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

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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
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, 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 [16-17], 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 prehistoric 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. 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, it is hoped that the 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 summarised first, with ancient evidence 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 framework for high interrelation degree of multiple environmental layers of the society. These included cultural practices, socio-economic positioning, occupation, income and education, and 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 mortality from the infant 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 DOHaD to explain patterns in data focusing on foetus development and maternal obesity [41], maternal hypertension and mental health in offspring [42], cancer susceptibility [43], and obesity and type 2 diabetes [44]. These models explaining extrinsic environmental factors influencing human health at the intrauterine and later life phases have extended to the social gradient of osteoporosis [45-50]. Developmental origins of osteoporosis have been considered based on bone mineral density (BMD) changes with premature births [45], birth size effect and low birth weight [46, 47], accepting that osteoporosis as a non-communicable disease [48-50] should be studied using the life-course approach.

Socio-economic disparities throughout the life-course have generally identified that those from adverse backgrounds, measured including income, education, 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 bone mineral density (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 [51] 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 [51]. Amongst several other findings, it was reported [51] that hip fracture occurrence decreased with increased SES of occupation.

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

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 postulated to have foundation in the epigenome considering the already discussed DOHaD acting *in utero* and postnatally, and manifesting in the adult life [31, 56, 57]. Coined by Waddington in 1942, knowledge of which has been greatly expanded and clarified 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, 57, 58]. 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 [59]. For example, while most cancers are caused by underlying occasional alterations to the DNA sequence [60], the predominant epigenetic mechanisms including DNA methylation (DNAm), histone and chromatin modifiers, and non-coding RNAs can also lead to the development of disease [61-66]. 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 [65, 66]. 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 [67]. Indeed, associations between SES and DNAm, and micro RNAs (miRNAs) [68-70] have been reported. For example, a global DNAm analysis [68] of Glasgow, Scotland based "Psychological, social and biological determinants of ill health" (pSoBid) cohorts [69] that encompassed a disadvantage gradient, reported hypomethylation in those of the lowest SES [68]. Another study where miRNA was investigated in esophageal cancer expression in the light of non-biological factors that included SES [70] found a reduction of miR-43 and miR-203 in individuals of low SES. 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 [71 – 73]. 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 [73]. 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.

As noted above, 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 [65-66]. 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 [74], and bone cell methylation differences in osteoporotic and control femur samples [75] 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 [76]. 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. 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 [77]. 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, 78], 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) [79, 80], 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 [81], 18th to 19th Century Edo, Japan [82], 300–750 BP Taumako, Solomon Islands [83], post- medieval Aalst, Belgium [84], or Industrial Revolution 18th - 19th centuries England [85]), but a large number of medieval cemeteries containing (in some cases) thousands of individuals offer large sample size for skeletal health examination [86].

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 [87, 88]. These are considered secondary evidence that can help explain observations made on the primary (skeletal) evidence [88]. 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, 89-92]. Additionally, environmental differences between the past and today cannot be overlooked, particularly differences in selective pressures and technological stages of societal advancement. 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 10^{th} – 16^{th} centuries, though the Middle Ages began in 5^{th} 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 [93-98]. In addition to strict political and religious structure, the population also experienced drastic demographic changes due to major plague pandemics such as the Black Death [96]. The feudal system dictated the low SES classes to work for a landlord, which in some cases involved slavery [98]. 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 [93-98]. While the medieval SES layering is more complex than a high and low SES dichotomy, with some evidence for middle-class (e.g. knighthood), there is written historical evidence that peasantry and noblemen engaged in vastly different lifestyles based on diet, occupation, and experience of stress [93, 94, 97, 98]. Multiple medieval cemeteries survive until today and many of them have undergone excavation, yielding human remains representing these SES divisions 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 [99] – 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, though 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 [100]. 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, but with limited initial directional predictive, context dependent, strength at this stage.

Several studies have presented medieval skeletons of low SES to be characterised by poor bone health in adulthood [**Table 1**] [e.g. 26, 89, 90, 101-104]. 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 [105] or Roman Britain [106], 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 [101]. Cortical bone loss data obtained using radiogrammetry of metacarpals mirrored the results from modern menopausal women in Finland [101]. The medieval peasant female skeletons also showed evidence of multiple healed fractures in the trabecular bone of their vertebrae, correlating with increased bone loss [101]. 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 [102]. 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 [103] 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 12th – 14th centuries Cedynia and low SES 14th – 17th Słaboszewo, found the low SES group to be characterised by a reduced skull base height, vertebral canal, and bone quantity in metacarpals [104]. Several studies examining 11th – 16th centuries low and high SES individuals from medieval Canterbury, UK have demonstrated social disadvantage to be associated with poorer bone health in adulthood, as well as experiences of increased physiological disruption in childhood and potentially reduced longevity [26, 89, 90, 92]. 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 [92] 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 [90], 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, 102] consider bone histology or DXA methods, and large enough sample sizes to infer medieval lifestyles. Those relying on gross anatomical morphometric [e.g. 29, 103] 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. 105-109, 111-113]. 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 [107]. Indeed, a study [107]

of an elderly female skeleton from 14th – 17th 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 [107] 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 [108-109, 111]. There is substantial evidence for its occurrence in medieval times [108-109], particularly afflicting older males originating from monastic backgrounds [108]. 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 [110]. Reports of medieval skeletons likely showing evidence of DISH have been published for different sites including the Merton Priory, Wells Cathedral (13th – 16th centuries) and the Royal Mint (14th century) in London, and S. Angelo Abbey in Montescaglioso in Italy (21th – 15th centuries) [108, 111]. 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 of secondary SES evidence (e.g. in [111], the authors acknowledge limited written SES records). Another example from medieval Italy (8th – 13th, 17th 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 [112]. The elevated data agreed with evidence for an increase in calcium consumption and higher physical activity in the low SES group [112]. This study particularly highlights that the direction of SES effect on bone health cannot be easily predicted just based on the level of SES status (i.e. high vs. low). Finally, a modified skeletal frailty index (SFI) that incorporates markers of sarcopenia

and osteopenia into its assessment can also be applied to medieval skeletons [113]. Marklein and Crews [113] explain that the traditional inclusion of all SFI biomarkers cannot be used on all medieval human skeletal assemblages due to fragmentary material. However, their [113] 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 [113], 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 [112], 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 [114], 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 [115-117]. While the predominant application of aDNA has been to trace population migration [118], or pathogen evolution (such us tuberculosis and leprosy [119]), seeing as aDNA is usually extracted from

surviving human skeletal elements, there is potential for these efforts to 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 patient bone health is the successful and effective identification of risk factors underlying the development of osteoporosis, and management and prevention of osteoporosis fractures [120-122]. 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 [123-128]. 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, 123, 129, 130]. 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 [131-134]. Recently, increasing focus has been placed on ethnicity and country-level osteoporosis management strategies [e.g. 135-139]. 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 [99] and the experience of osteoporosis around menopause [137]. 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 education and health care efforts for those more disadvantaged groups, hopefully

ultimately achieving equality in the human experience of bone health. As demonstrated through our medieval 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 (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 their 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 or recently deceased humans or animals. We supply an image of medieval human femur bone histology sample from an anthropological collection curated at the University of Kent, Canterbury. The collection pre-dates the Human Tissue Act, and was studied following the BABAO Code of Ethics 2008, BABAO Code of Practice 2010, AAA 2012 Code of Ethics, AAPA 2003

Conflict of Interest

The authors declare that they have no conflict of interest.

Disclosure

The authors are researchers (Miszkiewicz, PhD; Cooke, MSc) with no medical qualifications.

The recommendations made in the review are based on analysis of published results.

Ethical Approval

This article does not contain any studies with 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 high level of 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 thin section is stored as part of the Histology collection in the School of Archaeology and Anthropology at the Australian National University, Canberra, Australia. 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

Figure 1

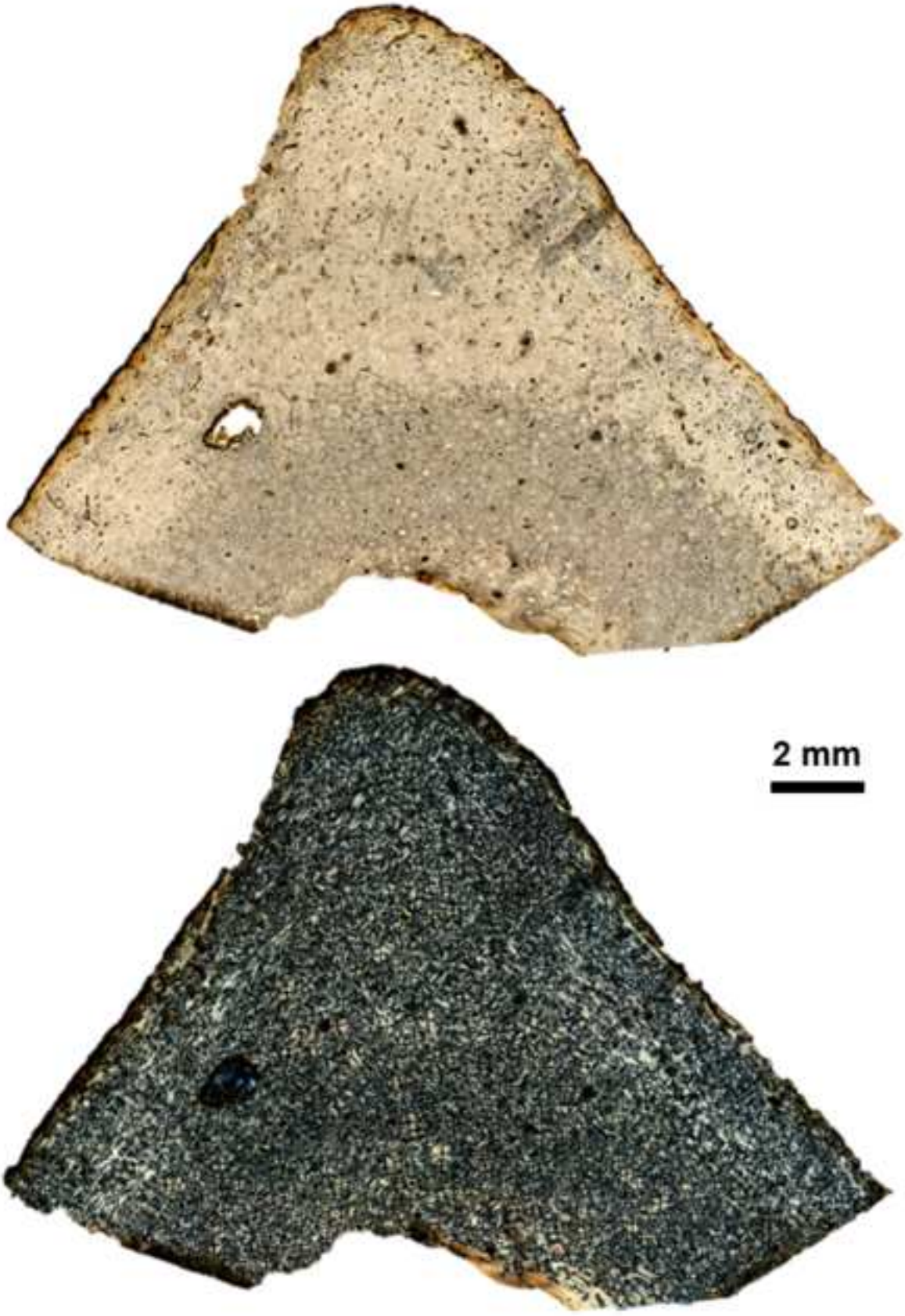

Figure 2

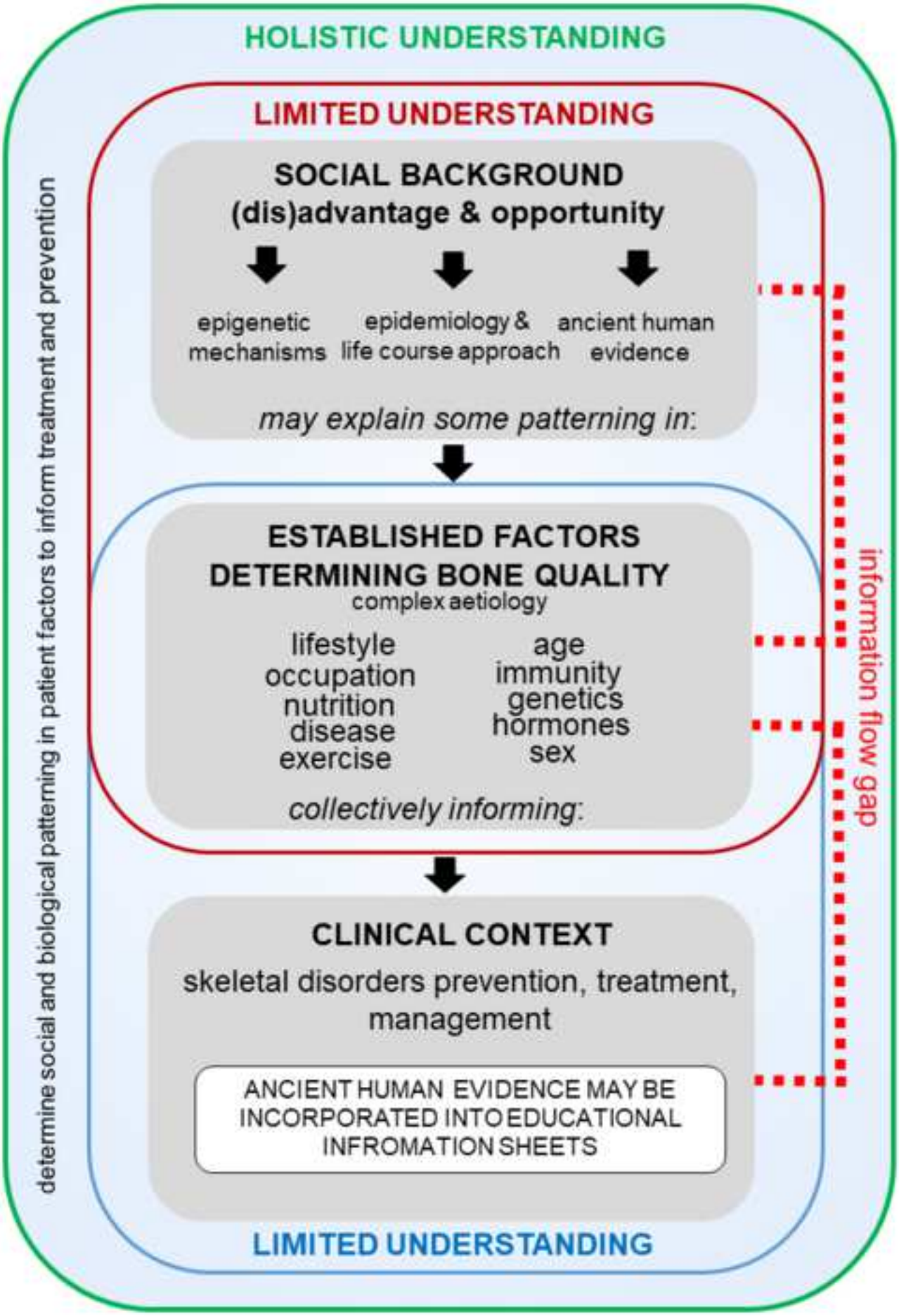

Table 1. Examples of medieval skeletal evidence for social determinants of bone health, which may serve as a source of useful information when undertaking educational communication in clinical settings of osteoporosis prevention efforts.

LOCATION	MATERIAL(S) AND METHOD(S)	FINDING(S)	REFERENCE	SOCIAL FACTOR(S)
St. Gregory's Priory and adjacent cemetery, Canterbury, UK 11th – 16th centuries	femur histomorphometry, bone collagen stable isotopes, dental anatomy in young and middle aged males and females of high and low socio-economic status (SES) in max. n = 450	higher bone density in high SES, but bone adapted to higher mechanical load in lower SES; higher bone density in higher SES despite experiences of ill health in childhood; higher experience of ill health and reduced longevity in low SES	[26, 92, 80-92]	more physically demanding occupations, poor nutrition, increased stress and exposure to pathogens in low SES
the Santa Clara-a-Velha Monastery, Coimbra, Portugal 14th – 17th centuries	gross anatomical examination and X-ray imaging methods applied to an elderly female skeleton (> 50 years old)	a unique case of osteoporosis related extracapsular fracture of the proximal femur	[107]	the skeleton likely belonged to an Italian nun from a privileged background, but she would have spent most time inside the monastery limiting her physical activity and sun exposure
churchyard of St. Olav's Church, Trondheim, Norway 11th – 16th centuries	BMD collected using DXA and prevalence of osteoporosis related fractures estimated in proximal femora of n = 63 males and n = 65 females	higher frequencies of osteoporotic fractures in medieval Norwegian women	[102]	living in a cold and built up environment determining lifestyle and falls, though age was highlighted as a key factor
San Michele's Church in Trino Vercellese, Piedmont, Italy 8th - 13th, 17th centuries	BMD collected using CT and DXA in lumbar vertebrae and femur cortical bone in n = 27 males and n = 28 females	low SES group had *increased* BMD	[112]	despite their low SES, the rural lay community consumed more calcium, was exposed to more daylight, and engaged in more physically demanding occupations than the high SES counterparts
Church and associated churchyard, Wharram	cortical bone thickness measured using metacarpal radiogrammetry and axial skeleton trabecular bone	ageing related cortical bone loss in females higher than those	[101]	samples represented low SES communities, though the finding emphasises

Percy, North Yorkshire, UK 11th – 16th centuries	fractures in low SES ("peasant") young, middle-aged, and old males and females (n = 83 males and n = 71 females)	reported in males, and also comparable to modern women		experiences of potential menopause driven osteoporosis both by modern and medieval women
monastic and non-monastic groups in medieval London - - high SES Merton Priory, Bermondsey Abbey, and lay community in Guildhall Yard, Spital Square, St. Mary Graces, and St. Benet Sherehog, UK 12th – 17th centuries	modified skeletal frailty index (SFI) analysis assessing phenotypic traits associated with sarcopenia and osteopenia, including skeletal markers such as dental developmental disturbances and lesions indicating long bone infection in max. n = 517	monastic (more privileged) individuals had higher aggregates of the SFI indices	[113]	lifestyle differences between monastic and non-monastic groups may have contributed to these differences, though the authors also emphasise age and sex as important variables underlying skeletal frailty
Merton Priory and Wells Cathedral, the Royal Mint in London, UK; S. Angelo Abbey, Montescaglioso, Italy; medieval Lithuania 12th – 16th centuries	diagnosis of diffuse idiopathic skeletal hyperostosis (DISH) in males recovered from high SES (and monastic) burial sites max. n = 539	increased prevalence of DISH with high SES	[108, 109, 111]	monastic lifestyles associated with lower degree of physical activity and higher consumption of meaty and fatty foods, though age and sex likely play a role in the results as well
Trino Vercellese, and San Lorenzo di Alba, Italy 7th – 15th centuries	skeletal size and shape, estimated stature, based upon morphometrics, in males and females of high and low SES in n = 20 females and n = 32 males [2011], and n = 20 females and = n = 30 males [2019]	males of high SES achieved greater adult body mass and stature when compared to individuals of low SES	[29, 103]	intra-populational plasticity affecting adult body size related to social structure of community
Cedynia, and Słaboszewo, Poland 12th – 17th centuries	cranial and axial skeleton indicators of stress, cortical bone loss assessed using metacarpals in n = 150 males and n = 69 females of high SES, and n = 85 males and n = 60 females of low SES	those of low SES were predominantly characterised by reduced height of skull base and narrower vertebral, along with reduced metacarpal bone quantity	[104]	environmental stress experiences in early life specific to SES may contribute to bone loss in the adulthood