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Item Type	Article
Authors	Papadopoulou, S.;Buckberry, Jo
Citation	Papadopoulou S and Buckberry J (2019) The relationship between Vitamin D deficiency and leprosy in two English medieval populations. 17: 11-26.
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Download date	2026-05-12 03:34:38
Link to Item	http://hdl.handle.net/10454/17508

The Relationship Between Vitamin D Deficiency And Leprosy In Two English Medieval Populations

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Abstract: In palaeopathology, a well-established approach to malnutrition and ill-health is the study of metabolic conditions. Leprosy is a mycobacterial disease that is manifested on the bones, and is commonly studied in archaeological contexts. Vitamin D is essential for maintaining a normal immune system, and thus a metabolic insufficiency could have a major effect in the resistance of an individual to invading pathogens. It has been indicated by clinical studies that there is an increase in the risk of contracting tuberculosis for individuals with Vitamin D deficiency, and like TB, leprosy is a disease of the poor, and it is more severe in individuals with low resistance to the pathogen. The project investigated the immunological aspect of leprosy by investigating the comorbidity of Vitamin D deficiency and the disease.

During the study, the prevalence rates of Vitamin D deficiency (residual rickets and osteomalacia) were compared for adults in two medieval populations: adults with skeletal evidence of lepromatous leprosy from the leprosarium of St James and Mary Magdalene in Chichester (n=62) and adults from the non-lepromatous population found in Box Lane, Pontefract (n=52), both in England. Macroscopic analysis identified only one probable case of residual rickets and two possible cases of osteomalacia, providing no statistical significance in the relationship between the conditions.

The present article focuses on these results, aiming to underline the reasons behind negative results in research, caused either by failed methodology or the insufficient collection of samples.

Key words: leprosy, malnutrition, metabolic conditions, negative results, vitamin D, rickets, osteomalacia, medieval cemeteries, Great Britain, Box Lane, Chichester.

Introduction

Leprosy is a chronic mycobacterial disease (predominantly *Mycobacterium leprae*) affecting the peripheral nervous system, the skin and certain other tissues, that has been identified in archaeological as well as present populations (Stanford and Stanford 2002; Roberts and Manchester 2007). The main documented aspects that affect the progression of the disease are genetic, environmental, domiciliary, bacteriological and immunological.

The immunological aspect of leprosy is crucial to the understanding of the disease, since the effective contact with the pathogen leads directly to disease or to apparent protective immunity (Stanford and Stanford 2002). Furthermore, the immune status of the infected individual before and during the disease is an

important factor in how leprosy is presented, and leads to three types of leprosy: lepromatous, borderline and tuberculoid leprosy. This classification by Ridley and Jopling (1962) is an elaboration on Rabello's (1937) polar concept, and it has been thought to be broadly comprehensible, especially for clinical and histological studies (Ridley 1974). Consequently, this categorization has been established and applied to bioarchaeological material, too.

Clinically, the typical form of the disease is known as lepromatous leprosy, and it entails massive destruction of numerous tissues that generally affects the entire body. On the other hand, the high-resistance form of the disease is known as tuberculoid leprosy, and it results to less pronounced evidence of the infection. Between these two polar forms there is a

wide spectrum of manifestations, generally characterized as borderline leprosy. Depending on the immune system of the affected individual borderline leprosy is divided in borderline tuberculoid and borderline lepromatous leprosy (Turk 1976). In osteological material, it is impossible to determine borderline leprosy, and tuberculoid leprosy could be identified with difficulty as it has a unilateral appearance and does not produce pathognomonic features. The most commonly found form of the disease is lepromatous leprosy, because of the severity of skeletal lesions, as well as the pathognomonic feature of rhinomaxillary syndrome that is evident in this form of the disease (Manchester and Roberts 1989).

Metabolic conditions are considered indications of immune deficiency and low health status in both archaeological and clinical studies. Leprosy is a disease that depends highly on the immunological status of the affected individuals. Following this reasoning, are the individuals who display evidence of metabolic conditions, and specifically Vitamin D deficiency, more susceptible to contracting leprosy and specifically the lepromatous form of the disease? The present research project investigated a possible relationship between leprosy and this deficiency.

Vitamin D deficiency

Vitamin D is a vital pro-hormone (it is even now erroneously categorized as a vitamin), which needs to be metabolised through synthetic means in order to assist with bodily functions (DeLuca 2004). It is imperative for the adequate mineralization of newly formed bone (osteoid) (Pitt, 1988; Berry *et al.*, 2002; Holick, 2003) and thus for the normal formation and development of bone.

Vitamin D deficiency has been documented to be caused by a combination of a dietary deficiency and a lack of exposure to sunlight (Parfitt 1997; Berry *et al.* 2002), factors that are dependent on both the environment and the living conditions of the affected individual (Ortner and Mays 1998; Al-Jurayyan *et al.* 2002; Reginato and Coquia

2003), and its production is highly dependent on the time of day, season of the year, latitude, and altitude (Holick 2003). A good example of its dietary aetiology is presented by the studied observation that populations with diets high in phytates are more likely to experience vitamin D deficiency (Groen *et al.* 1964; Berlyne *et al.* 1973). It is noteworthy that there are other causes for Vitamin D insufficiency that include intestinal malabsorption and genetically resistant forms of vitamin deficiency (Mankin 1974; Francis and Selby 1997; Parfitt 1998, cited in Brickley *et al.* 2007; Berry *et al.* 2002). Although in palaeopathology it is difficult to determine with certainty the factors responsible for the manifestation of the deficiency, it is logical to assume that the rarity and low survival rates connected with malabsorption syndromes in the past makes them unlikely causes of vitamin D deficiency in archaeological contexts.

For this project, it is important to investigate the role of vitamin D deficiency on the immune system of an individual, and therefore its relationship with contracting leprosy. More specifically, vitamin D is crucial for the normal function of multiple innate immune mechanisms, which are the primary defence against a possible pathogen invasion (Beutler 2004). The general effect of this insufficiency has been thoroughly observed in research done both in the clinical and the archaeological field (*e.g.* Holick 2006; Ginde *et al.* 2009a; Snoddy *et al.* 2016), as it has been thought to increase the risk of a wide range of pathological conditions like cancers and cardiovascular conditions, as well as infective and autoimmune diseases (Wayse *et al.* 2004; Garland *et al.* 2006; Adorini and Penna 2008; Ginde *et al.* 2009b; Gunta *et al.* 2013).

Rickets is a disease of infancy and childhood caused by deficiency of effective vitamin D. In the clinical literature rickets specifically refers to the disruptions in mineralization of the endochondral bone (Brickley *et al.* 2014), and therefore it relates specifically to disruptions at the growth plate. The insufficiently mineralised newly formed bone during endochondral growth results in porosity

beneath the epiphyseal growth plates that is mostly evident on the diaphyseal ends of long bones and the sub-periosteal cortical surface. In addition to the effects on bone growth, the apparent inadequate maintenance of existing bone tissue leads to deformation of skeletal elements under mechanical forces and bowing of the long bones (Ortner and Mays 1998; Mays *et al.* 2006). These bowing deformities can be retained throughout life and thus bowing deformities without active growth plate changes are seen as diagnostic of healed rickets. Bilateral bowing deformities are often seen in adults and these are indicative of childhood vitamin D deficiency, and are often referred to as residual rickets.

Osteomalacia, on the other hand, is a vitamin D deficiency that results in poor bone mineralisation during bone turnover. It is mainly seen during adulthood and is often used to describe vitamin D deficiency in adults in palaeopathology. This specification is important, as the term in the clinical literature is usually applied to describe changes in adults and juveniles, both of whom can have disrupted bone turnover (Brickley *et al.* 2007). Generally, osteomalacia is a metabolic condition that leads to the replacement of mineralized osteoid with non-mineralized osteoid during normal bone remodelling (Roberts and Manchester 2007; Brickley *et al.* 2014). Consequently, the cortical and trabecular bone structure and integrity are affected, and the organic matrix of the new bone remains soft, resulting in the subsequent weakening of the skeleton (Francis and Selby 1997; Parfitt 1998, cited in Brickley *et al.* 2007), resulting in pseudofractures.

Pertinent comorbidities

The present hypothesis is based on the possible relationship connecting Vitamin D deficiency and leprosy, and it is directly connected with the immunodeficiency factor that is fundamental here. Generally, one of the most reliable sources of evidence regarding nutritional deficiencies in skeletal remains is the macroscopic study of metabolic conditions, something that makes Vitamin D deficiency a valid topic in this case because of its significant dietary aetiology.

In order to recognise the strength of that hypothesis, it is imperative to understand the connection between malnutrition and the so called “diseases of the poor”.

Leprosy has been generally accepted as such a disease (Manchester and Roberts 1989), an opinion that is based on clinical research of present populations (Rinaldi 2005; Rivoire *et al.* 2014; Mondal *et al.* 2015; Henry *et al.* 2016). Furthermore, the dietary aspect in respect to the unavailability of certain foods is linked with leprosy, thus establishing a relationship between the disease and socioeconomic factors. A good example of that immunological aspect is a case-control study conducted by Wagenaar *et al.* (2015), which indicated that an insufficient intake of nutrients caused by dietary problems relates to the immune system and has an impact on the progression of the infection in clinical cases of leprosy.

Moreover, a good example of this type of relationship that comes from both clinical and palaeopathological research is the already studied, and now confirmed, hypothesis regarding the comorbidity of metabolic conditions and tuberculosis (Lewis *et al.* 2005). This connection is essential for the present project, since TB, like leprosy, is a pathology classified as “disease of the poor” (Collins *et al.* 2002; Eastwood and Hill 2004; Barter *et al.* 2012). *Mycobacterium tuberculosis* is quite an adaptable pathogen that often infects and stays inactive within the body of a healthy host awaiting until the immune system is endangered by stressors like malnutrition in order to be triggered (Philips and Ernst 2012). Recent epidemiological research has focused on this relationship at a population level and has produced relevant results (Gibney *et al.* 2008; Nnoaham and Clarke 2008). Furthermore, several current case-control studies found that low amounts of vitamin D, even at a subclinical level of the pertinent spectrum, produce a significant risk factor for secondary tuberculosis infection (Ustianowski *et al.* 2005; Gibney *et al.* 2008; Nnoaham and Clarke 2008).

Materials

For this comparative project two medieval English populations were examined, the

first one was found in Box Lane, Pontefract, West Yorkshire and the second in the cemetery of St. James and St Mary

Magdalene hospital, Chichester, West Sussex. Both collections are pre-examined and curated by the University of Bradford.



Figure 1 Map showing the location of Chichester and Pontefract.

St. James and St Mary Magdalene hospital was founded as a result of the spread of leprosy in Britain during the 11th century (figure 1). Its exclusive use as a *leprosarium* ceased in the 14th century during the decline of leprosy, at which point it became an almshouse for the poor (Magilton *et al.* 2008a). For this project, 62 adult individuals, previously diagnosed with lepromatous leprosy (19.5percent of the cemetery's individuals) were selected. All of these individuals were confidently diagnosed with lepromatous leprosy (see below). The preservation of the skeletons was fairly good. The examined skeletons were selected using the demographic report accompanying the analysis written by Magilton *et al.* (2008), since a re-examination of the skeletal material would

be impossible given the restricted time available. All individuals with lepromatous leprosy in the excavated sample were adult, thus this study investigated adult pathology only. The cemetery found in Box Lane, Pontefract (figure 1), served members of St John's Priory and the associated lay community. The priory was founded c.1090 and dissolved in 1539. It serves as the "control" population of the study, due to the limited variety of diagnosed diseases and an absence of leprosy in the skeletal population. 53 adult individuals were analyzed, and taphonomic damage and missing lower limbs were detected in a large portion of the population (Boylston 1991; Lee *et al.* 1991; Archaeological Services WYAS 1999). As the collection is pre-examined, previous

reports provided by the University of Bradford were used for sample selection. Skeletons so incomplete as to only have small parts of bones remaining were excluded as it would be impossible for them to be assessed in terms of general osteological characteristics or pathology. Following the same logic, disarticulated remains that comprised of multiple individuals stored in the same boxes were excluded as well.

Box Lane provides a good control population due to the similarity in time period and the size of the examined populations. Both sites are medieval and British. Furthermore, it was important for the validity of the results produced through this research that the total number of adult individuals analysed for this study from both sites is comparable.

Methods

The examination of the human remains in this research project included an osteological and a palaeopathological macroscopic and radiographic study, which were complemented with statistical analysis of the data.

Osteological examination

The skeletal individuals were re-examined osteologically to assess the completeness of the skeletons, as well as sex assessment and age estimation. The skeletal and dental inventory as well as the estimation of completeness was done using standard methods described by Buikstra and Ubelaker (1994). Their recording was conducted predominantly to aid with the interpretation of the observed pathological features, since the presence of incomplete skeletons is quite common in palaeopathological studies.

The sex assessment of the studied individuals was conducted using most of the available sexually dimorphic features, mainly because of the often fragmented condition of the examined material. The pelvic bone was examined using the method for adult individuals presented by Buikstra and Ubelaker (1994). The same volume was used to assess the sex

differences regarding the adult skull morphology.

Many methods were considered for age estimation, including those presented by Brooks and Suchey (1990) for the pubic symphysis, Lovejoy *et al.* (1985) and Buckberry and Chamberlain for auricular surface, as well as Meindl and Lovejoy (1985) for cranial suture closure. However, because of the fragmented condition of the remains and the differences in the variety of features available in each skeleton, transition analysis (Boldsen *et al.* 2002; Milner and Boldsen 2011) was deemed appropriate in this occasion. The use of a computerised system with a complete and easily applicable set of criteria that include most of the features described by the aforementioned methods, gave a quick, consistent and narrow age estimation even for the most fragmented skeletons. Nonetheless, there were individuals within the studied populations without a pelvis or a cranium, rendering this method impracticable. The age of those individuals was estimated using the fusion of long bones and the clavicle (Scheuer and Black 2000), as well as dental wear (Brothwell 1981).

Palaeopathological examination

The palaeopathological macroscopic examination included diagnoses for leprosy and vitamin D deficiency (residual rickets and osteomalacia). As only adults were considered, features of active rickets were not recorded.

For the diagnosis of lepromatous leprosy, the main criterion was the presence or absence of the rhinomaxillary syndrome, which usually presents a characteristic absorption of the anterior nasal spine and the alveolar process of maxilla, accompanied by inflammatory pitting on the palatine and alveolar bone (Andersen and Manchester 1992). In cases when the maxilla was absent, the bilateral appearance of leprosy skeletal changes such as knife-edge remodelling of metatarsals, concentric diaphyseal remodelling of phalanges and volar grooves in manual phalanges was determined as sufficient evidence of the disease. The bilateral presence of new bone formation on long bones (mainly

lower limbs) was seen in many of the leprosy individuals, but was not treated as a pathognomonic lesion for diagnosis. These features have been extensively used in both archaeological and clinical research (e.g. Andersen and Manchester 1992; Kustner *et al.* 2006; Taylor *et al.* 2006).

For vitamin D deficiency, residual rickets was diagnosed by the bilateral bowing of long bones as shown in figure 2, as well as the protrusion of the sternum and ventral projection and bending of the sacrum (Brickley *et al.* 2010:110-111). Osteomalacia was diagnosed by the detection of pseudofractures and osteomalacic fractures (figure 3); small, linear fractures, often surrounded by irregular calluses on bones affected by stresses (e.g. ribs, scapulae). The location of these pseudofractures is very specific, usually observed in the ribs, the vertebrae, the scapula, the clavicle, the ulna, the pelvis, the femoral neck, as well as the metacarpals and metatarsals (Steinbach *et al.* 1954; Mankin 1974; Brickley *et al.* 2005, 2007). Furthermore, the buckling of vertebral bodies was also deemed a diagnostic criterion for this form of the deficiency.

Statistical analysis

The statistical analysis for this project focused on the investigation of factors that create the demographic profiles of the populations based on the osteological data, as well as their palaeopathological comparison. The statistics of the studied conditions were focussed on the occurrence of leprosy and vitamin D deficiency.

Due to the varied levels of completeness per skeleton and its effect in the palaeopathological observations of the study, the completeness of the skeletons was taken into consideration. Specifically, the skeletons were assessed separately for cranial and postcranial completeness (classified as “observable” for the presence of more than 50 percent of the examined bones and “unobservable” for less than 50 percent) to provide a true prevalence and aid with an accurate statistical analysis of the studied conditions. This methodical

recording helped produce an accurate statistical analysis, while solving the problem of varied skeletal completeness that is so common in palaeopathology.



Figure 2 Example of bilateral bowing of the tibiae and fibulae caused by residual rickets. There is some post-mortem damage to the cortex, especially of the right tibia



Figure 3 Example of healed osteomalacic pseudofracture

The statistical analysis was conducted using SPSS 22. The chosen statistical tests for this project were selected using the general guides provided by Kirkpatrick and Feeney (2016), Cunningham and Aldrich (2016) and Elliot (2016). In terms of the statistical tests, a Mann-Whitney test (Mann and Whitney 1947) was used to compare the age, a Pearson's Chi-square test (Pearson 1900) for sex and the presence/absence of vitamin D deficiency and leprosy. For all the tests applied in this project, a significance level (p) of 0.05 was adopted.

Results

Demographic information

The chosen populations were similar in size enough to be comparable. However, there were significant differences in terms of age and sex.

The sex distribution varied between the examined samples. Male individuals formed 50percent of the sample from Box Lane compared to the 80.6 percent of the sample from Chichester, whereas females made up 28.8 percent 16.1 percent respectively. A major variance was detected in the indeterminate sex category; 21.2 percent at Box Lane and 3.2 percent Chichester, a fact easily justified by the completeness of the skeletons since the Box Lane population includes more incomplete skeletons than the Chichester one.

The association between the sex distributions in both populations was investigated using a Chi-Square test ($\chi^2=14.041$; $p < 0.001$), which indicates that the distribution of sex amongst the individuals in the studied populations is significantly different. This was expected given the already acknowledged dominance of male individuals within the Chichester population, however there is little clinical evidence to suggest that either disease affects the sexes at different rates.

The age distribution showed differences between the two samples. At Box Lane the age group with the most individuals is the one comprising of older individuals over c. 50 years (42.3 percent), in contrast with the Chichester populations in which most

individuals were younger, c. 20-30 years (38.7 percent). This difference was also anticipated, since the Chichester population was from a hospital cemetery, and therefore was likely to have a lower life expectancy.

In order to compare the age distribution of the studied populations, a Mann-Whitney test was applied. The test proved that the age levels in Chichester did not differ significantly from Box Lane ($U=1.507$, $z=-0.631$, $p=0.528$ and $r=-0.05$). This suggests we can eliminate age as a factor that could influence the palaeopathological results.

Palaeopathological information

The occurrence of vitamin D deficiency in both populations was quite rare. The total of possible and probable cases of vitamin D deficiency in both populations combined amounted to 3.

In Box Lane the only possible occurrence of vitamin D deficiency was detected on skeleton 44(a). A large (c. 1.5 cm long) possible pseudofracture across the lateral portion of the right clavicle was the only indication of osteomalacia on the skeleton (figure 4). This appearance could be taphonomic, as the relevant radiograph (figure 5) presented no evidence of healing (no radio density on the margins of the fracture), however this does not preclude a diagnosis of osteomalacia (Jennings *et al.* 2018). This skeleton was extremely fragmented and highly incomplete, which is common in osteomalacia. This case was classified as possible vitamin D deficiency.



Figure 4 Possible pseudofracture on the lateral part of the right clavicle in Box Lane skeleton 44(A) of the Box Lane population.

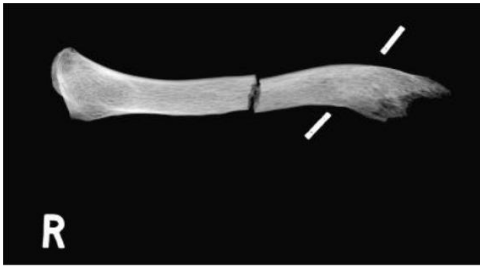


Figure 5 Radiograph of right clavicle in Box Lane skeleton 44(A). The lead markers indicate the area of the possible pseudofracture.

There were two cases of vitamin D deficiency in the Chichester sample: one possible and one probable. The possible case regarded an osteomalacic pseudofracture detected on skeleton 4 (figure 6). Specifically, a large (c.2.5 cm) possible pseudofracture was observed on the dorsal portion of the left os coxae above the obturator foramen, and there was no similar pseudofracture on the right os coxae. Similarly to the Box Lane case the appearance could be taphonomic. However, in this case the radiograph presented a slight thickening of the bone with evident radio density on the margins of the fracture (figure 7). The singularity of the element and the weak evidence of healing classified the case as possible and not probable osteomalacia.



Figure 6 Possible pseudofracture on the left pelvis on skeleton 4 of the Chichester population.



Figure 7 Radiograph of left pelvis of Chichester 4. The arrow points to the possible pseudofracture.

The only case of probable vitamin D deficiency was a diagnosis of residual rickets on skeleton 115. This skeleton presents bilateral medial bowing of the tibiae that creates an “S” shape on the anterior borders (figure 8). The diagnosis is supported by the thickening of the cortical bone of the affected elements as a biomechanical change, which is evident on the radiograph as radio density in the area (figure 9). A report for this skeleton has been written and published by Knüsel and Göggel (1993). However, the pathological observations focused on the multiple trauma throughout the skeleton. It is noteworthy that the authors did not suggest rickets as a possible pathology that could explain the bowed appearance of the tibiae. Furthermore, other pathological evidence leading to a diagnosis of residual rickets were detected radiographically in the form of thickening of the cortical bone on the tibiae. It should be noted that the decreased radiodensity of the left tibia is probably a result of disuse atrophy following fracture and osteomyelitis of the left femur, and it is not connected to the metabolic condition.

<i>Population</i>		<i>Vitamin D Deficiency</i>		
		Absent	Vitamin D deficiency	Total
<i>Box Lane (no leprosy)</i>	Count	26	1	27
	TPR	96.3%	3.7%	
<i>Chichester (Leprous sample)</i>	Count	56	12	58
	TPR	96.6%	3.4%	

Table 1 Table summarising the occurrence of vitamin D deficiency within the studied samples.



Figure 8: Bowed tibiae of Chichester 115



Figure 9: Radiograph of bowed tibiae (Chichester 115), showing thickening of the cortical bone.

The prevalence of vitamin D deficiency was investigated statistically using true prevalence rates (TPRs). 27 individuals from Box Lane and 58 individuals from Chichester were deemed sufficiently complete to be included in the calculation of TPRs. A summary of the occurrence of the deficiency within each population is depicted in table 1. A Fisher’s Exact test was followed due to low cell counts; $p=0.688$. These results indicate that the distribution of the deficiency does not differ significantly between the two populations.

Other indicators of health

While the primary aim of this research was to investigate the relationship between leprosy and vitamin D deficiency, we also investigated the relationship between scurvy, stress markers, stature and leprosy. The rest of the research produced both negative and positive results.

A non-significant difference was found between cribra orbitalia and leprosy ($\chi^2=1.471$ and $p=0.353$) and between stature and leprosy (the independent samples t -test produced: $t=.683$ and $p=0.603$ for males and $t=0.642$ and $p=0.829$ for females).

for females). However, there was a noticeable difference in the number of cases of cribra orbitalia, with 3 individuals in Box Lane and 10 in Chichester, that may be proven relevant for further research.

The positive results include a possible relationship between vitamin C deficiency (scurvy) and leprosy with significance levels of $\chi^2=5.713$ and $p=0.017$. Furthermore, higher rates of linear enamel hypoplasia were indicated in the leprosy sample. The presence of LEH was 28 percent in Box Lane/ 57.1 percent in Chichester on the central incisors, and 23.1 percent in Box Lane/ 62.5 percent in Chichester on the canines. The difference between the populations was significant ($\chi^2=9.832$, $p=0.002$ for canines; $\chi^2=5.004$, $p=0.025$ for central incisors). Both of these patterns need to be explored further.

Discussion

Interpreting the palaeopathological results

The occurrence of vitamin D deficiency was infrequent in this study, a fact that was quite surprising given the previous research used to form the original hypothesis. Despite the possibility that a connection could be observed in a larger scale study, another possible explanation for the negative results is that vitamin D deficiency and the occurrence of leprosy were completely unrelated during the medieval period. This may be because even if there was a lack of the appropriate dietary intake within the population, vitamin D can be synthesised from sunlight exposure (Brickley and Ives 2010).

The initial argument was based on the already proven clinical connection between malnutrition and leprosy that might be indicated in a palaeopathological context, as well as on the parallel consideration of leprosy and tuberculosis as diseases of the poor (Manchester and Roberts 1989; Collins *et al.* 2002; Eastwood and Hill 2004; Barter *et al.* 2012) and the already established comorbidity of the two (Wilbur *et al.* 2008; Brickley and Ives 2010). Moreover, there are historical studies that prove an

insufficient intake of fish, the main dietary source of vitamin D, in poor families of medieval populations (Drummond *et al.* 1957), something also detected in archaeological studies through isotope analysis (*e.g.* Müldner and Richards 2005, 2007) and zooarchaeological studies (*e.g.* Barrett *et al.* 2004). However, low levels of vitamin D deficiency were observed in the skeletal remains examined in this project.

On the other hand, though, it is important that the major source of vitamin D for most humans is casual exposure of the skin to sunlight, as 90-100percent of the required vitamin D can be obtained by cutaneous synthesis (Holick 2003). In past palaeopathological studies of this deficiency it has been commented that the detection of vitamin D deficiency in medieval England is rare, except for the noteworthy cases from late medieval Wharram Percy (Ortner and Mays 1998) and early medieval Jarrow (Anderson *et al.* 2006). This observation changes when the studies move on to the post-medieval populations, and it has been argued that the reasons behind this change are environmental (Roberts 2009). Considering this aspect of vitamin D acquirement, it is not unreasonable to contemplate that even if there was a lack of relevant dietary intake of vitamin D, it would not cause a deficiency when the prohormone was attained and synthesised from the environment. Therefore, that leads to questions on the chosen medieval period that has been the main focus of the study. However, it was necessary to undertake this research on medieval skeletal samples, as leprosy was much more prevalent at this time. Future study could shift its focus from the dietary to the lifestyle and socioeconomic aetiology of vitamin D deficiency.

Problematic methodology and sample collection

The negative results of the present study underlined several problems with the methods used and the selection of the skeletal populations. The predominant problem was the insufficient number of individuals studied in relation to the hypothesis of the project. Indicating a possible relationship between leprosy and vitamin D deficiency was proven difficult

based only on two populations with a total of 115 individuals, particularly given the poor levels of skeletal completeness at Box Lane (see below). The decision of studying those populations was made mainly due to the restricted time available. Despite the small collections, however, it was thought that the study could potentially produce reliable enough results to provide initial data for a future larger scale project. However, the results collected during this study and the analysis conducted after demonstrated a project too ambitious and complex for the initial research design.

Additionally, in Box Lane the examination of both rickets and osteomalacia was quite problematic. The extensive taphonomic damage within the population, either that was related to the completeness of the skeletons or the frail condition of the bones, compromised the study to some extent. This is a common problem in palaeopathology, but for this population the situation was quite extensive since only 52percent of the individuals had the bones necessary in order to detect evidence of vitamin D deficiency. That is especially evident in the detection of rickets, since the common loss of the lower limbs, predominantly caused by the nearing structures shaping the cemetery (Boylston 1991), may have obscured any evidence of bowed limbs. In addition, the frail and often fragmented condition of the bones may have destroyed a great amount of evidence regarding fractures and pseudofractures related to osteomalacia. The latter is a known problem in the study of osteomalacia (Brickley *et al.* 2005), especially when poor preservation is extensive throughout the skeleton. The examination of fragmented remains is not impossible, however, since the diagnostic features could still be detected when the affected bones are available (Brickley and Buckberry 2015). A good example of this issue was observed in individual 44(A) from the Box Lane population, where, although the skeleton is highly incomplete, there was a possible pseudofracture detected. Nonetheless, the frail and incomplete skeletons of one of the two populations restricted the data available, which could lead to misleading results.

The importance of negative results in this project

Negative results in the present project are important as they underline the significance of a realistic hypothesis and well thought out sample selection. These two major parameters could invalidate the results and the conclusions, and overpower a systematic and methodical approach. In this case, the research would have benefited greatly by the comparison of more and/or larger skeletal collections to approach safely such a complex research question.

These results could also indicate the limits of macroscopic palaeopathological examinations and therefore other methods that may be used to complement and strengthen the project. In this case, isotope analysis could have been used in the detection of vitamin D deficiency, something that has been applied in various cases in the past (*e.g.* Olsen *et al.* 2014). Furthermore, recent research has indicated that using interglobular dentin as a mineralization defect in dentin (*e.g.* D'Ortenzio *et al.* 2016; Brickley *et al.* 2017), as well as radiographically examined morphological deformities of the pulp chamber (D'Ortenzio *et al.* 2017) could be used to aid the diagnosis of Vitamin D deficiency.

Conclusion

A possible relationship between metabolic conditions and leprosy was not detected in the present study for Vitamin D deficiency due to the low numbers of possible cases identified and poor preservation of the control sample. These negative results may relate to the aetiology of the insufficiency, since malnutrition or physiological 'stress' in general seems to be associated with leprosy, as evidenced by the higher prevalence rates of enamel hypoplasia and scurvy. However, it could be possible to investigate this relationship further by using a larger sample size, and better preserved skeletal material.

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