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Article

Impact of urbanization on tuberculosis and leprosy prevalence in medieval Denmark

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With 4 figures and 7 tables

Abstract: The consequences of urbanization, such as increased exposure to pathogens, have long been considered detrimental to human health. During the first half of the Danish medieval period, towns were established and throughout the period population increased. The following study analyzes the relationship between urbanization and disease frequency – specifically leprosy and tuberculosis – in four skeletal samples from medieval Denmark using a paleoepidemiological approach. Skeletons from two urban sites (Ole Wormsgade and Ribe Grey Friary) and two rural sites (Øm Kloster and Sejet), all located in the Jutland region of Denmark, were selected for this analysis (n = 204). All skeletons included date to the middle part of the Danish medieval period (AD 1200-1400). Six skeletal leprosy indicators and six skeletal tuberculosis indicators were analyzed, and disease frequencies in the samples were estimated using a probabilistic approach based on lesion sensitivity and specificity. The effect of tuberculosis on survival in urban and rural samples was evaluated using Kaplan-Meier survival analyses. The frequency of leprosy at death varied between four and 19 percent among the four cemeteries with Ole Wormsgade having the highest frequency. The estimated frequency of tuberculosis at death varied between 39 and 69 percent. Here, Sejet cemetery had the highest frequency. There were significant differences in survival for those with and without tuberculosis-related lesions between sites, but there were no significant differences between urban and rural sites. The analyses presented in this paper suggest that disease prevalence in skeletal samples cannot be sufficiently explained by urbanization alone; rather, there are likely other biological and behavioral sources of heterogeneity that are contributing factors to past disease experience.

Keywords: urbanization; paleoepidemiology; leprosy; tuberculosis; medieval Denmark

Introduction

The topic of human health in relation to demographic change, such as urban development and agricultural intensification, is by no means a novel concept and is one that continues to be of interest to anthropological research. Classically, some scholars have correlated transitional periods associated with urbanization and subsistence changes with an increased risk of death and disease based on skeletal data (Cohen & Armelagos 1984; Goodman et al. 1988; Cohen 1989; Storey 1992; Steckel & Rose 2002; Cohen & Crane-Krammer 2007). The osteological findings of these studies pointed to a common pattern in which the shift to agriculture and increase in sedentary populations are associated with a reduced mean age at death and high frequencies of skeletal lesions related to stress and disease; these data have been interpreted as indicating a deterioration in health and increase in pathogen load (Cohen & Armelagos 1984; Cohen 1989; Cohen et al. 1994). This research suggested that the rapid increase in population density and development of urban centers in the Neolithic period – following the advent of agriculture – may have facilitated the transmission of infectious diseases, unsanitary living conditions, famine, and elevated mortality rates in human populations as they continued to urbanize and settle over time (Cohen & Armelagos 1984). This interpretation of the skeletal record has received criticism on the basis that they do not consider the conceptual issues of demographic non-stationarity, selective mortality, and heterogeneity in their interpretation of skeletal samples (Wood et al. 1992; DeWitte & Stojanowski 2015). Since the publication of the 'Osteological Paradox' (Wood et al. 1992), there have been considerable efforts in paleodemography to account for these issues in interpreting skeletal remains by improving methods of skeletal aging and developing statistical models on measuring how frailty distributions vary with demographic change (Usher 2000; Boldsen et al. 2002; Buckberry & Chamberlain 2002; Hoppa & Vaupel 2002; Wood et al. 2002; DeWitte & Wood 2008;

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Marklein et al. 2016; to name a few). Recent studies using parametric hazard models and paleodietary analyses show there are more nuanced differences between subpopulations in urban and rural settlements and that transitional changes are neither static or isolated (Yoder 2006; Yaussy et al. 2016; Walter & DeWitte 2017). There remains, however, considerable ambiguity as to why we observe heterogeneity in skeletal series regarding the presence and frequency of skeletal lesions and age-at-death distributions and what may cause these observed differences in skeletal populations and subpopulations (Wood et al. 1992; Larsen 1997; Roberts & Manchester 2005; Milner et al. 2008; DeWitte & Stojanowski 2015). Here, paleodemographic reconstructions from skeletal samples can provide temporal depth to human health and disease processes in different geographic samples that are otherwise unsupported by historical records (Thomas 2003; DeWitte & Stojanowski 2015; DeWitte 2016).

Two pathogens of historical and paleoepidemiological interest, particularly concerning urban development, are leprosy and tuberculosis. Historically, leprosy and tuberculosis have been associated with poverty and urbanization (Davies et al. 1999; Grange et al. 2001; Roberts & Buikstra 2003; Roberts & Manchester 2005). Leprosy or Hansen's disease is caused by a chronic bacterial infection of the acid-fast bacterium *Mycobacterium leprae* and involves the skin, nerves, bone, and other tissues (Hansen 1874; Irgens 1973). The bacterium affects bone by extension of the skin or mucosal lepromas or hematogenously, while secondary infections can develop from direct extension of infected soft tissue (Ortner 2003). *Mycobacterium leprae* has two clinical forms – tuberculoid (TT) or lepromatous (LL), as well as borderline forms – which are influenced profoundly by the degree of the host's immunological response and health status (Ridley & Jopling 1966; Aufderheide & Rodríguez-Martín 1998; Pardillo et al. 2007). The lesions considered in this study are the lepromatous form since this is the most severe form of leprosy that manifests on the skeleton and because this form has been clinically tied to deficient immune response (Aufderheide & Rodríguez-Martín 1998). The bacterium that causes the disease reproduces very slowly and may take up to and beyond ten years to incubate and before having any observable effect (WHO 2010). The interval between infection, symptom diagnosis, and manifestation of skeletal disease can be influenced by a variety of factors, including environment, population density, nutrition, the method of transmission, sex, age, and immunological status (Aufderheide & Rodríguez-Martín 1998; Ortner 2003). Furthermore, leprosy is not a highly contagious disease with approximately ten percent of people exposed to it showing clinical signs of infection afterward (Covey 2001). Leprosy is a well-studied chronic disease in paleopathology, and a number of studies on medieval Danish leprosy have found useful ways of disentangling leprosy from other afflictions and revealing something about its prevalence in skeletal samples (Boldsen 2001; Boldsen 2005a; Boldsen 2005b; Boldsen 2005c; Boldsen & Mollerup 2006; Boldsen 2007; Boldsen et al. 2013; Kelmelis et al. 2017). Historically, leprosy was common during the Middle Ages in Europe – reaching its peak prevalence between AD 1200 and 1400 – until it disappeared, at least in urban settlements, perhaps as early as the 15th century (Boldsen & Mollerup 2006). Recent genetic research has revealed that rather than being the result of one highly virulent strain of the bacterium, there may have been multiple sources of infection from different bacterial strains of leprosy. Also, other contributing factors such as malnutrition, co-infection, and host-genetics caused increased disease susceptibility (Krause-Kyora et al. 2018; Schuenemann et al. 2018). These findings coupled with previous osteological research suggest that there are potentially several factors contributing to the prevalence of leprosy during the medieval period, including increased population density and urban development.

Tuberculosis is a bacterial disease within the same family as leprosy, and humans contract the disease by exposure to pathogens of the *Mycobacterium* complex (Stone 2017). Of the various strains within this complex, *M. tuberculosis* and *M. bovis* are the main organisms considered to be responsible for tuberculosis in humans (Roberts & Manchester 2005). *M. tuberculosis* is transmitted between humans by inhalation of airborne infected droplets, which can lead to a primary infection of the lungs and from here further dissemination to the associated skeleton, including ribs and vertebrae; active infection can spread to other tissues throughout the body also here involving the skeleton (Ortner 2003; Roberts & Buikstra 2003). The bovine strain is a disease of cattle and other mammals, transmitted to humans mainly by the consumption of infected milk or meat (Roberts & Manchester 2005). Regardless of the source or evolutionary pathway of the various bacterial strains, this disease has significantly affected human populations across time and space (Roberts & Buikstra 2003; Roberts & Manchester 2005; Stone et al. 2009). Recent paleoepidemiological studies of tuberculosis in Danish archaeological skeletons have shown an increase in tuberculosis from medieval to early modern period (Dangvard Pedersen et al. 2018)[1]. This coincides with historical records from England, that suggest that tuberculosis increased steadily over the medieval period into the seventeenth century, where it was responsible for twenty percent of all deaths in London during non-plague years (Clarkson 1975; Roberts & Manchester 2005). Of course, by modern standards, diagnostic accuracy during this time was likely poor and, in many cases, individuals may have been burdened

[1] While there is a growing body of literature on the paleopathological and genetic discussion of tuberculosis in the New World, we explicitly focus on tuberculosis in the Old World as it pertains to the skeletal samples in this study and how the prevalence of this disease may have increased from the medieval to the early modern period.

by other lung-related diseases like bronchitis or non-tuberculoid pneumonia (Roberts & Manchester 2005). Nevertheless, skeletal data suggest that tuberculosis significantly increased in human populations from the twelfth century onwards in Britain and the rest of Europe (Roberts & Buikstra 2003; Roberts & Manchester 2005; Stone et al. 2009; Dangvard Pedersen et al. 2018). Modern tuberculosis and its involvement in the skeleton have been well researched based on modern case studies (Kelley & El-Najjar 1980; Kelley & Micozzi 1984; Roberts et al. 1994; Santos & Roberts 2001; Matos & Santos 2006; Santos & Roberts 2006; Steyn et al. 2013; Mariotti et al. 2015; Dangvard Pedersen et al. 2019). However, archaeological samples have yielded less information because of low skeletal involvement rates and the fact that similar looking lesions may have differing etiologies (Pálfi et al. 1999; Roberts & Buikstra 2003; Maczel 2004; Stone et al. 2009; Holloway et al. 2011; Dangvard Pedersen 2016). It has been generally assumed that *Mycobacterium* complex pathogens did not become prevalent in humans until the development of larger, sedentary communities and increased population density allowed the bacteria to spread enough to become epidemic (Roberts & Buikstra 2003). This assumption, coupled with the clinical knowledge that tuberculosis is opportunistic in its ability to infect those with a compromised immune response (Grange et al. 2001; Stone et al. 2009), suggests that urban development would lead to higher prevalence of tuberculosis during the European medieval period (Milner & Boldsen 2017).

The skeletal samples used in this study are derived from four cemetery sites in the Jutland region of Denmark (Fig. 1).

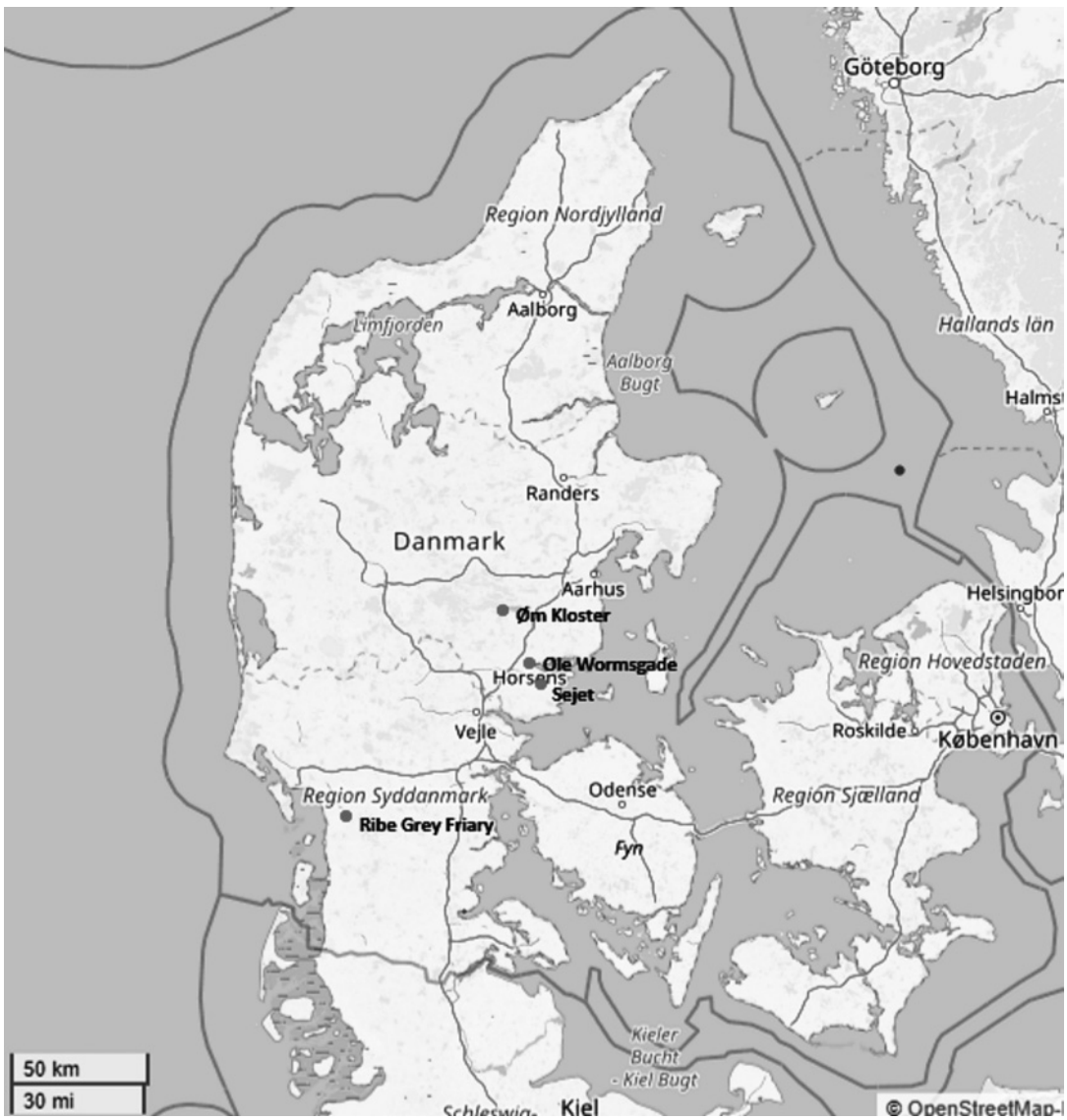

Fig. 1. Map of Denmark showing the Ribe Grey Friary, Sejet, Ole Wormsgade, and Øm Kloster locations. © OpenStreetMap contributors.

The samples differ in level of urban intensification based on estimated population size and historical documentation. Most Danish towns were established in the first half of the medieval period, a period that also witnessed rapid population increase (Andrén 1985; Boldsen 2000). By AD 1300, the urban landscape in medieval Denmark was essentially developed. The total population size in medieval Denmark is thought to have reached a maximum of 600,000–700,000 people c. 1350, with the majority living in rural areas and a small fraction residing in urban centers (Benedictow 2003; Vahtola 2003). By the early medieval period, urban centers such as Ribe may have numbered in a few thousand (no more than 5,000) while rural villages only in the few hundreds (Benedictow 2003). The distance between adjacent towns was roughly 20-30 km with minimal variance; meaning, rural villages were within an area with exclusive trade through an adjacent town (Boldsen 1989; Roesdahl 1999; Petersen et al. 2006). In paleodemographic terms, "urban living" differs from village life primarily because of the greater density of population and the greater economic and social diversity of the inhabitants (Storey 1992; Petersen et al. 2006). In medieval Denmark, what we normally call "urban communities" are more clearly defined as market towns, which were distinct from rural villages because they enjoyed specific economic privileges – most importantly a monopoly on trade within a designated area. In terms of what we understand about the daily life of medieval Danes, market town residents enjoyed similarly "rural" lifestyles insofar as they had household gardens and some livestock; however, the major differences in urban dwelling appears to be unstable access to fresh milk and the more densely populated environment causing an increased load of infectious diseases affecting child mortality (Boldsen 1989). This new development during the medieval period brought trade networks between urban centers and rural communities, thereby pulling rural communities into a developing economy while also promoting population growth (Roesdahl 1999; Petersen et al. 2006). It is possible that medieval market towns and villages experienced the frequent exchange of pathogens through migrants and economic exchanges and suffered similar detriments to health from food shortages, thereby resulting in broad similarities in patterns of mortality and morbidity. Another consideration is the importance of monasteries that became destinations for travelers and developed close economic connections to surrounding communities (Roesdahl 1999). It is possible that such destinations increased the transmission of infectious diseases, such as leprosy and tuberculosis, during the medieval period.

The question of whether urban development has led to an increase in contact with potentially deadly pathogens, thus leading to a decline in human health has received attention in the anthropological community for quite some time without a solid consensus being reached. We believe that a contribution to understanding these dynamics in the past is to examine multiple, contemporaneous skeletal collections that underwent varying levels of urban development using an epidemiological approach to estimate disease prevalence within and between samples. The following study is designed to gain insight into the health consequences of urban development during the Danish medieval period with respect to two specific diseases that were prevalent and associated with a heightened risk of death – leprosy, and tuberculosis. This is accomplished by investigating the relationship between disease prevalence of leprosy and tuberculosis in four skeletal samples from medieval Denmark that represent communities that experienced different population densities and degrees of social stratification. Using skeletal and paleoepidemiological methods developed by Boldsen (2001; 2005b; 2008), Dangvard Pedersen (2016) and Dangvard Pedersen et al. (2018; 2019), we test the hypothesis that leprosy and tuberculosis prevalence may have been affected by urban development in medieval Denmark.

Material and methods

The skeletal samples

The four skeletal samples included in the present study are assessed as either "urban" or "rural" according to available archaeological and historical sources about the demographic conditions of each site. For our samples, all selected individuals were chosen based on their level of preservation and completeness, as well as having archaeological evidence of being buried in the period AD 1200–1400 based on their arms being in so-called position B (Redin 1976; Kieffer-Olsen 1993). This form of chronological dating is relative, and, though it has been validated, it can only be used for dating of Danish skeletons within a wide time range. Here we use skeletons buried with arm position B because the region of study would have undergone urbanization by this point (Kieffer-Olsen 1993). This arm position captures the degree of urban development in medieval Denmark, as well as events that may support the claim that urbanization leads to increased vulnerability to famine and disease – for example, the agrarian crisis of the early fourteenth century and the Black Death of AD 1347–1148 (Yoder 2006).

Øm Kloster

The rural Cistercian monastery of Øm Kloster (AD 1172–1536), located on the shores of Lake Mossø approximately 32 km from Horsens, Denmark. The monastery and its associated cemeteries have been excavated over a hundred-year period beginning in 1896, yielding church and monastery building foundations and a total of 921 burials of which roughly 600 have been excavated (Mollerup 1999; Gregersen & Jensen 2003; Yoder 2006; Yoder 2012; Kelmelis et al. 2017). Social status was a significant factor determining where individuals were buried within the monastery complex, and the skeletal assemblage in this cemetery includes the monastery residents, beneficiaries, and layper-

sons from neighboring communities (Gregersen & Jensen 2003; Kelmelis et al. 2017; Mollerup 2018). The laymen's cemetery, located on the northern side of the monastery, was most likely started shortly after AD 1172; here, locals, lay brothers, and possible non-locals may have been buried (Rasmussen et al. 2008; Kelmelis et al. 2017). The majority of the individuals have been submitted for storage at the Unit of Anthropology (ADBOU) at the University of Southern Denmark; other portions are being held at the University of Copenhagen and the Øm Kloster Museum. For this study, we selected fifty-eight individuals from the north cemetery for analysis because they represent a rural sample.

Ole Wormsgade

One of the urban samples was selected from the parish cemetery of S. Hans off of Ole Wormsgade, located in the market town of Horsens and dated from the early Middle Ages to AD 1480. The size of the medieval town is unknown, but it received administrative rights as a market town in the 12th century and its favorable location on the Jutland east coast trading route likely aided in the town's development as an important trade and shipping port (Trap 1904). Archaeological evidence shows the area had been settled at least since the 9th century and a moat had been constructed around the settlement (Nyborg & Poulsen 2005; Krongaard Kristensen & Poulsen 2016). From January 2007 to April 2009, the Horsens Museum conducted an excavation of the street of Ole Wormsgade, where they unearthed parts of the parish cemetery and foundations of the S. Hans monastery (Pedersen & Boldsen 2010). The excavations yielded a total of 650 registered graves – 578 of which held skeletal material – and the remains were submitted for storage at the Unit of Anthropology (ADBOU) at the University of Southern Denmark, Odense in 2010. Of the primary graves, we selected a sample of fifty-six adults for analysis.

Sejet

The small modern village of Sejet is located approximately eight km southeast of the town of Horsens and has 358 inhabitants (Danmarks Statistik: Statistikbanken 2019). The village parish cemetery is likely to have been in use throughout the medieval period based on osteological evidence (Pedersen 2009). The cemetery was abandoned after the Protestant Reformation, and historical records described how parts of the original stone church were reused to erect another church in its vicinity during the 16th century (Nielsen et al. 1964). At the end of April 2006, the Horsens Museum excavated the Sejet churchyard cemetery and was completed in November of that year. Upon completing the excavation of the 400 m^2 area, skeletons from a total of 632 individuals were registered, of which skeletons found in situ in graves accounted for 435 individuals (Pedersen & Boldsen 2008; Nyborg & Poulsen 2010). The remains have been submitted for registration and storage at the Unit of Anthropology (ADBOU) at the University of Southern Denmark, Odense. Only twenty-nine adult individuals with arm position B were available from Sejet and all were included in this analysis.

Ribe Grey Friary

The urban sample from Ribe was selected from the Grey Friary parish cemetery. Ribe is one of the earliest urban settlements in Scandinavia, established in the early 8th century as a seasonal market center and continued as an important town throughout the medieval period (Feveile 2006; Hybel & Poulsen 2007). This Franciscan monastery was established in AD 1232 as the first of its kind in Denmark (Møller et al. 1984a). Parts of the parish cemetery outside the monastery complex and parts of the monastery complex itself were excavated in 1993. The archaeological excavation revealed that burial activities began from approx. AD 1250 (Jantzen et al. 1995; Andersen 2003). From historical sources, it is known that monastery and cemetery were in use until the Protestant Reformation in AD 1536 and the demolition of the church began the year after (Møller et al. 1984b). The 584 primary skeletons excavated from the site are stored at the Unit of Anthropology (ADBOU) at the University of Southern Denmark in Odense. Sixty-one adult skeletons from the site were selected for the present study.

Osteological methods

Lesions related to leprosy and tuberculosis were recorded dichotomously for each adult skeleton following the criteria of Boldsen (2001) and Dangvard Pedersen et al. (2019.). In addition to leprosy and tuberculosis, sex and age at death were recorded. Sex was estimated from the morphology of the cranium and pelvis, as well as the size and robustness of postcranial bones (Buikstra & Ubelaker 1994). Only adults, those where the ilium, ischium, and pubis have fused in the acetabulum, were included in this study. Adult age was estimated using transition analysis (Boldsen et al. 2002) and experience-based age assessment as discussed by Milner & Boldsen (2012) and Milner et al. (2016).

Leprosy

For this study, we employed the paleoepidemiological methods developed by Boldsen (2001; 2005b; 2008) for measuring the prevalence of leprosy based on the sensitivity and specificity of leprosy-related lesions (Table 1). The method described by Boldsen (2001) uses six osteological lesions indicating leprotic infection were recorded on each adult skeleton: 1) rounding of the edge of the nasal aperture, 2) degeneration of the anterior nasal spine, 3) degeneration of the alveolar process on the pre-maxilla, 4) porosity or perforation of the palate, 5) swelling of fibula, and 6) changes to the plantar surface of the 5th metatarsal. Each of the six leprosy-related lesions we recorded as "present", "absent", or "missing" because of taphonomic damage.

Table 1. Sensitivity and specificity of leprosy and TB-related lesions. Sensitivity and specificity measures for leprosy were derived from Boldsen (2001), and tuberculosis measures were derived from Dangvard Pedersen et al. (2019).

			Estimate	S.E.
Leprosy	Edge of nose	Sensitivity	0.662	0.108
		Specificity	0.854	0.021
	Anterior nasal spine	Sensitivity	0.486	0.082
		Specificity	0.976	0.012
	Alveolar process	Sensitivity	0.449	0.091
		Specificity	0.985	0.016
	Palate	Sensitivity	0.688	0.053
		Specificity	0.757	0.076
	Fibular swelling	Sensitivity	0.361	0.066
		Specificity	0.927	0.021
	Fifth metatarsal	Sensitivity	0.516	0.096
		Specificity	0.881	0.025
Tuberculosis	Visceral surface of ribs	Sensitivity	0.337	0.031
		Specificity	0.987	0.007
	Ventral part of vertebrae	Sensitivity	0.533	0.032
		Specificity	0.959	0.014
	Lateral body of ilium	Sensitivity	0.332	0.031
		Specificity	0.949	0.010
	Acetabular fossa	Sensitivity	0.420	0.032
		Specificity	0.935	0.016
	Iliac auricular surface	Sensitivity	0.296	0.030
		Specificity	0.942	0.016
	Olecranon process of ulna	Sensitivity	0.092	0.019
		Specificity	0.983	0.009

Tuberculosis

In this study, we scored each adult skeleton for six tuberculosis-related lesions in the following locations: 1) visceral surface of the ribs, 2) ventral part of thoracic and lumbar vertebral bodies, 3) lateral body of the ilium, 4) acetabular fossa, 5) iliac auricular surface, and, 6) olecranon process of the ulna. The presence of lesions associated with tuberculosis was recorded and analyzed using criteria described and tested on tuberculosis cases from the Terry Collection and tuberculosis controls from the Bass Donated Collection by Dangvard Pedersen et al. (2019). This study yielded the tuberculosis lesion sensitivity and specificity measures given in Table 1. Each of the six tuberculosis-related lesions was scored as "present", "absent", or "missing" because of taphonomic damage.

Statistical and epidemiological methods

It is important to recognize that no osteological symptom occurs exclusively among people with a particular disease. No single symptom is necessarily expressed by all who may have suffered from the disease (Wood et al. 1992; Milner & Boldsen 2017). In epidemiological terms, diagnostics of a given disease are based upon the probability measures sensitivity and specificity (Boldsen 2001; Dangvard Pedersen 2016; Milner & Boldsen 2017). Sensitivity is the probability that an individual affected by an illness will score positively for a lesion associated with that disease. Specificity is the probability that an individual not affected by a particular disease will score negatively for a lesion associated with that disease. Both sensitivity and specificity are probabilities conditioned on disease status and are independent of the actual frequency of the disease in the sample (Boldsen 2005a). Lesions related to a particular disease can be defined as skeletal conditions for which the sensitivity is larger than one minus the specificity – in other words, a condition that is more commonly seen among people affected by the disease than among those not affected by the disease (Boldsen 2008). Because sensitivity and specificity are directly related to the biology of the disease, lesions can be assessed statistically regarding their ability to indicate a particular disease. If we have known sensitivity and specificity values of lesions, the population prevalence – frequency of people who suffered from a given disease at the time of death – can be estimated from the observed numbers of positive and negative lesion scores (Tables 2 and 3). For leprosy, this is done through the estimation of λ – the individual probability

Table 2. Frequency of the observed six leprosy-related lesions in the four skeletal samples.

Lesion	State	Site								*p*-value
		Øm Kloster		Ole Wormsgade		Sejet		Ribe Grey Friary		
		N	%	N	%	N	%	N	%	
Edge of nose	positive	4	11.4	2	7.7	0	0.0	4	12.9	0.537
	negative	31	88.6	24	92.3	16	100.0	27	87.1	
Anterior nasal spine	positive	0	0.0	0	0.0	0	0.0	0	0.0	–
	negative	12	100.0	12	100.0	5	100.0	25	100.0	
Alveolar process	positive	1	4.3	2	8.3	0	0.0	1	3.2	0.711
	negative	22	95.7	22	91.7	17	100.0	30	96.8	
Palate	positive	14	36.8	9	36.0	4	18.2	8	21.6	0.272
	negative	24	63.2	16	64.0	18	81.8	29	78.4	
Fibular swelling	positive	7	18.9	14	41.2	10	34.5	8	16.0	0.032
	negative	30	81.1	20	58.8	19	65.5	42	84.0	
Fifth metatarsal	positive	2	7.4	5	22.7	5	21.7	3	9.1	0.258
	negative	25	92.6	17	77.3	18	78.3	30	90.9	

Table 3. Frequency of the observed six TB-related lesions in the four skeletal samples.

Lesion	State	Site								*p*-value
		Øm Kloster		Ole Wormsgade		Sejet		Ribe Grey Friary		
		N	%	N	%	N	%	N	%	
Visceral surface of the ribs	Positive	0	0.0	1	2.3	1	4.0	3	5.7	0.843
	Negative	0	0.0	43	97.7	24	96.0	50	94.3	
Ventral part of vertebrae	Positive	11	29.7	12	29.3	8	66.7	17	33.3	0.094
	Negative	26	70.3	29	70.7	4	33.3	34	66.7	
Lateral body of the ilium	Positive	8	16.0	12	25.0	10	37.0	17	29.8	0.191
	Negative	42	84.0	36	75.0	17	63.0	40	70.2	
Acetabular fossa	Positive	11	21.2	9	20.0	9	34.6	8	16.3	0.335
	Negative	41	78.8	36	80.0	17	65.4	41	83.7	
Iliac auricular surface	Positive	5	9.8	5	10.6	4	16.7	9	15.8	0.727
	Negative	46	90.2	42	89.4	20	83.3	48	84.2	
Olecranon process of ulna	Positive	2	4.3	3	7.1	2	11.1	17	34.0	< 0.001
	Negative	44	95.7	39	92.9	16	88.9	33	66.0	

of leprosy. From this, the sample frequency of leprosy at death (p) is estimated. For a complete description of the statistical approach and equations performed, we refer to the previous work of Boldsen (2001; 2005b; 2005c; 2008). For tuberculosis, the disease frequency was calculated through the estimation of τ – the individual probability of tuberculosis. From this, the sample frequency of tuberculosis at death (p) is estimated. This statistical approach was developed by Dangvard Pedersen (2016) and Dangvard Pedersen et al. (2018.) and is based upon the previously described work on leprosy by Boldsen. All frequency estimates of leprosy and tuberculosis for each site are reported with 95 percent confidence intervals.

To evaluate both differences of disease frequency in the samples and to perform survival analysis to examine the effect of urban development on survivorship, the estimated disease probability measures of leprosy (λ) and tuberculosis (τ) were computed into disease status variables. Here, knowledge about the sample from which the skeleton came is taken into account by adding the log of the odds of the diseases to the raw data (Boldsen 2005b). From the population-based λ and τ values leprosy status is defined as either "not leprotic" ($\lambda < 0$) or "leprotic" ($\lambda \geq 0$) and tuberculosis status is similarly defined as either "not tuberculoid" ($\tau < 0$) or "tuberculoid" ($\tau \geq 0$).

Table 4. The λ-distribution and estimated leprosy frequency at death in the four samples.

Site	N		λ			Leprosy frequency	
			Observed	Simulated Positive	Simulated Negative	*p*	95% CI
Øm Kloster	58	Mean	−1.01	1.91	−1.25	0.08	0.02–0.14
		Variance	3.09	6.39	2.01		
Ole Wormsgade	48	Mean	−0.53	2.02	−1.25	0.19	0.11–0.30
		Variance	4.57	7.01	1.97		
Sejet	29	Mean	−1.18	2.41	−1.54	0.13	0.04–0.23
		Variance	4.82	7.66	2.27		
Ribe Grey Friary	57	Mean	−1.45	2.26	−1.39	0.04	0.00–0.09
		Variance	3.35	8.68	2.45		

Table 5. The τ-distribution and estimated TB frequency at death in the four samples.

Site	N		τ			TB frequency	
			Observed	Simulated Positive	Simulated Negative	*p*	95% CI
Øm Kloster	55	Mean	0.10	2.05	−1.13	0.49	0.33–0.67
		Variance	7.58	5.19	1.17		
Ole Wormsgade	56	Mean	0.06	2.62	−1.36	0.39	0.26–0.54
		Variance	7.95	7.80	1.33		
Sejet	29	Mean	1.23	2.40	−1.24	0.69	0.43–0.96
		Variance	10.26	7.23	1.24		
Ribe Grey Friary	61	Mean	0.70	2.82	−1.47	0.45	0.32–0.62
		Variance	8.06	8.30	1.39		

Potential differences in variation of individual probability of disease and disease status on the sites are tested by analyzing the difference in variance of λ and τ values by ANOVA and analyzing differences in disease status by Fisher's exact tests. Kaplan-Meier survival analyses are performed to examine the effect of urban development on survivorship. Here Mantel-Cox statistics are used to test the equality of the survival distributions between sites. Due to the low frequency of leprosy in the four skeletal samples only very few skeletons were found to be leprotic. Therefore, statistical evaluation of survivorship with and without leprosy was not performed.

All data manipulation and analysis were carried out using IBM SPSS v. 25 statistical program.

Results

Tables 2 and 3 provide the raw data used in the analysis for each of the four cemetery samples. Among the six leprosy-related lesions, only the fibula has a significant difference in frequency among the sites ($p = 0.032$) with Ole Wormsgade having a frequency of 41 percent. There were no apparent differences among the tuberculosis-related lesions, except for the ulna ($p < 0.001$) where Ribe Grey Friary has the highest frequency (34 percent). From these data, we calculated the λ and τ values leading to the respective maximum likelihood estimates for the prevalence of leprosy and tuberculosis at death. Table 4 gives the estimates of λ and leprosy prevalence for each of the four cemetery samples. Table 5 gives the estimated τ-values and tuberculosis prevalence for each sample. The observed λ and τ values fall within the range of simulated positive and negative values of λ and τ. The point estimate for the prevalence of leprosy at death (p) is 8 percent (CI 2–14 percent) for Øm Kloster, 19 percent (CI 11-30 percent) for Ole Wormsgade, 13 percent (CI 4–23 percent) for Sejet and 4 percent (CI 0–9 percent) for Ribe Grey Friary. The estimated point prevalence of tuberculosis at death (p) is 49 percent (CI 33–67 percent) for Øm Kloster, 39 percent (CI 26–54 percent) for Ole Wormsgade, 69 percent (CI 43–96 percent) for Sejet and 45 percent (CI 32–62 percent) for Ribe Grey Friary. Tables 6 and 7 describe the goodness of fit tests (χ^2) of the estimation model to the λ and τ distributions in the four skeletal samples. The only site that showed a discrepancy in the goodness of fit tests was Øm Kloster for the τ distribution ($p = 0.038$). Figures 2 and 3 show the estimated frequencies of leprosy and tuberculosis at death for each of the four sites.

Table 6. Goodness of fit test of the estimation model to the λ-distribution in the four samples.

Site	$f(\hat{p})$	df	*p*-value
Øm Kloster	< 0.01	1	0.965
Ole Wormsgade	0.07	1	0.791
Sejet	0.14	1	0.708
Ribe Grey Friary	0.83	1	0.362

Table 7. Goodness of fit test of the estimation model to the τ-distribution in the four samples.

Site	$f(\hat{p})$	df	*p*-value
Øm Kloster	4.29	1	0.038
Ole Wormsgade	0.22	1	0.639
Sejet	1.13	1	0.288
Ribe Grey Friary	1.39	1	0.238

To test whether there are observed differences of the variance of individual probability of the two diseases and the disease statuses in the samples, we conducted analyses of variance (ANOVA) of λ and τ values and performed Fisher's exact tests of leprosy and tuberculosis disease status. The ANOVA results yielded no significant differences when testing all four samples (leprosy, $df = 3$, $F = 1.947$, $p = 0.124$; tuberculosis, $df = 3$, $F = 1.46$, $p = 0.227$). Additionally, no significant results were shown when we binned the sites into "urban" and "rural" categories (leprosy, $df = 1$, $F = 0.013$, $p = 0.909$; tuberculosis, df = 1, $F = 0.048$, $p = 0.826$). When testing differences in disease status for individuals, the Fisher's exact tests revealed significant differences between the four samples (leprosy, $df = 3$, $p = 0.005$; tuberculosis, $df = 3$, $p = 0.010$), but no significant results when sites were binned into "urban" and "rural" categories (leprosy, $df = 1$, $p = 1.000$; tuberculosis, $df = 1$, $p = 0.772$).

The analysis of the effect of tuberculosis on survival in the four sites is illustrated in Fig. 4. A significant result was found between those with ($\tau < 0$) and without ($\tau \geq 0$) tuberculosis for all sites except Øm Kloster (Øm Kloster, $p = 0.554$; Ole Wormsgade, $p = 0.034$: Sejet, $p < 0.001$; Ribe Grey Friary, $p = 0.011$).

Discussion

The analyses of the disease frequencies for each site yield mixed results between urban and rural samples, which do not consistently support the hypothesis that urbanization cause increased disease prevalence at death. The leprosy prevalence of the four sites range from 4–19 percent and considerable overlap in their confidence intervals was observed (Fig. 2). Additionally, the ANOVA tests do not support that there are significant differences in the individual probability of leprosy either between the individual sites or as binned in rural and urban sites. We do, however, observe significant differences between sites when testing for differences in leprosy status using Fisher's exact test ($p = 0.005$). This may be explained by the observed difference in the two urban samples for leprosy. The difference between Ole Wormsgade and Ribe Grey Friary is interesting because we would expect similar disease dynamics in urban settings. One possible explanation for Ribe Grey Friary being on the low end of the distribution and Ole Wormsgade being on the higher end is the establishment of leprosaria. The leprosarium in Horsens is mentioned for the first time in AD 1492 and was presumably established relatively late in the medieval period (Knudsen & Schiørring 1992). In contrast, Ribe had probably maintained a leprosarium from before AD 1280 (Nielsen 1985). The establishment of leprosaria would have led to the selective exclusion of people with apparent signs of leprosy, especially facial lesions, and such exclusion has been illustrated in examinations of non-leprosarium in medieval Odense (Boldsen & Mollerup 2006). The skeletons of this study are dated within the temporal frame AD 1200–1400 and a selection process of individuals with stigmatizing lesions in Ribe would have resulted in a lower frequency of lesions in Ribe Grey Friary skeletons compared to Ole Wormsgade, where individuals generally have a higher frequency of leprosy-related lesions (Table 2). With this selective exclusion in mind, Ole Wormsgade might be said to be representative of an urban population with leprosy because of how late the leprosarium was in the greater Horsens area, while Ribe might represent an urban population that was affected by this selection factor.

The frequency of tuberculosis in the four sites is notably higher than leprosy, with a range of 39–69 percent. It is important to note that the confidence intervals for all four samples have considerable overlap, which supports the idea that there is no clear divide between urban and rural sites in tuberculosis frequency. As in the case for leprosy, the ANOVA tests do not support that there are significant differences in the individual probability of tuberculosis, but we do observe significant differences in disease status between the four sites. This cannot, however, be explained as differences between rural and urban sites. The site with the highest prevalence was Sejet with a very wide confidence interval range (43–96 percent), which may be attributed to its small sample size and high frequency of lesions in the sample (Table 3 and Fig. 3). As is often the case in bioarchaeology, we cannot ignore the possibility that our results are affected by sample size. However, there is also the possibility that tuberculosis did have a high prevalence at death in all the samples for other reasons. Tuberculosis was by no means a rare disease in pre-modern Denmark (Dangvard Pedersen 2016; Dangvard Pedersen et al. 2018), and we have several examples of skeletal lesions consistent with the disease dating from the Neolithic period onward (Holloway et al. 2011). While we do have recent genetic research on

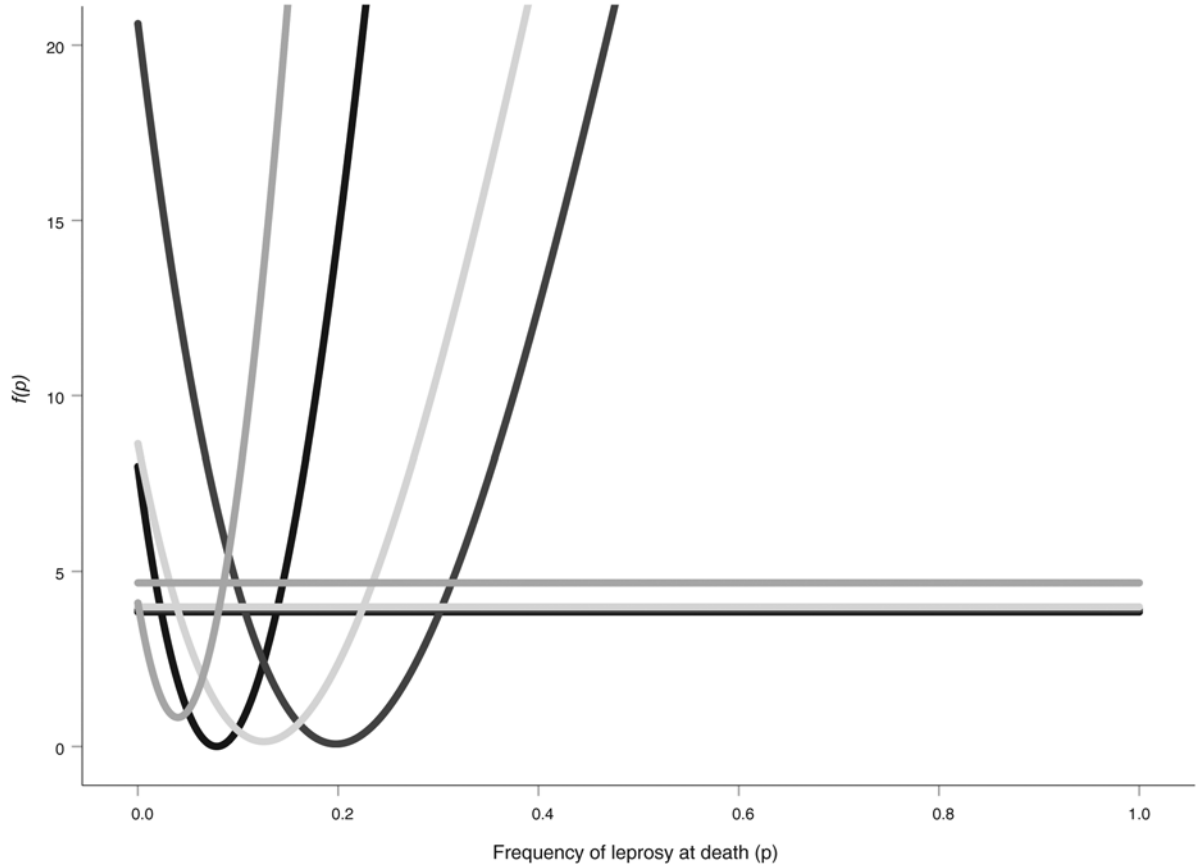

Fig. 2. Frequency of leprosy at death on the four sites. Black: Øm Kloster. Dark grey: Ole Wormsgade. Grey: Ribe Grey Friary. Light grey: Sejet.

the various strains of leprosy that may have been active in medieval Europe (Krause-Kyora et al. 2018; Schuenemann et al. 2018), the same cannot be said for strains of tuberculosis. It is possible that rural and urban settlements may have been affected differently by *M. tuberculosis* and *M. bovis*. Rural villages could have been more frequently exposed to *M. bovis* from close contact with cattle, which may explain some differences in the disease frequencies. However, it is unknown whether these two forms of tuberculosis manifest as different lesion patterns based on their different routes of infection (Dangvard Pedersen 2016; Dangvard Pedersen et al. 2018). Alternatively, the urban dwellers may to a larger degree have experienced the pulmonary *M. tuberculosis* infection – a more virulent strain that to a greater extent, than *M. bovis*, would cause deaths of individuals before skeletal lesions developed (Francis 1950). The higher prevalence of TB in the small rural sample from Sejet may be attributable to this difference in disease strain. Unfortunately, until we can accurately estimate the difference in lesion development of these two strains, we are unable to determine if this is a possibility.

Our analyses of the goodness of fit for the τ model do show a discrepancy in observed mean and variance of the Øm Kloster sample. Without disregarding the possibility of sampling error, we propose that there may be underlying heterogeneity in the sample that may lead to this result. The monks at Øm were not unlike other Cistercian orders in that the Cistercians tenured monastery-owned land to farming families, and that those families were buried in the lay cemetery. There is, however, a notable surplus of males in the north cemetery, which has been discussed in previous publications (Mollerup 1999; Kelmelis et al. 2017; Mollerup 2018). It is possible that these males were lay brothers from outlying communities who were buried in the north cemetery. Another possibility is that the surplus of males does not represent a local population; rather, they may be the remains of individuals who traveled to Øm and requested to be buried there. Up until the 16th century, the monastery experienced considerable expansion in land ownership and influence in the neighboring market town of Rye (Gregersen 2018). Before the Protestant Reformation, the monastery owned over 200 properties whose landlords and tenants often

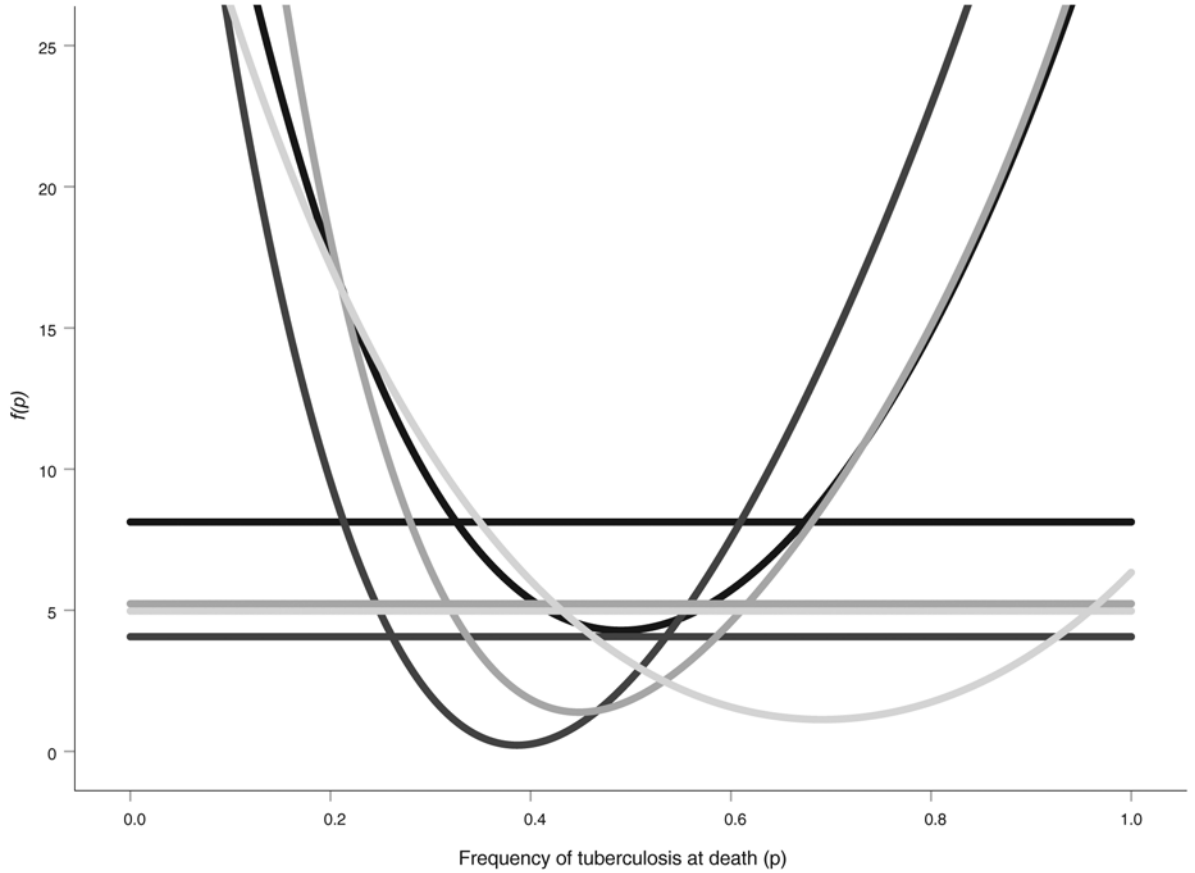

Fig. 3. Frequency of tuberculosis at death on the four sites. Black: Øm Kloster. Dark grey: Ole Wormsgade. Grey: Ribe Grey Friary. Light grey: Sejet.

requested burial at the monastery or in the north cemetery. During the 15th century, the neighboring town of Rye became a very popular destination for pilgrims and merchants as it grew in influence because of its markets and wealthy benefactor: Øm Kloster (Gregersen 2018). In light of these economic and territorial expansions, Øm Kloster may have allowed for the burial of non-locals suffering from various illnesses, and there is evidence to suggest that the monastery infirmary did treat diseases such as leprosy (Rasmussen et al. 2008). Therefore, it is possible that the discrepancy in the mean and variance of tuberculosis in the sample is because we are observing different patterns in disease experiences between a local and non-local community. This is only one possible source of heterogeneity that may explain the observed discrepancy, which leads to the need for further data collection and analyses.

The mortality patterns of each site with disease status as a co-variate also show conflicting results. The general trend in survivorship between individuals with and without tuberculosis suggests that individuals with the disease were living longer than their non-lesioned counter-parts. Those individuals who survived with tuberculosis-related lesions may have done so because they had a stronger immune response than their age-peers without lesions, implying that individuals who died without lesions were likely to be more frail than those surviving longer with lesions (Wood et al. 1992). Alternatively, non-lesioned individuals may have never been exposed to the pathogen or were able to fight it off at the onset; however, our analyses do show that those without lesions generally died earlier than their lesioned counterparts which are strongly suggestive that those individuals were at higher risk of death for one reason or another. In the circumstance where tuberculosis is primary and is usually contracted in childhood in individuals who had not been previously exposed, the individual either survives the infection, or they die; post-primary or secondary tuberculosis occurs when a latent infection is reactivated (possibly because the immune system has become depressed for one reason or another), or the individual is infected again with another large or repeated dose of tubercle bacilli, which results in the formation of skeletal lesions (Roberts & Manchester 2005: 187). Based on this mechanism of the host-pathogen

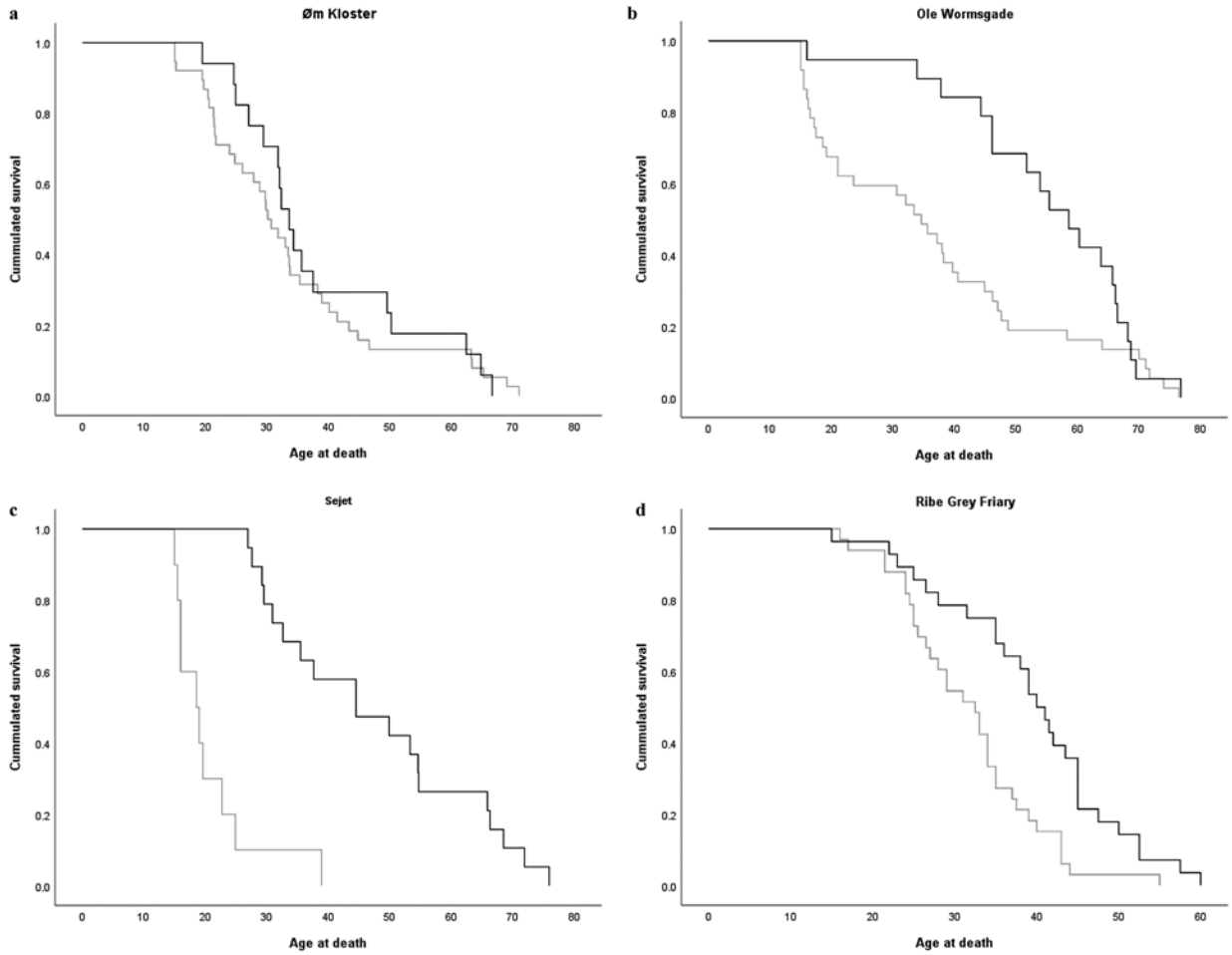

Fig. 4. Kaplan Meier survival curves showing the difference in survival of individuals with tuberculosis absent: $\tau < 0$ (grey) and tuberculosis present: $\tau \geq 0$ (black) on the four cemeteries. The equality of survival distributions of the levels of tau status was tested by Mantel-Cox tests. Øm Kloster ($p = 0.554$), Ole Wormsgade ($p = 0.034$), Sejet ($p < 0.001$), Ribe Grey Friary ($p = 0.011$).

interaction, we suggest that those who died without lesions may have done so because they could not fight off primary infection or that they had died from other causes related to underlying frailty. Tuberculosis is often referred to as an opportunistic disease because it kills when a host has an already compromised immune system, and this opportunism is something observed in modern HIV-affected clinical samples (McMichael & Rowland-Jones 2001; Roberts & Buikstra 2003). It is possible that those individuals who died with lesions had a stronger immune response to infection, while others with compromised immune systems died before they could form skeletal lesions. This is one possible explanation that we should consider, but it is by no means the only explanation. There are many hidden sources of heterogeneity that we cannot account for directly from skeletal material because of the nature of skeletal series and the behavior of pathogens (Milner et al. 2008). This study only considered a few factors in our attempt to address the role of urban development in disease prevalence at death in skeletal samples. A future direction that is being undertaken to deal with other sources of heterogeneity is the execution of a comprehensive frailty hazard model that includes various sources of specific and non-specific disease and stress from childhood and adulthood using a fully Bayesian approach to estimate differences in frailty and selective mortality in skeletal samples.

Overall, there are potentially several biological and behavioral factors contributing to the subtle differences in disease frequencies; however, the overall set of analyses does not support the idea that urban and rural sites were remarkably different. Based on historical and archaeological evidence discussed in the previous sections, these sites represent what would have been typically “urban” and “rural” for the medieval period in Denmark; however, the differences in lifestyle do not appear to vary to such a degree that we would observe significant differences in disease prevalence in the

skeletal samples. If lifestyle and diet varied to a significant degree, we would expect to see significant differences in disease prevalence and mortality patterns. Even if such lifestyle differences existed, it is important to take into consideration the role of migrating travelers and goods in the transmission of diseases. Travelers and goods that flowed between villages and market towns were likely vectors for disease and the distance between settlements was likely not significant enough to completely isolate populations from disease. For example, the village of Sejet is a mere eight km from Horsens which may result in some variation in disease prevalence but not enough to be significant, at least not for this portion of the medieval period. It would be interesting to make the same comparison for tuberculosis in skeletal samples dated to early modern period, where towns are larger and have a more 'urban' lifestyle. Here we will expect more clear differences because we know from historical data from the first half of 20th century that urban towns had greater numbers of deaths due to tuberculosis compared to rural areas of the country (Madsen et al. 1942). Unfortunately, we have very few skeletons from rural areas dating to early modern period because many of the cemeteries are still in use today.

It is interesting that we observe generally higher frequencies of tuberculosis than leprosy among the four sites. There are several potential explanations for this observation. At the end of the medieval period, leprosy had all but disappeared from Europe while the prevalence of tuberculosis increased dramatically. There has been some conjecture about the shifting prevalence of leprosy and tuberculosis over the medieval period to the early modern period, suggesting that tuberculosis may buffer against leprosy, and, under certain conditions, tuberculosis would have replaced leprosy as the more virulent disease after the medieval period into the early modern period (Manchester 1991; Donoghue et al. 2005). These conjectures should take into account the role of leprosaria as a societal measure against the spread of the disease. The establishment of leprosaria would have isolated those who were markedly sick with the disease, thus preventing the possibility of infecting susceptible hosts, and the strict exclusion of those affected by leprosy from society is unparalleled in the case of tuberculosis. Tuberculosis, acting as an opportunistic disease, could have removed previously infected individuals from the population before they could develop leprotic lesions. Clinical research shows that tuberculosis is rarely the direct cause of death to those infected with the pathogen – especially those who have survived primary infection – because it is more likely to remain dormant in a host's system until their immune system is depressed by an additional malady – either another bought of tubercle bacilli or anything that compromises the immune system – which may lead to death. A modern example is HIV and TB co-infection, which is common in many developing countries where TB is endemic (Roberts & Buikstra 2003; Sharma et al. 2005; Stone 2017). Leprosy has an extended incubation period and could compromise a host's immune response allowing co-infection (Donoghue et al. 2005; WHO 2010). In connection to co-infection natural vaccination could be an important explanatory factor for the differences of leprosy and tuberculosis frequencies found in the samples. The active agent in the BCG-vaccine used for protection against tuberculosis in modern populations is *M. bovis* (Smith 1994). The BCG vaccine is also used for protection against leprosy. Therefore, it is likely that *M. bovis* transmitted through infected products from cattle could cause natural vaccination both against the more virulent *M. tuberculosis* infection and leprosy (Dangvard Pedersen 2016). This may explain the disappearance of leprosy in northern Europe followed by the rapid resurgence of TB in 18th century Western Europe and North America (Roberts & Buikstra 2003; Barberis et al. 2017). We do observe a higher prevalence of tuberculosis than leprosy overall in our study samples, which could illustrate a combination of exclusionary selection of leprosy-infected individuals and the rise of tuberculosis as a more virulent pathogen.

As a final point of discussion, there are several limitations to this study and those involving skeletal material worthy of mention. An integral part of understanding population changes in the past lies in reconstructing and interpreting patterns of health and mortality from cemeteries, which is neither a simple nor direct task (Milner et al. 2008; Wood et al. 1992). Issues of preservation biases, differential burial and recovery, inaccuracies associated with age-at-death estimation, and hidden heterogeneity and selective mortality within populations are just a few of the intrinsic and extrinsic issues that bioarchaeologists face when inferring patterns of health and mortality from skeletal samples (Bocquet-Appel & Masset 1982; Wood et al. 1992; Milner et al. 2008). A practical concern is that excavated skeletons undergo several postmortem processes that determine the likelihood of their survival from the ground to the research facility, and these processes have a profound influence on the accuracy of paleodemographic analyses (Milner et al. 2008). This process undoubtedly affected the size of our study sample, which is something to consider in our results. Of a more theoretical nature, our study – as are all studies involving skeletal samples – is affected by the inconvenient fact that skeletal series are not direct representations of the once-living populations (Wood et al. 1992; Milner et al. 2008). Mortality is selective for any number of preexisting conditions of heterogeneous frailty, and individuals who are at risk of dying at any given age are not a random sample from the living as they tended to have higher frailty at that particular age than those who survived (Usher 2000; Wood et al. 1992). Therefore, the skeletons we observe are never considered "healthy" because some biological, genetic, behavioral, or cultural source of observed or hidden heterogeneity has removed them from the living population into the dead population. A further consideration that we raise concerns the interpretation of skeletal lesions in relation to population prevalence. The inherent issue of osteological lesions is that, for one to

be visible, the individual must survive the condition long enough for it to form on the skeleton, meaning that individuals with lesions may have a stronger immune response to pathogens than those who die without lesions (Wood et al. 1992). While the methods we employed in this study have a basis in epidemiology and were designed explicitly to deal with skeletal samples, there is a likelihood that many individuals in our samples carried the bacteria for leprosy and tuberculosis without having developed lesions. This means that there is a portion of our sample that may not yield any data concerning these two diseases and that other biological, genetic, or behavioral factors may be contributing to their risk of death. This consideration is critical to bear in mind as we continue to build paleoepidemiological models examining past disease experience and heterogeneous frailty.

Conclusion

In this study, we examined two diseases that have long been correlated with increased urban intensity and whose involvement in skeletal material allows for paleoepidemiological analysis: leprosy and tuberculosis. Our results do not indicate that the general trend of urban development led to a decline in health. Rather, we observed significant variation on a site-to-site basis and not based on the broad categorization of sites. This conclusion reinforces the point that we should carefully consider the historical and cultural context of archaeological sites in our interpretation of osteological and statistical analyses. Leprosy prevalence was generally low across all sites. On the other hand, tuberculosis prevalence was considerably higher, and those with the disease appeared to be living longer than those without tuberculosis-related lesions. These observations may have a lot to do with the biology and evolution of the two diseases during the medieval period. It is likely that we are encountering an issue of selectivity, as was observed in the case of Ribe Grey Friary where visibly sick individuals likely moved to the leprosarium. There is also the likelihood that many individuals carried these diseases but died before they could express disease-related lesions because they had pre-existing health issues that were unobserved in the skeleton. This point highlights the limitations of this study insofar as human health and the measure of frailty are inherently complex. There are many sources of heterogeneity that we can observe and account for – leprosy and tuberculosis happen to be two of them – but that there are many hidden sources of heterogeneity that we cannot directly measure in this current approach. One potential future direction that is being undertaken involves applying this paleoepidemiological approach to an encompassing frailty hazard model, which examines multiple paleopathological lesions from stress and chronic infection in relationship to age-at-death distributions to understand the lasting effects of frailty on the once living population. Lastly, we acknowledge that results are insignificant because they truly are or that they are directly affected by the size of our samples.

The study of health and disease experience in the past is not without its challenges. Still, it is possible to gain insight into past disease experience using a paleoepidemiological approach based on the sensitivity and specificity of suites of osteological lesions. In doing so, it is possible to broaden our understanding of the effects of urban development on disease experience in the past.

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