Authors: Justyna J. Miszkiewicz[1,2], Karen M. Cooke[1]

Title: **Socio-economic determinants of bone health from past to present.**

Affiliation(s):

[1]Skeletal Biology and Forensic Anthropology Research Group, School of Archaeology and Anthropology, Australian National University, 44 Linnaeus Way, Canberra 2601, Australian Capital Territory, Australia

[2]Skeletal Biology Research Centre, School of Anthropology and Conservation, University of Kent, Canterbury CT2 7NR, Canterbury, United Kingdom

Corresponding author e-mail: Justyna.Miszkiewicz@anu.edu.au

Tel: +61 2 6125 9295

Justyna J. Miszkiewicz ORCID: 0000-0002-9769-2706

Karen Cooke ORCID: 0000-0002-3022-6508

Abstract:

Increasing epidemiology evidence amounts for social determinants of bone health underlying musculo-skeletal conditions such as osteoporosis. Amongst different facets influencing skeletal health, socio-economic status (SES) has been identified as a critical factor determining one's access to resources, health care, education, nutrition, and physical activity. Recent conceptual and epigenetic studies assessing SES links with DNA methylation offer further support for the adverse effects of social disadvantage in early life on bone quantity and quality in adulthood. However, this evidence for socially patterned risks in bone fragility is not restricted to the contemporary society. Data exist for ancient human skeletal samples deriving from SES stratified cemeteries to also reflect bone changes consistent with lifestyles specific to social standing. Similarly to modern data, the conclusion drawn from the ancient times has been for a negative effect of low SES on bone growth and maintenance. Some contradictory results, mirroring previously reported inconsistencies in epidemiological studies, have also been reported showing that high SES can equally result in poor bone health. It becomes clear that ancient evidence can offer a further line of support into these ongoing epidemiological and epigenetic research efforts. Taken together, a holistic approach to clinical understanding and practice of bone health is recommended, building upon ancient and modern findings to target living groups who are most at risk of developing low bone mass and compromised bone micro-architecture.

Keywords: socio-economic status, osteoporosis, inequality, inequity, DNA methylation, bone loss, histomorphometry, lifestyle, epigenetics, social epidemiology, bioarchaeology, biological anthropology

Abbreviations

aDNA – ancient DNA
BMD – bone mineral density
CT – computed tomography
DISH – diffuse idiopathic skeletal hyperostosis
DXA - dual-energy X-ray absorptiometry
DNAm – DNA methylation
DOHaD - Developmental Origins of Health and Disease
GWAS – henome-wide association study
LEH – linear enamel hypoplasia
MES – minimum effective strain
miRNA - micro RNA
PTH – parathyroid hormone
RANKL - receptor activator of nuclear factor kappa-B ligand
SDoH - Social Determinants of Health
SES – socio-economic status
SFI – skeletal frailty index

1. Introduction

The biological and biochemical complexity of bone development, growth, and maintenance throughout human lifespan is now well understood to be affected by multiple factors that include disease, mechanical stimuli, nutrition, hormonal balance, biological sex, and genetic underpinning [e.g. 1-5]. In addition to these direct influences on the skeleton, increasing social epidemiological evidence amounts, identifying extrinsic determinants of bone health that may arise as a result of gender and ethnicity, and/or structural and economic opportunities at a society level; showing that social disadvantage, or low socio-economic status (SES), increase the risk of osteoporosis development [e.g. 6-14]. Given that conditions such as osteoporosis are of major social and economic global concern in the modern ageing populations [15-17], identifying groups who are most at risk of developing bone fragility and subsequent related fractures is of utmost importance for effective management of osteoporosis in clinical contexts [18]. Reports of osteoporosis under-treatment and diagnosis difficulties per gender and age continue to surface particularly when considering those with already fragile bone or experiencing fragility fractures [19-21]. The mechanisms explaining the social gradient of osteoporosis are yet to be elucidated though recent conceptual models and data propose an epigenetic foundation whereby *in utero* conditioning arising from maternal health and pregnancy, as well as environmentally induced persistent stress and inflammation, result in long term effects on skeletal health [22-24].

The social patterning with potential epigenetic foundation to bone loss and maintenance observed in the contemporary society can be further supported by ancient human data [e.g. 25-30]. Evidence exists for human skeletal samples that derive from historic and archaeological cemeteries stratified by stark layers of SES inequality, illustrating that human bones have long suffered the consequences of societal wealth and power inequality and inequity. The surviving skeletal physical evidence for medieval people who would have lived subject to the feudal

system offer an illuminating source of skeletal macro- and micro-architectural phenotypic characteristics reflecting SES stratum specific lifestyles [26]. This review aims to cast a light on these medieval bones analysed in the context of SES to a) support the ongoing modern research in epidemiology and epigenetics, and b) highlight how studies of well preserved human bone samples [**Figure 1**] from historical and archaeological contexts can help us understand current social gradient of osteoporosis models [31]. As a result, we hope that this review will encourage a holistic approach to further understanding bone fragility, and when identifying groups who are most at risk of developing osteoporosis. Epidemiological and epigenetic insights are briefly summarised first, with the ancient perspective presented second.

2. Modern perspective through social epidemiology and epigenetics lenses

A model summarising the social determinants of health (SDoH) was outlined in the 1990s with Dahlgren and Whitehead [32] presenting a policy framework addressing an interrelation of several environmental layers of the society that impact wellbeing. These included cultural practices, socio-economic positioning, occupation, income and education, community networks amongst other variables influencing our health at an individual and group level [32]. The SDoH model clearly demonstrated that a series of correlated factors that often arise beyond one's control determine health outcomes. Support for SDoH has subsequently been shown, for example, using links between low SES uninsured individuals and type 2 diabetes [33], mental health and addiction and ethnic disparities [34], as well as social risk based upon factors such as education and income related to frailty that includes chronic illness, physical and emotional health [35]. To better understand the mechanisms behind these bio-social relationships, life course approaches to studying health, disease, and mortality from the foetal to adult stages resulted in the Developmental Origins of Health and Disease (DOHaD) paradigm, also known as the Barker hypothesis [36-40]. It encapsulated the associations between early life, *in utero* and post-natally, experiences of adversity and long term effects on health in later adulthood.

Several research lines have since used the DOHaD framework to explain, for example, maternal obesity and foetal development [41], maternal hypertension and mental health in the offspring [42], susceptibility to developing cancer [43], obesity and type 2 diabetes [44] in later life. These models explaining extrinsic factors influencing human health at the intrauterine and later life phases have extended to osteoporosis [45-50]. For instance, developmental origins of osteoporosis have been considered based on bone mineral density (BMD) changes with premature births [45], and birth size and low birth weight effect on bone size [46, 47]. It is now accepted that osteoporosis is a non-communicable disease [48-50], and should be studied using the life-course approach.

Similarly to the classic report by Barker [39], where undernutrition during gestation and early in life led to a greater risk of diabetes in adulthood, variability in environmental and lifestyle factors during childhood and adolescence determine the attainment of peak bone mass accrued in our third life decade [51]. For instance, adult BMD measured as part of a prospective cohort study in Finland (Cardiovascular Risk in Young Finns Study), differed substantially with smoking, exercise, and calcium intake regimes recorded during childhood and adolescence in a group of 264 adults [51]. Femoral neck and lumbar spine BMD was increased in individuals who had exercised regularly, lower in men who were smokers, and higher in women who had consistently consumed higher levels of calcium. In this case, lifestyle factors, which are strongly associated with one's socio-economic standing, of the youth had clear implications for their bone mass building later in life.

Studies investigating SES disparities throughout the life-course have generally indicated that those from adverse backgrounds, measured including income, education, and residential address, experience increased bone fragility, fracture risk, and prevalence of osteoporosis [8-14, 50-55]. For example, Brennan et al [9] investigated SES, controlling for age and sex, using 2006 – 2007 data of fractures experienced by Australian adults aged > 50 years. In this study

[9], a total of 3943 radiology records of fractures held by the Australian Barwon Statistical Division were correlated with SES inferred from residential address. Men and women of low SES were estimated to have increased odds of six-fold and two-fold respectively for fracture incident when compared to high SES groups [9]. Intriguingly, in another Australian study [50], where BMD and SES were examined in 1494 adult women, both low and high SES was associated with reduced BMD. Bone mineral density data were measured from skeletal sites using dual-energy X-ray absorptiometry (DXA), and adjusted by lifestyle factors such as diet, smoking, alcohol consumption, and physical activity [50]. Earlier studies using Australian cohorts investigating SES via measures of income and occupation reported similar results. For example, Suen [52] examined the effect of early life occupation related physical activity on incidences of hip fractures in later life in Sydney based patients. A total of 416 patients were examined for sedentary occupations between 20 and 50 years old, and coded according to the Australian Classification of Standard Occupations [52]. Amongst several other findings, it was reported that hip fracture occurrence decreased with increased SES of occupation [52].

Data from European populations mirror the results from Australian cohorts [52-55]. For example, the effect of disadvantaged social background on bone density and fractures evaluated in Spanish women showed low SES to be associated with reduced BMD [53]. Data obtained using radiographs and physical examination, in addition to measuring 25-hydroxy-vitamin D (25-OHD) and PTH from blood samples, were lower in those from disadvantaged backgrounds [53]. Additionally, the frequency of fracture occurrence was higher in the low SES cohorts as well [53]. Recent distal radius fracture data from the UK [54] were linked to social deprivation. Using a sample of 4463 patients assessed against the Index of Multiple Deprivation, higher fracture experiences were apparent, in addition to sex and ethnicity factors, in those from disadvantaged backgrounds [54]. Social support with an SES framework has also been considered as a factor contributing to hip fracture incidences in Swedish cohorts [55].

Farahmand et al [55] evaluated SES and marital status against 1327 hip fracture cases from 1993-1995 in Swedish females of post-menopausal age to find that higher income and single living women had an increased risk of developing hip fractures. On the contrary, women in cohabitant households and of higher income had a lower record of hip fractures. In a sample of 6160 Italian females of post-menopausal age, highest level of education was also related to lower prevalence of osteoporosis [56]. Using multiple logistic regression analysis, Varenna et al [56] reported a predictive relationship based on education, calcium, exercise levels and other variables that include age, and age at menarche, whereby increasing educational background decreased the risk of developing osteoporosis.

An additional facet for consideration are population history factors which can offset or add to skeletal health within the SES framework [57-60]. Both lifestyle and melanin levels contribute to sunlight exposure levels across populations, having implications for vitamin D photosynthesis and, ultimately, mineral metabolism in the skeleton [61]. Ongoing investigations into the prevalence of vitamin D deficiency and nutritional rickets include ethnicity-specific factors (such as skin melanin content) within latitude and type of dwelling contexts, highlighting the need for multidisciplinary efforts tackling vitamin D status within and beyond SES and ethnic minorities [62].

Taken together, a growing body of social epidemiology evidence exists confirming that links between SES and osteoporosis and related fractures are apparent [31, 50]. While these do not manifest consistently in all individuals and communities, ongoing research ought to focus on complementary univariate and multivariate analyses of biological and social markers of bone health, which clearly play a role in accelerating or slowing down bone fragility experiences.

Further support for social determinants of bone health can be found in epigenetic research efforts. Indeed, the social gradient of osteoporosis, mechanisms of which are still not fully

understood, can be hypothesised to have foundation in the epigenome considering the already discussed DOHaD acting *in utero* and postnatally, and manifesting in the adult life [31, 63, 64]. Coined by Waddington in 1942, knowledge of which has been expanded over the past few decades [22], epigenetics refer to the influences acting on the link between genotype and phenotype that result in gene expression changes with no direct DNA sequence interference. Epigenetic modification of gene expression can be achieved in a stable and heritable manner through cell division, meaning that a whole genome may be transformed into multiple transcriptomes [23, 63, 64]. Epigenetic modifiers act on the genome in a way that changes the regulation of gene transcription, up- and down regulating their expression through the availability of gene sequences to transcriptional enzymes [65]. For example, while most cancers are caused by underlying occasional alterations to the DNA sequence [66], the predominant epigenetic mechanisms including DNA methylation (DNAm), histone and chromatin modifiers, and non-coding RNAs can also lead to the development of disease [67-70]. As these occur at a molecular level, their association with skeletogenesis cannot be ignored, with epigenetic marks potentially mediating the biological processes impacting bone development and later health, through epigenetic modification of osteoblastogenesis and osteoclastogenesis, bridging the interactions between genetics and the environment [71, 72].

When considering individuals of low SES who develop and grow within disadvantaged intrauterine and postnatal environments, indeed the array of SES related factors (such as nutrition, lifestyle, exogenous environmental variables such as pollution) may have epigenetic significance [73]. Indeed, associations between SES and DNAm, and micro RNAs (miRNAs) have been previously reported [74-76]. For example, a global DNAm analysis [68] of Glasgow, Scotland based "Psychological, social and biological determinants of ill health" (pSoBid) cohorts [75] that encompassed a disadvantage gradient, reported hypomethylation in those of the lowest SES [76]. Another study where miRNA was investigated in esophageal cancer

expression in the light of non-biological factors that included SES found a reduction of miR-43 and miR-203 in individuals of low SES [77]. The Dutch famine of October 1944 to May 1945 acutely demonstrates the effects of environment on individuals *in utero*. Those exposed to the peak famine conditions (<900 kcal per day) during the first 10 weeks of gestation had significant differences in DNAm of genes linked to development, growth, and metabolism, including hypomethylation of insulin-like growth factor II [78-80]. Alternatively, those that experienced the peak of the famine later in gestation did not show significant alterations, demonstrating a critical window of epigenetic modification in development [80]. While future research in this area requires methodological refinement [see 22, 23], insights into SES and bone cell function can be extrapolated to further explain social patterning of osteoporosis.

Bone cell genesis and activity have been linked to epigenetic influences, particularly DNAm, affecting osteoblastic function that drives bone development in early life phases, and its involvement in bone deposition when remodelling bone throughout the lifespan [71, 72]. Bone metabolic activity balance is crucial for its healthy physiology, and so epigenetic alterations at cell level have the potential to ultimately elevate the risk of osteoporosis [22, 23]. Limited data still exist to support these associations, though hypomethylation using blood cells samples in osteoporotic women post-menopause [81], and bone cell methylation differences in osteoporotic and control femur samples [82] have been reported. These DNAm studies, however, did not include SES in their analyses. Brennan Olsen et al [22], and Riancho and Brennan-Olsen [23] indicate that an epigenetic link to SES can be made through an accumulation of stress responses affecting the skeleton. Their model [22, 23] outlines how long-term stress and inflammation can affect skeletal homeostasis resulting in ultimate bone mass reduction, likely as a result of the inhibition of osteoblast and acceleration of osteoclast function following stress. Hormones and proteins such as glucocorticoids and inflammation cytokines are possible candidates acting on the skeleton as a result of ongoing inflammation.

Both glucocorticoids and some cytokines affect skeletal cells by inhibiting bone deposition and enhancing bone resorption through PTH, RANKL, and Wnt signalling pathways [82]. Individuals from adverse backgrounds may experience prolonged stress, inflammation, poorer nutrition, and higher susceptibility to disease, all of which may be accompanied by psychological distress.

Several studies have sought to test this association between DNAm and SES experimentally at a population level, targeting genes associated with stress-response and inflammation [83-85]. The conclusion has been that those of low SES show patterns in DNAm level change at targeted sites when compared to those of high SES [83-85]. Furthermore, genome wide association studies (GWAS) have assessed changes in DNAm across the entire genome, scoping for new possible regions associated with epigenetic adaptation of SES [86-88]. For instance, a recent study examined leukocyte DNAm at 2546 CpG sites (associated with 1537 genes) against SES inferred from educational, resource, and income background in 489 young adults from the Philippines [89]. Methylation data differed across SES, with the low SES group having higher DNAm at an increased number (1777) of CpG sites. These sites were found to be biased towards pathways linked to immune function, a factor associated with low SES which has been previously investigated [88], as well as nervous system and skeletal development, with population specific growth previously shown to be affected by SES [90]. However, overall, little research into epigenetic changes of skeletal development has been conducted to date. While the use of GWAS can assist in the identification of biological processes undergoing epigenetic adaptation, such as McDade et al.'s [89] over-representation of genes in skeletal development, the difficulty remains (and will be an ongoing issue) in comparing GWAS results between different studies. This is mainly due to different arrays being used per study whereby various sets of CpG loci, both in number and location, are included [83, 86, 88, 89]. Considering that genome methylation changes across the genome by cell type [91], this may

influence epigenetic interpretations pertaining to skeletal development when assaying blood or leukocytes. Further investigations into the epigenetics of skeletal development should focus on the skeletal tissue itself. While these mechanisms require further research, evidence is hinting on the interrelated epigenetic links supported by epidemiological data [22, 23, 31].

3. Ancient perspective using medieval society structure and data from surviving human skeletal remains as a model for understanding social determinants of bone health

In the clinical realm, bone fragility is understood using data that derive from living people and modern skeletal biology experimental perspectives. Investigations into osteoporosis can take many forms and methods, but all centre on elucidating the complexity of factors determining reduced bone mineral content, poor bone micro-architecture, overall bone fragility, and incidence of fracture [92]. However, we should not underestimate the contribution that ancient human skeletal remains can make to our current understanding of bone health in the living [30], and by extension the effect of SES on bone growth, development, loss and maintenance in adulthood [26, 31]. While there are many different research areas concerned with the analysis of ancient human skeletons (i.e. spanning palaeoanthropology, palaeopathology, bioarchaeology, broader biological anthropology) [93-95], their findings can be translated into today's explanations of bone health [see e.g. 25, 28, 30]. Acknowledging the limitations of these disciplines is crucial to appreciating the difficulty in undertaking direct comparisons between human bones of the present and the past, but their educational and informative value in clinical contexts can be substantial. In this section, focal attention is paid to human skeletal remains curated as part of medieval anthropological collections. Insights are gleaned into the adverse effect that living as part of the European feudal system had on human bone health. Of course, there are multiple other time periods and archaeological sites found globally that were characterised by SES stratification (e.g. the Classic Maya of Mexico [96], 18th to 19th Century Edo, Japan [97], 300–750 BP Taumako, Solomon Islands [98] post-medieval Aalst, Belgium

[99], or Industrial Revolution 18th - 19th centuries England [100]), but a large number of medieval cemeteries containing (in some cases) thousands of individuals offer large sample size for skeletal health examination [101].

Unlike in clinical settings, the examination of archaeologically derived skeletal remains is limited by the absence of truly experimental study design, where living people can be interviewed, observed, or their detailed medical records accessed. Therefore, there is much reliance on interpreting ancient human skeletal data in broader contexts that are a combination of extracting information from surviving literature, description of material culture uncovered as part of excavations (such as grave goods), historical documentation, and in some cases ethnographic (ethno-archaeological) records [102, 103]. These are considered secondary evidence that can help explain observations made on the primary (skeletal) evidence [103]. While blood samples to measure PTH from a potentially osteoporotic patient cannot be collected, other bone phenotype examination techniques of clinical and bio-medical significance, ranging from gross anatomical examination to bone histomorphometric analysis [**Figure 1**], can be used to evaluate the degree to which bone fragility characterises a set of surviving medieval skeletons [26, 31, 104-107]. Additionally, the environmental differences, such as selective pressures, between the past and today cannot be overlooked. Thus, as much as we cannot make absolute comparisons between ancient and modern human bone, we can undertake medieval population (context) specific interpretations as models illustrating how medieval SES was reflected in bone health [31].

The European High and Late Middle Ages (approximately 10th – 16th centuries, though the Middle Ages began in 5th century) was a time when the society was under the feudal ruling of land, property, and work, resulting in stark inequality and inequity in the distribution of wealth and power [108-113]. In addition political and religious structure divisions, the population also experienced drastic demographic changes due to major plague pandemics such as the Black

Death [111]. The feudal system dictated the low SES classes to work for landlords. Therefore, the society was under a clear SES divide with those in the higher SES categories (e.g. royals, noblemen) leading more privileged lifestyles, and those of the lower SES experiencing disadvantage [108-113]. While the medieval SES structure was certainly more complex than a simple high and low SES dichotomy, with some evidence for the existence of middle-class (e.g. knighthood), historical evidence indicates that peasantry and noblemen engaged in vastly different lifestyles as reflected in their daily diets, occupations, and experiences of stress [108, 109, 112]. Multiple medieval cemeteries survive until today and many of them have undergone excavation, yielding human remains representing these SES divisions. These collections are now curated at universities and museums offering valuable bone biology data. In some cases, the collections encompass thousands of individuals, spanning juveniles and adults, serving as a complementary sample to modern clinical trials [31]. As established earlier, factors (nutrition, biomechanical stimulus) impacting complexity of bone modelling and remodelling are in some degree tied to our social and economic opportunity [114] – medieval people's bones mirror the experiences of contemporary societies.

Multiple lines of evidence for social determinants of bone health can be drawn from medieval human skeletal remains. However, they are difficult to categorise into single factors as, for example, bone functional adaptation will in some way relate to one's nutritional conditioning. Even then, the bone adaptation thresholds the minimum effective strain (MES) may be imposing on one's skeleton cannot be ruled out [115]. Seeing as the factors are interwoven, we present cases of medieval SES effect on bone health in both directions, i.e. where both low and high SES has a negative bone health outcome, and where both high and low SES can also result in good bone health. The reader is invited to consider our review form the perspective of clear SES-bone associations that are context dependent, but have limited (at this stage anyway) directional predictive strength.

Several studies have reported medieval human skeletons of low SES to be characterised by poor bone health in adulthood [**Table 1**] [e.g. 26, 104, 105, 116-119]. Perhaps of the most relevance joining past and present in bone research is the aetiologically multi-factorial osteoporosis. Not only has potential experience of osteoporosis been reported in female skeletons dated to XIIth Dynasty Egypt [120] or Roman Britain [121], its social gradient extends to medieval SES groups as well. For example, age related bone loss in peasant females was demonstrated in a skeletal sample dated to 11^{th} – 16^{th} centuries Wharram Percy in North Yorkshire, England [116]. Cortical bone loss data obtained using radiogrammetry of metacarpals mirrored the results from modern menopausal women in Finland [116]. The medieval peasant female skeletons also showed evidence of multiple healed fractures in the trabecular bone of their vertebrae, correlating with increased bone loss [116]. In another study, BMD measured via DXA from proximal femoral samples dated to 11^{th} – 16^{th} centuries Trondheim, Norway, reported increased osteoporotic fracture prevalence in females who lived in colder and more built up areas [117]. Of further interest to the clinical realm is the achieved human adult skeletal size. Male and female long bone morphometric data representing high and low SES in 8^{th} – 13^{th} centuries Trino Vercellese, Italy indicated greater adult body mass in males of high SES [29]. A recent follow up study [118] of similar design replicated these results using a neighbouring Italian sample from San Lorenzo di Alba (7^{th} - 15^{th} centuries), where high and low SES differences in skeletal morphometry and stature were apparent between males, but not females. Skeletogenesis traits measured in Polish samples deriving from medieval high SES 12^{th} – 14^{th} centuries Cedynia and low SES 14^{th} – 17^{th} Słaboszewo, found the low SES group to be characterised by a reduced skull base height, vertebral canal, and bone quantity in metacarpals [119]. Bone remodelling in adulthood has also been investigated in medieval SES contexts. Several studies examining 11^{th} – 16^{th} centuries high and low SES individuals from medieval Canterbury, UK have demonstrated social disadvantage to be associated with poorer

adult bone health, as well as experiences of increased physiological disruption in childhood and potentially reduced longevity [26, 104, 105, 107]. Using femoral histomorphometry, increased bone density at midshaft femur was reported in high SES, though cortical bone microstructural geometric properties aligned with increased experiences of mechanical strain in the low SES [26]. Earlier investigations [107] in this sample used linear enamel hypoplasia (LEH, dental marker of physical development upsets in childhood) and age-at-death estimates to demonstrate higher and lower values respectively in the low SES groups. A recent related samples analysis further elucidated a relationship between these variables only in the high SES group [105], whereby ill health experienced in childhood may be accounted for by developing increased bone density in adulthood in privileged settings. The above studies offer support for the adverse relationship between medical social disadvantage and the skeleton, though only few of them [e.g. 26, 105] consider bone histology or DXA methods, and large enough sample sizes to infer medieval lifestyles. Those relying on gross anatomical morphometric [e.g. 29, 118] examination of the skeleton may be un-accounting for adult bone remodelling.

On the contrary, skeletal data from medieval individuals of high SES have also indicated that advantaged lifestyle does not always result in healthy bones [**Table 1**] [e.g. 122-125]. For example, even though medieval nuns in Italy may have held a privileged status, they spent most of their days inside monasteries limiting their sun exposure [122]. Indeed, a study [122] of an elderly female skeleton from 14^{th} – 17^{th} centuries Coimbra, Portugal described presence of an extracapsular fracture of the proximal femur to have been likely a result of osteoporosis. While the association between limited sun exposure and osteoporosis in this individual can be made loosely, the female elderly age would have played a key role in advancing her bone quality deterioration. Evidence of fracture healing allowed the authors of this study [122] to also infer extended care and support system surrounding this female who would have been disabled for a period of time otherwise. Cases of Forestier's disease, or diffuse idiopathic skeletal

hyperostosis (DISH), a form of skeletal arthritis that is a metabolic disorder, have been reported in association with high SES [123]. There is substantial evidence for its occurrence in medieval times [126, 127], particularly afflicting older males originating from monastic backgrounds [123]. This is likely because the aetiology of DISH includes factors such as the male sex, limited physical movement, and elevated consumption of nutritionally poor diet [128]. Reports of medieval skeletons likely showing evidence of DISH have been published for different sites including the Merton Priory, Wells Cathedral (13^{th} – 16^{th} centuries) and the Royal Mint (14^{th} century) in London, and S. Angelo Abbey in Montescaglioso in Italy (12^{th} – 15^{th} centuries) [123, 127]. While the association between monastic background and DISH prevalence appears reasonable in these cases, we must not forget the differential diagnosis of DISH as well as reliance on interpretations made using secondary SES evidence (e.g. in [127] the authors acknowledge limited written SES records). Another example from medieval Italy (8^{th} – 13^{th}, 17^{th} centuries) is a case of increased BMD in lumbar vertebrae and femoral samples analysed using computed tomography (CT) and DXA in individuals of low SES [124]. The elevated data agreed with evidence for an increase in calcium consumption and higher physical activity in the low SES group [124]. This study particularly highlights that the direction of SES effect on bone health cannot be easily predicted. Finally, a modified skeletal frailty index (SFI) that incorporates markers of sarcopenia and osteopenia into its assessment can also be applied to medieval skeletons [125]. Marklein and Crews [125] explain that the traditional inclusion of all SFI biomarkers cannot be used on all medieval human skeletal assemblages due to fragmentary material. However, their [125] modified SFI measured through a series of skeletal indicators that include LEH as a proxy for developmental disturbances, and abnormal skeletal lesions as an indication of bone infection, showed increased skeletal frailty in monastic individuals (when compared to non-monastic lay communities) across multiple sites in

medieval London. The authors [125], however, do not rule out the effect of age and sex preponderance in the monastic sample that may have contributed to their results.

Whether the relationship between SES and measures of bone health is positive or negative, what clearly emerges from the medieval analyses is that social determinants of skeletal fragility should be considered within a population specific context. Nevertheless, the medieval evidence supports patterns reported in epidemiological and epigenetic accounts, whereby SES plays a role in determining our bone health in adulthood. Even if this means, such as in the study by Borrè et al [124], that medieval individuals of low SES may show an unexpected increase in BMD, it can be explained by their SES specific lifestyle (i.e. physically demanding occupations, dietary calcium, and increased sun exposure). A series of behaviours related to our occupation and habitual lifestyles, coupled with unequal access to resources, nutritious diet, health care, social support system, and even health literacy [129], may contribute to the expression of human skeletal phenotypes, both in the past and in the present [31].

Finally, increasing interest in investigating DNAm in ancient DNA (aDNA) samples (palaeoepigenetics) has been emerging recently, with anthropologists recognising it as a powerful tool for researching stress in prehistoric populations [130-132]. The predominant application of aDNA has been to trace population migrations [133], or pathogen evolution (such us tuberculosis and leprosy [134]), seeing as aDNA is usually extracted from surviving skeletal elements. However, there have been successful attempts at determining surviving methylation in ancient skeletal tissue, including a case of Pleistocene bison remains [132]. Therefore, avenues for future applications in ancient human skeletal remains cannot be underestimated. These efforts can shed new light on experiences of osteoporosis with SES in the past. However, access to confirmed osteoporosis diagnosed and healthy control ancient individuals would be needed to undertake robust epigenetic comparisons. These will no doubt contribute further to modern epigenetic research.

4. Clinical relevance

One of the biggest treatment and prevention challenges that clinical researchers and practitioners face when dealing with their patients' bone health is the successful and effective identification of risk factors underlying the development of osteoporosis, and management and prevention of osteoporosis fractures [135-137]. Much data are available for the biomechanical, nutritional, smoking and alcohol drinking effects on bone, all considered within one's context of genetic predisposing factors [138-143]. Ongoing life-course and DOHaD approaches, both applied in past and modern bone fragility contexts, are increasingly recognising the crucial role that SES plays in human opportunity inequality and inequity [e.g. 31, 50, 144, 145]. As presented in our review, those from less privileged backgrounds usually appear to experience fractures at an earlier age, sustain poor bone quality and quantity in adulthood. Interventions preventing from subsequent fracture occurrence in affected individuals from diverse community backgrounds (and age and gender groups) are available and efforts to improve strategies are ongoing [146-149]. Recently, increasing focus has been placed on ethnicity and country-level osteoporosis management strategies [e.g. 57, 58, 150-152].

Targeting two key bone aspects that may shift with SES (and opportunity), in addition to other direct biological influences on bone, are peak bone mass attainment [114] and the experience of osteoporosis around menopause [150]. By considering patients' SES, and that of their parents, it may become easier to identify those groups who are most at risk of developing osteoporosis, or at least likely to suffer from increased bone fragility. Resources can be directed towards increasing bone health education and health care efforts for those more disadvantaged groups. As demonstrated through our ancient perspective in this review, much evidence can be found in the medieval times for SES disparities affecting adult human skeletons. One way to incorporate this ancient perspective into clinical and educational communication is to include medieval examples as part of information sheets that can be distributed to patients (e.g.

referring to examples summarised in **Table 1**) [**Figure 2**]. Both young men and women (in their "bone bank" building age until around 30 years old), and older females (in their menopausal age) may benefit from 1) learning that bone health problems have affected us throughout the human history usually due to social reasons beyond our control, and 2) identifying their own occupation or generic habitual lifestyle tendencies as likely contributing to future bone health problems, both to themselves and to future generations. This may further encourage the consideration of lifestyle over the life course, focusing on any potential differences in lifestyle between the earlier and later life phases. The practical applications of medieval human bone research may be limited compared to the modern clinical observations and management practices, but its educational and informative value may prove helpful when communicating with patients and those at higher bone fragility risk.

5. Conclusions

The aim of this review was to provide an ancient perspective on social determinants of bone health. In addition to the increasing social epidemiology and epigenetic support for more than just direct biological influences on bone quality and quantity in adult life, we presented examples from medieval research undertaken on surviving human remains where social and economic factors may have played a role in adult skeletal health. While the consensus, in both from social epidemiology and ancient examples, has been that a more disadvantaged background has adverse effects on bone health, we also discuss cases where privileged lifestyles can equally result in reduced bone mineral. We emphasised a population specific contextual interpretation of each case or group, as it is clear that human skeletal phenotypic characteristics are underlined by a combination of biological and social factors. While the medieval evidence offers limited practical applications in clinical practice, it serves great educational value during communication with patients suffering from fragile bone. Ultimately, the ongoing research into social determinants of bone health, both using past and modern

samples, will help elucidate further the global social and economic patterning in bone fragility, helping with the identification of human groups who are most at risk of having accelerated bone loss.

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Compliance with Ethical Standards

This article does not feature data from living humans, human autopsies, or animals. We include an image of medieval human femur bone histology sample from an anthropological collection curated at the University of Kent, Canterbury, UK. The collection pre-dates the Human Tissue Act, and was studied following the 2008 British Association for Biological Anthropology and Osteoarchaeology (BABAO) Code of Ethics, 2010 BABAO Code of Practice, 2012 American Anthropological Association Code of Ethics, and 2003 Code of Ethics of the American Association of Physical Anthropologists.

Conflict of Interest

The authors declare that they have no conflict of interest.

Disclosure

The authors are academic researchers (Miszkiewicz, PhD; Cooke, MSc) with no clinical qualification or authority. The recommendations made in the review are based on an analysis of research results published in peer reviewed articles.

Ethical Approval

This article does not contain any studies with living human participants or animals performed by any of the authors.

Informed Consent

Not applicable.

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Figure captions:

Figure 1. Example of excellent microscopic preservation of cortical bone in a sample taken from a medieval English individual (ID NGB 89 SK 22). This transverse section is from the

posterior midshaft femur, and is approximately 100 microns thick. The preservation of cortical bone histology makes the sample suitable for histomorphometric analyses (see methods in [26: p. 48]) to assist in reconstructing bone remodeling despite the antiquity of this human skeleton. The top image was taken using transmitted light, whereas the bottom image shows linearly polarised bone histology.

Figure 2. Simplified conceptual chart illustrating how ancient evidence can be incorporated into a more holistic understanding of bone health issues in clinical contexts.

Table caption:

Table 1. Examples of medieval skeletal evidence for social determinants of bone health, which may serve as a source of useful information when undertaking educational communication in clinical settings.