conditions described above. This possibly negatively influenced their subperiosteal development during adolescence and increased their susceptibility to contracting and dying of TB in later life. If this specific mechanism is the cause of the results two predictions can be made: 1) the pattern would not be present using a similar documented sample of male adults coming from a more temperate environment with adequate sunlight exposure, and 2) the pattern would not be present in females from the same area. In fact, low vitamin D leads to low serum oestrogen levels in females (Kinuta et al., 2000), which may produce increased bone size during growth as result of removal of inhibition of periosteal apposition (Seeman, 2002), the opposite pattern of that found in males. Future research will aim to test those hypotheses.

As stated above, there is considerable overlap between the two groups in terms of TA. It is possible that some individuals may have suffered from long-term, chronic disease, or even TB, either in the past or at the time of death even if their recorded cause of death was different, especially considering the number of violent deaths in the sample (see supplementary material). Since no further skeletal elements, such as the ribs or vertebrae are present in the collection, possible skeletal markers left by TB could not be investigated or assumed to exist. Only a small fraction of the individuals who suffer from TB will develop lesions in the skeleton and diagnosis can be difficult even during autopsy examination. Accordingly, most group differences in TA seem to be in the upper end of the range of variation, whereby very few individuals in the TB sample have reached the top end of the distribution. This pattern is also clear from the scatterplots, which show that although in terms of bone length/body mass the individuals from the two groups are similarly represented in the lower part of the range of variation, there is almost a 'ceiling TA' for individuals who died of TB. In particular this is the case in the femur where only one TB individual is found in the upper part of the TA distribution. This, in addition to the difference in sample size between the two groups, also contributes to explaining the difference in the range of variation in TA between the cause of death groups for all three skeletal elements.

Malnutrition, frequent infections or any other severe growth disturbance could be expected to result in reduced endochondral growth, and adult stature has been shown to reflect overall well-being during the earlier phases of growth (NCD-RisC, 2016). In contrast, there are no statistically significant differences in humeral, femoral or tibial maximum lengths (and therefore stature) between the TB and the non-TB samples. This result could be related to endochondral catch up growth, which has been shown to occur even when an improvement in the growth environment is not sufficient for catch up growth in bone width (Mays, 1995). In addition, there was no significant difference in estimated body mass between the two groups. This was expected given that body mass was estimated from the femoral head diameter; articular size dimensions appear to be more genetically canalized than both bone length and cross sections, and are less sensitive to environmental factors (Auerbach and Ruff, 2006; Ruff and Runestad, 1992; Ruff et al., 1993, but see Lieberman et al., 2001).

Although the tibiae of the TB sample have on average smaller TA when compared with the non-TB group, the result does not reach statistical significance ($P = 0.109$). This result could be influenced by the fact that distal segments, such as the tibia, are more optimized for tissue economy to minimize the mass and the energetic requirement for movement (Stock, 2006). In contrast, proximal elements can afford to maintain greater variation that is not directly related to functional constraints on the bone (Stock, 2006). In a large sample of hunter-gatherers from various latitudes and different mobility patterns, Stock (2006) found that, while CSG robusticity correlates with mobility in both the midshaft femur and the midshaft tibia, the influence of climate on diaphyseal rigidity seem to decrease from proximal to distal elements. Differences in subperiosteal area due to factors other than major differences in terrestrial mobility levels (e.g. runners versus sedentary people, see Shaw and Stock, 2009) would therefore have a relatively smaller influence on tibial midshaft TA rather than femoral midshaft TA, which is the pattern observed here in a context of overall sedentary subsistence.

Differences in age at death between the two groups should be discussed, due to the well-known evidence of continued diaphyseal periosteal apposition with aging (Martin and Atkinson, 1977; Ruff and Hayes, 1988). The TB grouping has slightly higher mean age-of-death for the humerus sample (0.78 years) and lower for the femur and tibia samples (8.68 years for the femur; 11.84 years for the tibia). The increase in TA in males with age has been estimated in around 1.8–2.5% per decade. However, the greatest differences in TA were present in the humerus (9.79%, Table 2), the skeletal element for which there is the

smallest difference in age between the samples. In addition, tibiae, for which there is a statistically significant age difference, do not show significant differences in TA between the two groups. It is therefore unlikely that differences in mean age at death between samples had significantly influenced the results.

Still, the mean age differences between groups, particularly in the tibia, could have biologically relevant impacts on relative cortical thickness, which is not captured with laser scans (Macintosh et al., 2013). These examinations may be possible through the analysis of computed tomography (CT) scans and radiographs taken during a recent study (Ruff et al., 2015). Future work will investigate whether individuals in the Finnish sample with cause of death TB differed in terms of cortical thickness and bone mineral density from those with cause of death not TB.

Whilst the above limitations are important, the difference in TA based on cause of death found here further highlights the contribution that the study of structural properties of long bones might have for understanding the effects of disease on the skeleton, which is particularly relevant for paleopathology (e.g. Trinkaus et al., 2001; Cowgill et al., 2012; Sparacello et al., 2016). In addition, this research demonstrates the importance of considering a wide variety of environmental variables when investigating cross-sectional bone parameters in past populations, not solely those that may be indicators of habitual activity patterns. The model proposed to explain the results in this setting, i.e. vitamin D deficiency causing halted periosteal apposition and later increased susceptibility to TB infection and poorest prognosis, generated some testable hypotheses to be investigated in future research. We hope that this will stimulate further investigations on the relationship between bone structural properties and disease and in particular TB.

5. Conclusions

This study compared long bone structural properties between individuals who died of tuberculosis and those with another recorded cause of death in a 19th and early 20th century Finnish documented skeletal collection. Results show that, when bone cross-sectional total area was standardized for body size, TB individuals had smaller values, significantly so in the femur and humerus, than the non-TB grouping. This could be due to malnutrition, vitamin D deficiency, and/or reduced childhood activity affecting both subperiosteal development during adolescence and, later, biological 'frailty' in terms of susceptibility to contracting and dying of TB. This model generated testable hypotheses that may be explored in future studies. Due to the relatively small sample sizes and considerable overlap between the two samples based on cause of death, future studies with other identified samples are needed to further investigate the observed relationship between TB and bone cross-sectional size.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ijpp.2017.12.005.

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