Compounding Vulnerabilities: Syndemics and the Social Determinants of Disease in the Past

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Abstract

Objective: This article explores the theory and utility of a syndemic approach for the study of disease in the past. Syndemic principles are examined alongside other theoretical developments within bioarchaeology. Two case studies are provided to illustrate the efficacy of this approach: Tuberculosis and vitamin D deficiency in 18th and 19th century England, and malaria and helminth infections in Early Medieval England.
Materials: Public health studies of present syndemics, in addition to published bioarchaeological, clinical and social information relating to the chosen case studies.
Methods: The data from these two historical examples are revisited within a syndemic framework to draw deeper conclusions about disease clustering and heterogeneity in the past.
Results: A syndemic framework can be applied to past contexts using clinical studies of diseases in a modern context and relevant paleopathological, archaeological, and historical data.
Conclusions: This approach provides a means for providing a deeper, contextualised understanding ancient diseases, and integrates well with extant theoretical tools in bioarchaeology
Significance: Syndemics provides scholars a deep-time perspective on diseases that still impact modern populations.
Limitations: Many of the variables essential for a truly syndemic approach cannot be obtained from current archaeological, bioarchaeological, or historical methods.
Suggestions for Further Research: More detailed and in-depth analysis of specific disease clusters within the past and the present, which draws on a comprehensive analysis of the social determinants of health.

Keywords: syndemics, tuberculosis, vitamin D deficiency, malaria, helminth infections, Great Britain

1.1 Introduction

Paleopathology has contributed substantially to global understandings of disease, providing long-term perspectives and revealing the biocultural patterns and complexities in human/pathogen interactions. Study of ancient disease must rely on an assumption of biological and ecological uniformitarianism, allowing extrapolation of factors such as disease transmission and virulence to different cultures, ecologies, and time periods. By contrast, the actual complexities of ancient disease are easily downplayed as confounders, exceptions, and idiosyncrasies in our often incomplete and patchy skeletal data. Within populations these complexities can take the form of 'hidden heterogeneities', which have formed the basis of considerable interpretive challenges in the discipline (Wood et al., 1992). Here we suggest that a syndemic approach allows bioarchaeologists to think more deeply about the social and economic, in addition to the biological, contexts associated with disease.

The SARS-Cov-2 virus exemplifies the heterogeneity of risk and outcomes experienced by different subsections of a population exposed to the pandemic. COVID-19 very quickly became a global disease, but its effects were locally disparate. A particular pattern was the high levels of morbidity and mortality amongst low socio-economic status and minoritized ethnic groups. Initially this was linked to the high frequency of comorbid conditions in the communities hardest hit, such as obesity, diabetes mellitus, and hypertension. Public health researchers, however, soon rejected the biological determinism that underpinned these initial assessments, arguing instead that SARS-Cov-2 should be understood in relation to existing health disparities rooted in long-term structural inequalities (Gravlee, 2020; Pirtle 2020; Singer et al., 2021). The virus was not landing on a level playing field – instead it was interacting with individuals who had varying inherent vulnerabilities due to intersectional, inter-generational and socio-cultural inequality. COVID-19 thus exposed the fault lines within society (Wade 2020). To understand the patterns of morbidity and mortality associated with the pandemic, it is essential to do so in relation to existing diseases, but also, crucially, the socio-cultural and historical milieu.

Understanding disease processes and prevalence in terms of the synergistic interaction between a pathogen and existing morbidities within specific socio-economic, cultural and natural environments has been coined the 'syndemic' approach ('*Syn*ergistic Epi*demic*, Singer 1996, 2009). Syndemics is a concept developed by Singer in the 1990s for explaining the relationship between substance abuse, violence and HIV/AIDS (known as the SAVA syndemic). It is defined as "a set of enmeshed and mutually enhancing health problems that, *working together* in a context of noxious social and physical conditions, can significantly affect the overall disease burden and health status of a population" (Singer, 2009, xiv). Syndemics are not restricted to infectious diseases and can involve the spectrum of disorders, including psychiatric or psycho-social conditions (Singer et al., 2017; Tsai, 2015). These elements synergistically compounded biological and social ills, with AIDs essentially classified as an opportunistic infection within that context.

When Singer (1996) applied this concept to HIV/AIDS it facilitated understanding of the complex interactions and vulnerabilities associated with this condition; for example, co-infection of HIV and tuberculosis resulted in a synergistic interaction between the bacterium and virus, which exacerbated the rapid progress of each. These co-infections were syndemic because they disproportionately occurred amongst minoritized and impoverished groups living within specific socio-political contexts (Singer 2017, p. 941). Likewise, the heterogeneity of impacts of COVID-19 are best understood within a syndemic framework because the pandemic hit communities with socially determined patterns of chronic disease, and these pre-existing conditions interacted synergistically with COVID-19 to produce greater morbidity and mortality risk. The syndemic approach has been applied across health-related disciplines to other "syndromes" that cluster in particular environments: childhood sexual abuse, depression, and partner violence and HIV in men who have sex with men (Stall et al., 2003), alcohol use, illicit drug use, depression, childhood sexual abuse, and intimate partner violence in men who have sex with men (Tomori et al., 2018), metabolic disease, mental illness, poverty, and infectious diseases such as HIV (in Kenya), tuberculosis (in India), and depression (in South Africa) (Mendenhall et al., 2017), and violence, immigration, depression, type II diabetes, and abuse (or the VIDDA syndemic)

in Mexican female immigrants in the U.S. (Mendenhall, 2012) (for a recent summary of examples, see Singer et al., 2021).

Paleopathology has recently moved towards a deeper theoretical and methodological analysis of sources of disease heterogeneity – paying attention to the many shades of gray to explore the meaning within. This exploration has been assisted by the sociological turn over the last two decades within the discipline, including an increased emphasis on osteobiographical narratives, and a consideration of the interplay between aspects of identity and disease over the life course (Argawal 2016, Baker and Argawal 2017). The recent incorporation of perspectives relating to the Developmental Origins of Health and Disease (DOHaD) framework have further emphasized the key role of developmental, biographical and inter-generational dimensions when interpreting disease risk and expression. The discipline has also adopted a more 'particularized' biocultural analysis through the adoption of Margaret Lock's (1993) concept of 'local biologies', which emphasizes the need to interpret disease/body interactions in terms of local entanglements of history, culture, geography, and ecology (Lock 1993, Niewöhner & Lock, 2017, p. 687). Finally, recent work has also drawn upon Black feminist research on the intersectionality between identities such as gender, low socio-economic status and ethnicity, and how these exacerbate or mitigate exposure to disease risk and biological responses (Crenshaw 1989, Geller 2021, Mant et al. 2021, Yaussy 2019, 2022). What all these perspectives have in common is that they each emphasize the socio-cultural and historical embeddedness of disease risk and the consequent heterogeneity of individual responses within populations.

Medenhall et al. note (2022, p. 2) "Everyone concerned with past health would gain considerably by viewing epidemic clusters through the lens of syndemic theory" (see also Newfield, 2022). With this in mind, we outline here the potential and application of the syndemic framework for bioarchaeological and paleopathological analyses. We start with the present-day pandemic as an exemplification of syndemic effects and follow this with two examples of past diseases (tuberculosis and malaria), illustrating how the interpretation of each within specific geographic and temporal contexts can be substantially enhanced by a syndemic approach. We discuss how this framework intersects with other theoretical approaches recently adopted in

palaeopathology, including the life course and inter-generational insights provided by the Developmental Origins of Health and Disease hypothesis, and the need to ground biological effects within an understanding of intersectional, socio-cultural environments that shape disease clustering and interaction (Gravlee, 2020; Singer et al., 2017, 2022).

1.2 A syndemic perspective of COVID-19

Well over two years into the COVID-19 pandemic, statistics on disease mortality, now exceeding 6 million deaths globally, have become a familiar part of the news cycle. Early messages from the government suggested that COVID-19 was an 'equal opportunities' virus - it did not discriminate between rich or poor. This myth was promptly dispelled when public health researchers soon noted the increased mortality risk from COVID-19 for those with underlying health conditions (e.g., cardiovascular disease) (Bambra et al., 2021; Bambra et al., 2020). The pre-pandemic pattern of chronic disease is strongly linked to the social determinants of health, such as occupation, living conditions, nutrition, exposure to pollutants, marginalization and subsequent psycho-social stress. Furthermore, those in low-income jobs, often on contracts with no sick pay or holiday pay, or those classed as essential workers, could not 'lockdown' and socially isolate (Bambra et al. 2020; Gravlee 2020), The synergistic interaction between COVID-19 and pre-existing health problems, in concert with socially-conferred vulnerabilities and risks, meant that at a local level the pandemic was experienced syndemically (Mendenhall, 2020)

In the U.S., Hispanic/Latino, Native American, and Black individuals have been disproportionately represented among those with poorer COVID outcomes in relation to their representation in the population throughout the pandemic. CDC age-adjusted data from late winter 2022 indicate that risks for hospitalization and death due to COVID-19 are anywhere from 1 to almost 4 times higher for Native Americans, Black, and Hispanic persons than for White, non-Hispanic individuals (Centers for Disease Control, 2022). Age-adjusted data from the UK from February 2022 also demonstrate that during the Omicron surge, Bangladeshi and Pakistani males and females were over two times more likely to die from COVID-19 than White British individuals, statistics that have not

changed dramatically from before Omicron became the main variant (Ahmad et al., 2022). Even adjusting for the presence of pre-existing medical conditions that increase the risk of COVID-related mortality, deaths of BAME (Black, South Asian, mixed, or other ethnicities) individuals of all ages were up to 1.5 times higher compared to Whites in the UK (Mathur et al., 2021; Williamson et al., 2020).

Biological and racial determinism, often prevalent in medical research, does not provide a sound or useful approach to COVID-19 (Gravlee, 2020). Instead, these statistics reflect the coalescence of multiple, historically routed, intersectional social disadvantages and their impact on disease risk and biological response to SARS-Cov-2 (Bambra et al. 2020; Pirtle 2020). The synergistic interaction between COVID-19 and poverty-associated chronic disease elevated mortality in vulnerable communities. Legacies of structural violence and inequalities over the centuries have been highlighted, which for the USA pointed to the root causes of slavery (Gravlee 2020). This was exacerbated by a culture of systemic racism and biased treatment of people of color by doctors and other medical practitioners and assumptions regarding genetics and race (Gravlee, 2020, 2009). Meanwhile, in the UK the chief medical officer Professor Chris Whitty highlighted the similarities between the map of COVID-19 mortality and areas with high child mortality (linked to poverty) in the 19th century (Jeavans, 2021). The importance of a historical perspective on the social determinants of health have come into stark focus during the course of this pandemic.

The disparate impact of COVID-19 across communities have lead epidemiologists, public health researchers, and anthropologists to argue that, due to the diverse experiences with the disease in some contexts, COVID-19 is not actually pandemic, but a series of different, localized syndemics (Bambra et al., 2020; Freeman, 2020; Gravlee, 2020; Mendenhall, 2020; Mendenhall et al., 2022). Thus, while COVID-19 has been described as a ‘global syndemic’ (Horton, 2020, p. 874), Medenhall et al. (2020) and Singer et al. (2021, 2022) argue that the biological and social interaction, and clustering of COVID-19 are driven by different factors both locally and between countries. Instead, Singer et al. (2021, p. 8) refer to COVID-19 as a ‘syndemogenic disease’ in that it forms adverse syndemic interactions with many other infectious and non-communicable diseases. In order to understand these interactions, however, it is

essential to understand the localized and historically embedded drivers of disease ecology and health inequalities. Our lived experience of this pandemic reveals the utility of the syndemic perspective and here we discuss the usefulness of this application within paleopathology.

2.1 Syndemics and Bioarchaeology

Anthropology provides a holistic view of human experience, and anthropological approaches to health and disease have always emphasized the importance of social, economic, ecological, and cultural contexts and how these interact with human biology (Dimka et al. 2022). Evidence of this holism is seen in the anthropological relevance of disease ecology (Brown et al., 1990; Inhorn and Brown, 1990), biocultural anthropology (Singer, 2015; Wiley and Cullin, 2016; Zuckerman and Martin, 2016), the One World + One Health approach (Brown and Nading, 2019; Craddock and Hinchliffe, 2015; Woldehanna and Zimicki, 2015; Wolf, 2015), Developmental Origins of Health and Disease (DOHaD) (Gluckman et al., 2005, 2010, 2008; Gowland, 2015), and critical medical anthropology (Baer et al., 1986; Goodman and Leatherman, 1998; Leatherman and Goodman, 2020, 1997; Singer and Baer, 1995). Despite the apparent interconnectedness of these approaches, in many ways they have been siloed rather than integrated in the anthropological study of disease both past and present (Dimka et al. 2022; Leatherman and Goodman, 2020; Singer, 2015).

The syndemic model seeks to incorporate all aspects - biological, social, environmental - that lead to high prevalence of certain diseases within a particular population. The multiple components of the syndemic model include synergism between diseases of all types (infectious or non-communicable), mental health issues, structural racism, environmental toxicity, inadequate nutrition, and co-existing social and economic situations within the community that increase the prevalence of disease and the chance of poor disease outcomes. This “biosocial complex” goes beyond simply noting comorbidities (the biological interaction between diseases) to include how social and economic factors may contribute to increased morbidity and mortality from these diseases in the community (Gravlee, 2020; Singer et al., 2017). Identification of a

syndemic necessitates a multi-level approach that highlights broad-scale economic, ecological, and social factors affecting the community and the pathways by which they interact (Singer et al., 2017; Tsai et al., 2017). There is as much concern for how the confluence of deleterious factors affects an individual as in how the presence of such factors in the community may exacerbate the problem, even if an individual is not directly affected (see Tsai, 2018; Tsai et al., 2017). For example, high rates of home foreclosure in a community could amplify individual-level risk for other elements of a syndemic, such as mental health issues, regardless of whether or not an individual personally experienced home foreclosure (Tsai, 2015). In addition, rather than just focusing on blanket variables such as "poverty" the syndemic model seeks to identify the specific pathways in which social contexts and behaviors linked to poverty affect disease. Therefore, clustering of disease alone is not enough to qualify a situation as a "syndemic" (Mendenhall et al., 2022; Tsai, 2018). It is the "additive" adversity of disease interaction that is key (Singer et al., 2021; Tomori et al., 2018) (see Table 1).

Table 1: Examples of disease interactions classified as "syndemic" according to Tsai (2018)

Disease Interaction	Definition	Example
Mutually Causal Epidemic	Diseases within the syndemic have shared etiologies	The SAVA syndemic: substance abuse, HIV acquisition, and violent victimization (Singer, 1996)
Synergistically interacting epidemics	Diseases within the syndemic have synergistic effects	HIV and tuberculosis, HIV and hepatitis B (Singer and Clair, 2003)
Serially causal epidemics	Diseases or health risks accumulate through time (potentially utilizing a DoHAD or life history approach)	Political violence, humanitarian crises, gender discrimination, PTSD and depression in former female child soldiers in Nepal (Kohrt and Carruth, 2022)

The syndemic approach has only rarely been applied by medical scholars to historical contexts; for example, Sawchuk and colleagues' (2022) study of the 19th

century syndemic in Gibraltar, driven by cholera and smallpox, within the context of overcrowding, poor sanitation, and the regular influx of pathogens due to the island's strategic location. Paleopathologists have begun recognizing the value of a syndemic approach, although in depth applications are relatively limited to date (e.g., DeWitte and Wissler 2022; Larsen and Crespo, 2022; Robbins Schug and Halcrow, 2022). This is perhaps surprising given the embeddedness of this discipline within biocultural perspectives. Larsen and Crespo (2022) argue for the value of a 'paleosyndemic' lens for understanding 'how epidemics end' in the past, focusing on leprosy in Medieval Europe, and the Black Death in Europe in the 14th century. While paleopathological evidence can be especially challenging, the discipline is well placed to provide valuable insights into disease interactions and clustering within specific socio-cultural contexts and over time.

A syndemic perspective requires a deep understanding of the potential biocultural and environmental pathways involved in the clustering and comorbidity of particular diseases. Some of these factors may be invisible in the archaeological and skeletal record, and thus impossible to integrate into the model. Many bioarchaeologists, however, regularly contextualize their results within the social and natural environment and explore the antagonistic effects of co-morbid or multi-morbid diseases that could provide the basis for a syndemic approach. In addition, bioarchaeology often utilizes multi-scalar analysis through which individual life histories or osteobiographies have been used to generate population- or group-level characterizations of disease burdens in a community. Paleopathologists have frequently explored comorbid conditions and the co-occurrence of epidemics in the past, but often from the perspective of 'cumulative adversity' (Tsai, 2018). Essential components of the syndemic approach would include an analysis of the synergistic interaction of these disease processes with each other, and crucially, in concert with socio-cultural inequities.

Bioarchaeologists furthermore have called for understanding the sources of inequity that create heterogeneous experiences, risks and outcomes of disease. Intersectionality in bioarchaeology and bioanthropology seeks to construct how the interplay of identities result in systematic oppression and social inequity that impacts

biology (Blakey 2001; DeWitte and Yaussy, 2021; Dimka et al, 2022; Franklin and Wilson 2020; Torres-Rouff and Knudson 2019; Watkins 2012, 2020; Yaussy 2019). The syndemics model approaches disease much in the way intersectionality approaches inequity - more than just the sum of its parts, but instead fully embracing the "intersectional experience", (Crenshaw, 1989, p. 140), or the cumulative effects of each element that uniquely build upon and magnify the other(s). One critique of this approach argued that syndemic theory provides no additional value to that supplied by intersectionality and, worse, fails to analyze the forces creating inequity (Sangaramoorthy and Benton, 2022). These sentiments have been countered, however, by others who argue that "intersectionality-informed syndemics may offer entry into settings that perpetuate invisibilization of people with multiple identities that are subjected to forms of oppressions" (Kline, 2022). By turning away from the concept that the poor are to blame for their problems, syndemics theory "seeks to identify the role of power and structural injustices in creating pathology and recognizing how pathology can intensify inequalities and multiple forms of oppression' (Bulled et al., 2022).

Other recent theoretical innovations within medical anthropology yield further synergies with the syndemic perspectives that are applicable to disease in the past. For example, the focus on 'local biologies' (Lock 1993) underscores the simultaneously biological and cultural materiality of the skeleton, which can only be understood within its specific historical, social and ecological relationships. Linked to this, the Developmental Origins of Health and Disease (DOHaD) framework emphasizes the importance of life histories, and in particular the sensitivity of early life and inter-generational adversity for later life frailty and disease risk (Barker 2012). Intrauterine circumstances are closely linked to social and environmental variables and if maternal health is compromised via malnutrition, this can have repercussions for subsequent generations (Barker 2012, Gowland 2015). Jonathan Wells (2010) highlights the importance of 'maternal somatic capital' for interpreting links between social inequality and health, arguing that mothers living in poverty may have low 'somatic capital', leading to disadvantageous consequences for their off-spring, such as low birth weight and increased risk of chronic disease later in life. Wells (2010) refers to the transmission

of the effects of poverty across the generations in this way as a form of ‘metabolic ghetto’.

Crespo (2021) and McDade et al. (2012; 2010) note the sensitivity of the immune system to ecological and social factors during the first 1000 days of life and the impact of this for longer-term inflammatory responses. Crespo (2021) highlights the utility of a syndemics in addition to a DOHaD perspective for interpreting inflammatory skeletal responses (described as a skeletal inflammatory index - SINDEX). He argues that because of the ‘complex heterogeneous biosocial landscapes’ (2021, p. 87) there will be no uniform inflammatory model yielded by the SINDEX. Indeed, such rampant heterogeneity is observed in many paleopathological studies, such that interpreting pathological skeletal lesions can be extremely challenging. The reason, of course, is that like COVID-19 today, diseases are not landing on an equal playing field, but are interacting with bodies that have their own socio-culturally, biographically and intergenerationally subscribed biological response.

Dimka and colleagues’ (2022) provide a model for understanding differential risks in morbidity and mortality in recent historical epidemics using three different episodes as examples (the 1918 influenza epidemic, the 2009 influenza epidemic, and COVID-19). They found similar patterns but different magnitudes of heightened risk for disease by sex/gender, race/ethnicity/indigeneity, and comorbidities/disabilities across all three epidemics. They imply that this intersectional approach should be the beginning of understanding “local biologies” and interconnected variables related to health, and greater engagement with syndemic theory will move this type of investigations forward.

DeWitte and Wissler (2022) approach the 14th century Black Death in England as a syndemic, during which certain communities were disproportionately impacted by agricultural crises of the 13th and 14th centuries. This could have led to intergenerational health disparities that continued until the Black Plague epidemic, resulting in a disproportionate mortality amongst individuals of lower socioeconomic status. The survivors of the epidemic had reduced frailty and higher survivorship than pre-Black Death groups (DeWitte 2014, 2018), highlighting the long-term impacts of disparate susceptibility.

While Battles and Gilmour (2022) and Franklin and Wilson (2020) do not explicitly take a syndemics approach in their studies on ancient disease, they include a multitude of socioeconomic and other biological factors impacting disease outcomes. Battles and Gilmour (2022) focus on the after-effects of infection, providing one example of how cessation of an infection can either prolong a syndemic or initiate a new one. They focus on the experiences of polio survivors with lingering disability and the stigma they face as a result of the infection, and how these individuals may have increased mortality as a consequence. As they note this can have a group-level impact in a community.

Franklin and Wilson's (2020) research exploring the confluence of sexism, racism, economic subjugation, migration, and poverty in African American communities after emancipation and their impacts on health also closely aligns with a nuanced syndemic approach. They found that choosing to stay in the rural South versus moving to urban areas resulted in disparate patterns of morbidity and mortality reflecting the unique social, environmental, and economic contexts of each experience. Bioarchaeologists clearly recognize the compounded effects of biological and socio-economic variables on health, but often do not "close the circle" by exploring the specific pathways by which these factors result in disease clustering. Upon recognizing a cluster of diseases affecting the skeleton, a syndemics approach encourages a deeper exploration of the biological interactions between these conditions, and how local social and environmental determinants of health will further exacerbate the effects (Figure 1).

3.1 The Rickets-Tuberculosis-Poverty Syndemic in 18th and 19th Century England

Vitamin D deficiency has been implicated as a risk factor in the current COVID-19 pandemic and has been linked to the severity of the disease (e.g., Dror et al. 2022). Vitamin D therapy provided to certain groups infected with COVID, such as older adults, has improved mortality risk and disease outcomes (Annweiler et al. 2022). The mechanism behind this relationship largely lies in the impact of vitamin D on the immune system, particularly the cells involved in fighting respiratory infections. Another

example of a respiratory disease that has a synergistic relationship with vitamin D deficiency is the one caused by the *Mycobacterium tuberculosis* (MTB) complex. MTB and vitamin D deficiency are both conditions that can affect the human skeleton and have been reported on extensively in the paleopathological literature. They have been found to co-occur in some historical and archaeological contexts, particularly 18th and 19th century Britain (Donoghue, 2017; Redfern et al., 2015; Roberts et al., 2016; Roberts and Brickley, 2019; Snoddy et al. 2016). Employing a syndemic approach allows paleopathologists to better understand the underlying interactions of these two diseases, the social environment that increases poor disease outcomes, and possible undernumeration of individuals with the condition.

3.1.1 Tuberculosis (MTB)

Tuberculosis (MTB) is a droplet infection tied to mycobacteria mostly included within the *Mycobacterium tuberculosis* complex. Primary infection can occur in the lungs or the gastrointestinal system, and only a small fraction of those infected develop symptoms after initial infection (Roberts and Buikstra, 2019). The bacilli can lie latent for many years until either additional exposure or a decline in immune system functioning reactivates the pathogen, resulting in a delayed emergence of symptoms (secondary or post-primary TB). Infection with *M. tuberculosis* complex pathogens may result in the development of skeletal lesions in 3 - 5% of untreated cases (Jaffe, 1972). MTB bacilli travel to bone through the circulatory system and favor areas of hematopoietic marrow in the skeleton such as the vertebral bodies and long bone epiphyses in adults with additional foci in flat bones of the crania and diaphyses of long bones in children (Lewis, 2018; Roberts and Buikstra, 2019). The common diagnostic lesions of skeletal MTB are resorptive foci in the vertebral bodies and joint regions, with the less-specific abnormal bone formation on the pleural surface of ribs providing an additional indicator (Roberts and Buikstra, 2019).The extraction and identification of *M. tuberculosis* complex DNA in skeletal remains has provided an additional pathway to diagnosis (Harkins et al., 2015; Kerudin et al., 2019; Müller et al., 2014; Sabin et al., 2020; Zink et al., 2003), and has demonstrated that MTB diagnosis based on skeletal lesions alone undercounts the number of people infected in ancient communities.

3.1.2 Vitamin D Deficiency

Vitamin D is a prohormone critical for metabolism of the essential bone minerals calcium and phosphorus. A deficiency in vitamin D triggers the release of stored calcium from the skeleton causing osteomalacia, pseudofractures, poor bone density, and biomechanical-related shape deformities (Brickley et al., 2020). Vitamin D primarily is obtained through UVB exposure that initiates the synthesis of the vitamin from 7-dehydrocholesterol (Holick, 2007, 2005). Diet and nutritional supplements also provide a source of vitamin D for the body. Vitamin D synthesized through UVB radiation or ingested via dietary sources undergoes hydroxylation in the liver to form the circulating form of the vitamin, 25(OH)D. A second hydroxylation in the kidney by the enzyme 1-α-hydroxylase (CYP27B1) produces the active form, $1,25(OH)_2D_3$ (calcitriol), which regulates calcium and phosphate levels in the skeleton, gut, and kidneys (Chanchlani et al., 2020; Holick, 2007).

Vitamin D deficiency impacts bone mineral metabolism by increasing PTH activity that stimulates renal tubular reabsorption of calcium, increases production of $1,25(OH)_2D_3$ in the kidney, increases renal excretion of phosphorus (hypophosphatemia), and stimulates osteoblast activation (Holick, 2007). This last process triggers RANKL expression, causing preosteoclasts to transform into osteoclasts that dissolve the bone matrix to release calcium and phosphorus into the blood (Brickley et al., 2020, p. 93). Genetic polymorphisms affecting phosphorus regulation (hypophosphatemic rickets) (Bitzan and Goodyer, 2019), calcium-sensing receptors (CaSR) (Wu et al., 2017), or VDR function (vitamin D-resistant rickets) (Liberman, 2007) can also result in skeletal rickets. Many diseases and iatrogenic factors also affect the bioavailability, synthesis, or metabolism of vitamin D, such as hyperparathyroidism, celiac disease, cystic fibrosis, chronic kidney disease, or medications used to treat high cholesterol (Holick, 2007).

A “deficiency” of vitamin D clinically depends on having a serum 25(OH)D level below 30 nmol/L, and an “insufficiency" is marked by levels between 30 to 50 nmol/L (Munns et al., 2016). Vitamin D deficiency manifests skeletally in non-adults as rickets, or poorly mineralized bone subject to biomechanically-caused shape changes due to

the pull of gravity as well as connective tissue during movement (Brickley et al., 2020, pp. 97–105). Adults with active vitamin D deficiency also have bone with low mineral content (“osteomalacia”) and thinned cortices susceptible to repetitive microfractures (Brickley et al., 2020, pp. 117–121).

3.1.3 Interactions between Vitamin D Deficiency and MTB

The benefits of vitamin D and UVB radiation for management of MTB arose early in the search for its treatment. Vitamin-D-packed cod liver oil (Grad, 2004) and sunlight exposure (Roberts and Buikstra, 2003, p. 228) were important elements of the sanitarium regime in the U.S. and Britain in the 19th and 20th centuries. Current clinical research has identified vitamin D deficiency as a risk factor for tuberculosis infection, particularly pulmonary tuberculosis, and is linked to a higher bacillus load, reactivation of latent MTB, and poor disease outcomes (Aibana et al., 2019; Chocano-Bedoya and Ronnenberg, 2009; Jaimni et al., 2021; Jolliffe et al., 2017; Talat et al., 2010). MTB is held in latency by macrophage-filled granulomas that surround bacilli-infected cells, which must be maintained at some cost (Wilson et al., 2019). Failure of the granuloma results in unfettered spread of the bacilli. 1,25(OH_2)D_3 is essential for development of the antimicrobial peptide cathelicidin located in macrophages that limits the growth of MTB bacilli (Liu et al., 2007; Prietl et al., 2013) and 1,25(OH_2)D_3 prevents MTB bacilli from hindering macrophage maturation (Hmama et al., 2004; Houben et al., 2006). Maintenance of adequate vitamin D levels thus is essential for maintaining the macrophage-filled granulomas that keep the MTB bacilli in check.

Conversely, infection with granulomatous diseases such as MTB can cause interferon gamma (IFNγ) to up-regulate the VDR and 1-α-hydroxylase genes (CYP27B1), resulting in increased production of 1,25(OH_2)D_3 and hypercalcemia (Holick, 2007; Moloney et al., 2018; Sharma, 2000). This would presumably prevent worsening of vitamin D deficiency during an MTB infection. However, hypercalcemia in TB patients can result in renal failure, which has been documented in clinical settings (Rajendra et al., 2016). In addition, an individual suffering from an active MTB infection often has insufficient nutritional intake (Feleke et al., 2019), which may result in vitamin D deficiency and allows MTB to progress more quickly.

3.1.4 Environmental Contexts of Vitamin D Deficiency and MTB in 18th and 19th century England

In addition to the synergistic impacts of vitamin D deficiency and MTB on the immune system and lesion progression, demographic and environmental factors indicate why they also thrive in the same contexts. Tuberculosis often is referred to as a "disease of poverty" (Roberts and Buikstra, 2003, p. 55), with many of the social determinants of the disease linked to poor living conditions and economic inequity, usually crowded and unsanitary housing and poor nutrition (Lönnroth et al., 2009). Researchers point to social improvement and economic growth as primary factors for reduction in MTB in many regions (e.g. McFarlane, 1989; McKeown and Record, 1962), although others suggest innate immunity through successive MTB exposures across generations or acquired immunity through *Mycobacterium bovis* or other mycobacteria exposure played a role (Davies et al., 1999; Grange et al., 2001).

Vitamin D deficiency, particularly in children, also was a hallmark disease of poverty during the Industrial Revolution in England and other northern European countries. Rickets was particularly entrenched in 17th to 19th century England to the point that it was referred to by doctors as the "English disease". The combined effects of low UVB exposure due to living and working conditions, other metabolic deficiencies, and comorbid diseases created a "perfect storm" for high rates of rickets in working class urban industrial communities in Britain and the Netherlands (Ives, 2018; Mays, 2018; Mays et al., 2009; Snoddy et al. 2016; Veselka et al., 2021, 2015). Nineteenth-century British doctors noted links between the condition and early weaning, poor nutrition, bad air, northern climates (although John Snow noted it as more common in southern England, particularly London, than northern England and Scotland), and even heredity (Hardy, 2003). Domestic coal fires for heating and cooking also contributed to the extensive air pollution that blocked UVB radiation and the poor air quality sent many individuals indoors (Hardy, 2003). Thus, a multitude of environmental and social risk factors linked to poverty or low socioeconomic status are shared between vitamin D deficiency and MTB.

The interaction between vitamin D deficiency and MTB and their shared socio-economic and environmental factors resulted in a Rickets-Tuberculosis-Poverty syndemic in Industrial-era England (Figure 2). The co-occurrence of these conditions is of no surprise to a paleopathologist or bioarchaeologist, and their high comorbidity rates even led some physicians of the time to postulate TB caused rickets in children (Parry 1872). Outlining the pathways of exactly how these diseases and their risk factors intertwined provides a deeper perspective of the impacts on communities in urban 18th and 19th century England. In addition, it highlights that MTB cases based on paleopathological evidence alone are likely undercounted, a methodological issue already highlighted by recent aDNA research. In addition to the undernumeration of MTB victims based on skeletal lesions alone, skeletal rickets, located at one extreme end of the spectrum of vitamin D deficiency symptoms, may be the “potential tip of an unseen epidemiological iceberg” (Snoddy et al. 2016, p. 193). The environmental factors present in this context, and the known interactions between these conditions, also support the likelihood that MTB and rickets were both pervasive conditions in

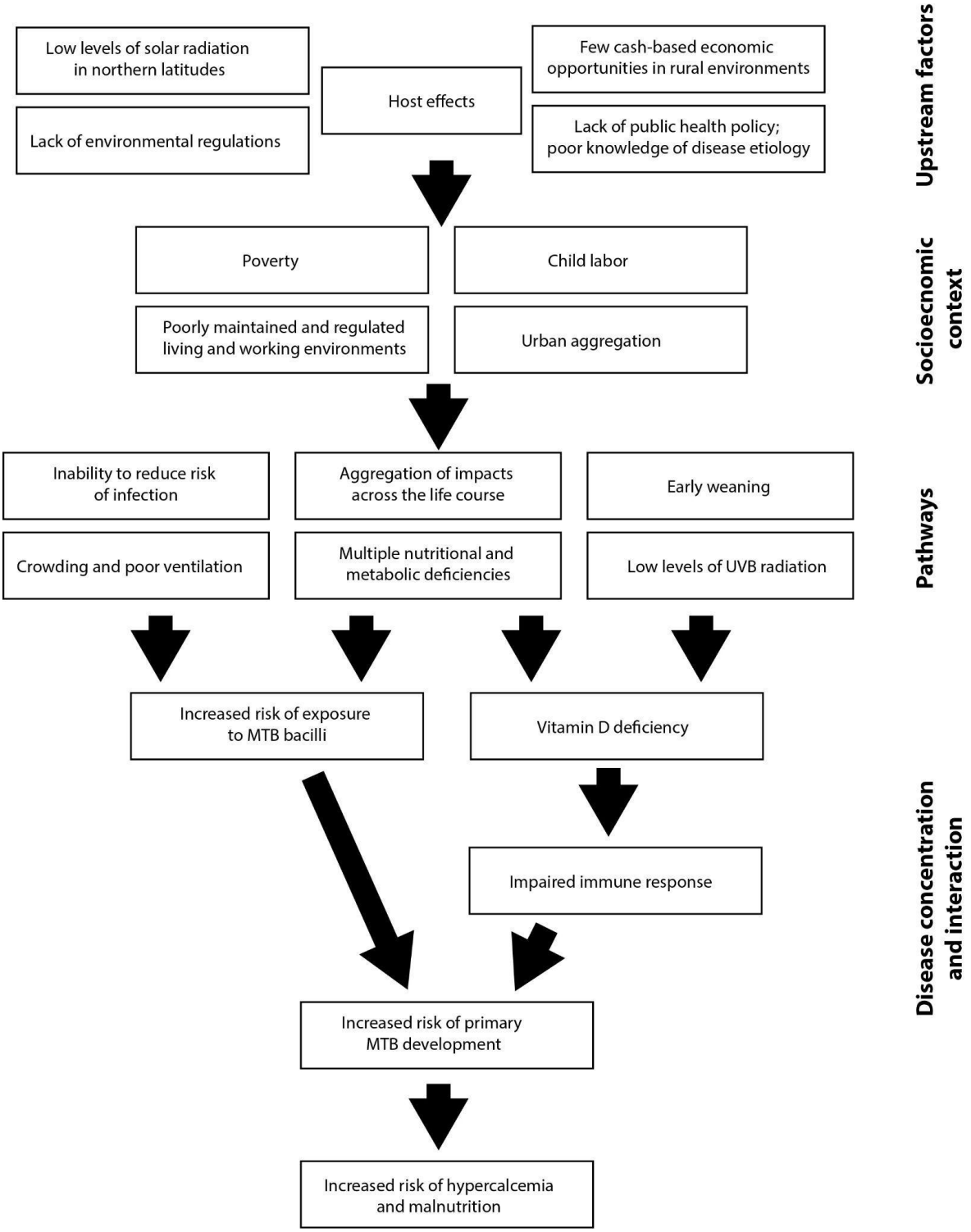

Figure 2: The Rickets-MTB syndemic in 18th and 19th century England (organization based on Gravlee 2020)

particular socioeconomic and environmental contexts and should be treated as a syndemic. The syndemic approach then can be used to build a model of disease interaction and biocultural contexts in antiquity against which to assess the available paleopathological data and identify additional factors perhaps reducing the synergistic effects or illuminating methodological limitations (as illustrated in Figures 1 and 2).

The longer-term and intergenerational effects of both conditions heighten their impact in this context. Vitamin D-deficient pregnant women have increased risk for pregnancy complications such as eclampsia, preterm births, low birth weight babies, and gestational diabetes (Hollis and Wagner, 2017; Lucas et al., 2008). Maternal and newborn 25(OH)D levels tend to be correlated, and vitamin D deficient mothers give birth to babies with lower vitamin D levels than normal (Lee et al., 2007; við Streym et al., 2013). Epigenetic effects of vitamin D deficiency during critical intrauterine periods may be implicated in abnormalities in lung, bone, liver and immune system development and increased risk of Type 1 diabetes (see Ideraabdullah et al., 2019; Zhu et al., 2016).

In addition to skeletal rickets, infants with vitamin D deficiency have risk for seizures and convulsions (tetany), delayed motor skills, hyperparathyroidism, underdeveloped musculature, anemia, and even cardiomyopathy or failure (see Pettifor et al., 2018). Longer term effects of infant deficiency in vitamin D include impaired immune functioning, persistent hyperparathyroidism, reduced kidney functioning, inhibited expression of vitamin D receptors (VDRs), and an increased risk of Types 1 and 2 diabetes, obesity, some cancers, neurological and behavioral disorders, cardiovascular diseases, or multiple sclerosis (Hollis and Wagner, 2017; Ideraabdullah et al., 2019; Jensen et al., 2017; Lucas et al., 2008; Pettifor et al., 2018; Reichetzeder et al., 2014). Some infants whose mothers were vitamin D deficient during pregnancy may not experience its impacts until well after birth. Tetany, convulsions, or cardiac issues can emerge up to 6 months of age in these infants (Pettifor and Prentice, 2011), and can have lower than expected bone mineral density from later in infancy through to adulthood (Javaid et al., 2006; Viljakainen et al., 2011; Zhu et al., 2014).

MTB infection during pregnancy also increases the chance for poor outcomes of the mother and fetus. Women with active TB infections have a much higher risk of developing anemia during pregnancy, or having a miscarriage or perinatal death,

preterm birth, low birth weight infant, or distressed fetus (Miele et al. 2020). In addition, women with latent TB are more likely to develop active infections after giving birth, likely due to the immunological changes that occur with pregnancy (Miele et al. 2020). Congenital TB, while rare, is still a possibility, and breastfeeding may transmit the bacilli from mother to infant (Flores et al. 2021). Results from studies exploring the increased risk of infants with vitamin D deficiency developing TB are mixed (Martinez et al. 2022).

In 18th and 19th century England, this cycle of infection and deficiency would have contributed to the perpetuation of ill health that characterized many urban environments at the time based on textual data. The intergenerational impact meant that unless the social and environmental determinants of the syndemic shifted, the syndemic would continue. Acceptance of the nutritional foundations of rickets in the early 20th century resulted in a temporary reduction in cases in most regions in England. Similarly, the discovery of the TB bacillus, the development of antibiotics such as penicillin, recognition of living conditions leading to increased transmission, and possibly slight commensalism through repeated infections resulted in a decline in the incidence of active TB cases around the same period. Since then, both diseases experienced a resurgence, rickets in the 1960s with the arrival and subsequent marginalization of immigrants from former British colonies (Bivins 2014; Zhang et al. 2016), and TB in the 1980s with immigration from TB-prevalent countries and the rise of HIV/AIDs (Pealing et al. 2013). Despite the reemergence of these conditions, the sociocultural and economic frameworks of these diseases have changed dramatically from the late 19th century, highlighting that the context rather than the presence of disease(s) alone is fundamental to the syndemic concept (Singer et al. 2022).

3.2 The Malaria and Gastrointestinal Parasite Syndemic in Early Medieval England

The current climate crisis is a key factor affecting human health globally, resulting in reemerging infectious diseases, food shortages, fire, floods, damage to housing and infrastructure, population movement and overcrowding. As Singer and colleagues' (2021, p. 8) note, there is "no single climate change syndemic, there are, however, multiple climate change syndemics requiring responses that are informed by locally

grounded assessments". The discipline of bioarchaeology is well-placed to contribute to a deeper understanding of human/environment/pathogen interactions in response to a range of climatic fluctuations over time, and this is a growing disciplinary focus (e.g. Robbins Schug, 2021). One disease that features prominently in concerns around climate change is malaria: an infectious disease with one of the highest morbidity and mortality rates in the world today. Malaria is caused by the mosquito-borne eukaryotic protozoan parasites of the genus *Plasmodium* (*Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium malariae*, and *Plasmodium ovale*). In many parts of the world malaria, helminths and *Giardia* are endemic in the same areas and are often co-morbid (Geus et al., 2019). Malaria and helminth/*Giardia* parasite syndemics today have been linked to climatic shifts, living conditions, subsistence strategies, and low socio-economic status. Here we revisit an analysis of *Plasmodium vivax* malaria in Eastern England during the early Medieval period by Gowland and Western (2012) using a syndemic approach to better understand the social determinants and the potential impact of synergistic co-morbidities. In addition to the early medieval data, we draw upon clinical information relating to: recent and current helminth/*Giarda*/malaria syndemics; evidence for the higher than expected fatalities from *Plasmodium vivax* recorded in historical documents from England in the 18th to 19th centuries; and the unique social/ecological milieu of the Fenlands.

3.2.1 Malaria

Much has been done to tackle malaria over the last 20 years, resulting in a halving of mortality from malaria during this time. The World Health Organization's Annual Malaria Report from 2021, however, reported an increase in malaria cases (estimated 241 million) and deaths (estimated 627,000) during 2020 (WHO Malaria Program, 2021). Disruption associated with COVID-19 was a primary cause of this increase, despite efforts to mobilize relief in anticipation of the effects of the pandemic on vital services. A number of authors have highlighted the syndemic interaction between COVID-19 and malaria transmission potential in a number of countries in sub-saharan Africa where malaria is endemic (Shi et al. 2021, Velavan et al. 2021). The symptoms of malaria can also, to some degree, overlap with those from COVID-19, leading to diagnostic

complications and under-reporting of co-infections of both diseases (Velavan et al. 2021). The profound effect of COVID-19 on malaria mortality highlights the fragile nature of such hard-fought progress in tackling this disease and the need for persistent and holistic strategic health interventions in the face of changing climate and disease ecologies.

Bioarchaeological studies are well-placed to provide longer-term perspectives on malaria prevalence and syndemics over time and in relation to climatic fluctuations, land management strategies and cultural change. There has been a growing interest in the historical and bioarchaeological evidence for malaria over the last two decades (e.g. Sallares 2002; Scheidel 2003; Soren 2003; Gowland and Garnsey 2010, Gowland and Western 2012, Smith-Guzmán 2015, Smith-Guzmán et al., 2016, Newfield 2017, Marciniak et al. 2018, Kendall et al. 2020). Such work is hindered, however, by the fact that malaria leaves no specific diagnostic skeletal lesions and historical evidence is slim and often vague (Newfield 2017). Direct evidence in the form of pathogenic aDNA evidence of *P*. *falciparum* malaria has been recovered from archaeological skeletons (e.g. Sallares and Gomzi 2001, Marciniak et al. 2016, Loufouma Mbouaka et al. 2021). These studies have great value in terms of confirming the presence of malaria and understanding the particular biosocial pathways of infection (Marciniak et a. 2018). Ancient DNA analyses, as well as immunological assay's to detect antigens associated with malaria (Loufouma Mbouka et al. 2021), are increasingly important to the study of malaria in the past. However the destructive and expensive nature of such techniques mean that they are currently limited in terms of insights into the overall burden of disease and its broader epidemiology.

While malaria leaves no diagnostic skeletal lesions, it is known to be a major cause of anemia in malaria endemic regions (Shankar 2000, Rodriguez-Morales et al., 2006; Douglas et al. 2012). *Plasmodium vivax* (endemic in temperate as well as tropical climates) has been associated with more frequent and severe cases of anemia than the more fatal *Plasmodium falciparum* (present in more tropical climes). *Plasmodium vivax* results in functional and structural impairment of erythrocytes of infected people (Rodriguez-Morales et al. 2006). There is an established link between malaria, haemolytic anemia and subsequent marrow hypertrophy, thus producing lesions known

as cribra orbitalia (CO) and porotic hyperostosis (PH) in the skeleton (Gowland and Western 2012). These conditions have multiple etiologies, therefore context is essential to interpreting the epidemiology of both. Paleopathological studies of malaria have relied upon integrating environmental, historical and clinical evidence for malaria endemicity, with skeletal indicators of anemia (CO and PH). For example, Gowland and Western (2012) and Smith Guzmán (2016) found correlations between habitats that were known breeding grounds for the mosquito vector in the past and high frequencies of cribra orbitalia. Malaria has long been recognised to exist alongside a range of comorbidities that can also produce anemia and associated skeletal lesions, but bioarchaeological analyses have yet to examine these interactions using a syndemic framework. For example, co-infection with parasites such as helminths is known to contribute to the burden of anemia (e.g. Webb et al. 2020). The multiplied effects of co-infection results in a cycle of poor health from which it is difficult to recover, particularly in marginalized social and environmental contexts.

3.2.2 Interactions between helminth and malaria infections

Clinical studies have shown the detrimental impact of co-infection with parasites such as hookworm and malaria in a way that aligns with syndemic principles (Adegnika and Kremsner 2012). For example, Webb (2020) discusses the malaria/hookworm syndemic amongst Chinese and Tamil laborers in British Malaya in the early 20th century. Here, sanitation issues were a key factor in hookworm infestation, while insufficient drainage exacerbated malaria infection: medical investigators were unable to differentiate between anemia caused by either hookworm or malaria (Webb, 2020, 3). These comorbidities each resulted in anemia as part of their own pathological process, and interacted with and mutually enhanced the deleterious effects of the other parasites (Anstey *et al* 2009:222; Echeverri *et al*. 2003).

Fernandez (2008, 2) noted that working in contact with the soil in rural agricultural areas with endemic malaria (conditions similar to the early medieval Fenlands) carries a greater risk of both malaria and geohelminthiases. Co-infection with malaria and helminths is extremely common in tropical and subtropical regions of the world today (Jepkogei et al. 2016, Geus et al. 2019). One clinical study revealed that

amongst 0-14 year-old children with vivax malaria, 71% exhibited intestinal parasitic infections and 100% of those with helminthiasis were anemic (Da Silva et al. 1999). In wetland areas fish consumption is an important source of dietary protein and if undercooked is a known source of parasitic infections. For example, the helminth *Diphyllobothrium latum* is common in areas of river catchment drainages or lacustrine communities (Dick *et al*. 2001: 67, Peduzzi and Boucher-Rodoni 2001:44). Additionally, *Giardia lamblia* is a parasitic infection associated with contaminated water supplies from rivers and lakes (Stuart *et al* 2003). Transmission of the disease occurs through ingestion of the infective, water-borne *Giardia* cysts, which can originate from feces of humans, livestock and wild animals. Infection by either of these parasites has been identified by Walker *et al* (2009:110, 114-115) as directly causing megaloblastic anemia and thus may result in *cribra orbitalia* lesions in skeletal remains that would have compounded the anemia of chronic disease associated with vivax malaria.

This interaction is complex, for while hookworm, for example, has a deleterious impact on the pathogenesis of malaria, some helminths such as *Ascaris lumbricoides* may actually provide protection against the disease (Adegnika and Kremsner 2012). In addition, malaria infection stimulates the production of pro- and anti-inflammatory cytokines such as tumor necrosis factor alpha. Chronic helminth infections stimulate a type 2 and anti-inflammatory immune response that can modulate the high inflammatory cytokine output in response to a vivax malaria infection (Hartgers and Yazdanbakhsh 2006; Mishra et al. 2014). However, chronic infection increases the appearance of clinical malaria, particularly early in the disease process. In addition, acute helminth infections have a deleterious effect on the pathogenesis of vivax (Hartgers and Yazdanbakhsh 2006). Finally, it is their dual impact on anemia that results in higher morbidity and mortality. It is the ‘multiplicative, not just additive, effects’ (Gravlee 2020, 5) of these disease interactions and their shared context that results in increased lethality of malaria and falls within scope for a true syndemic.

3.2.3 Malaria in the Wetlands of England

Historical and clinical evidence attests to the presence of endemic malaria in the form of *Plasmodium vivax* in the wetlands of Eastern England from at least the 17th century. In

her seminal study, Mary Dobson (1997) noted that the late summer/early autumn seasonal mortality peaks in the wetlands coincided with the life cycles of both the *Anopheles atroparvus* mosquito vector and the *Plasmodium vivax* parasite. The origins of malaria in England are debated, although its presence may date to the Roman occupation (1st to the early 5th centuries AD), introduced from the Mediterranean and other regions where the disease was rife (see Newfield 2017, Bankoff 2018). During the Roman period in Britain, exploitation of the rich resources of the wetlands increased, aided through the development of land reclamation infrastructure including drains, canals and causeways (Rippon 2000). An unintended consequence, however, was the creation of stagnant pools of brackish water in coastal marshes and fens, which provided an optimum breeding ground for the *Anopheles atroparvus* vector of malaria (Kuhn et al. 2003).

Prior to the 19th century, malaria in Britain was variously referred to as ‘marsh fever’, ‘Fen ague’, ‘spring fever’ or ‘tertian fever’ (Dobson 1997). Earlier historical descriptions of ‘ague’ closely align with the symptoms and progress of malaria caused by *Plasmodium vivax*, which is characterized by intermittent and relapsing fevers, which can reoccur for several years (Reiter 2000). Early twentieth century blood samples provided unequivocal evidence of *Plasmodium vivax* in Fenland dwelling ‘ague’ sufferers. Vivax malaria is generally held to be less fatal than *Plasmodium falciparum* but unlike the latter can survive and thrive in temperate parts of Europe. There was a sharp decline in malaria in Britain during the latter half of the 19th century in England, attributed to improved living conditions and land drainage (James 1929, Shute and Maryon 1974, Reiter 2000, Hutchinson and Lindsay 2006).

The early medieval period (AD500-1000) in Britain heralded some climatic fluctuation, including periods of rising sea levels. The earlier Roman drainage systems would have been overwhelmed, resulting in flooding of areas of the coastal wetlands (Cracknell 2005, Rippon 2000). As Gowland and Western (2012) discuss, this would have created an environment in which the anopheles mosquitoes could thrive. Far from abandoning this land during the post-Roman period, there is evidence for continued exploitation of the rich natural resources of the wetlands (Higham 2010). People living in this area likely experienced a seasonally transient existence to optimize subsistence

strategies (Rippon 2002). Housing consisted of simple earthen-floored, wooden structures, and during the winter months the inhabitants would have shared parts of these modest dwellings with their livestock. They were not alone: one of the mosquito vectors of malaria, *Anopheles atroparvus*, is also known to over-winter within houses, thus often infecting multiple inhabitants of the same household (Reiter 2000, Serandour *et al*. 2007). Livestock would have been the preferred blood meal, but if humans are in close proximity then they too are at risk of being infected.

Gowland and Western (2012) found that those areas of the Fenlands associated with malaria in the past (identified via historical records of 'ague' and the presences of anopheles) were 'hotspots' for cribra orbitalia in the early Medieval period. They concluded that malaria was a contributing factor to the high levels of anemia observed. In a later study, Kendall et al (2020) undertook incremental dentine stable isotope analysis of individuals excavated from an early medieval site in the Fens (Littleport, Ely) where, according to Gowland and Western's (2012) analysis, malaria was likely to have been present. Kendall and colleagues (2020) found evidence of significantly higher levels of *cribra orbitalia* compared to a nearby and contemporaneous site (Edix Hill, Cambridgeshire) where malaria was not endemic. They also found much higher levels of opposing covariance in the δ13 carbon and δ15 nitrogen isotope values (δ15 nitrogen increases and δ13 carbon decreases) from the site of putative malaria endemicity when compared to the 'non-malarial' site (Figure 2). Opposing covariance in these isotopes is associated with physiological stress such as starvation (Beaumont and Montgomery 2016) but other forms of stress, such as parasite infection, may produce this effect (Kendall et al. 2020, Kendall and Kendall 2021). This supports the argument that the malarial environment contributed to a complex of stressors, placing the population under significant health strain.

3.2.4 Social Determinants of Malaria in the Wetlands

The 9th century medical text Bald's Leechbook refers to 'spring fever' – a malaria-type disease manifesting seasonally (Bruce-Chwatt 1976, Cameron 1993). The wetlands of Eastern England during the early medieval period were often described as inhospitable, and ascribed supernatural characteristics (Gowland and Western 2012,

Kendall and Kendall 2021). They were the subject of numerous myths and the inhabitants of these damp and misty places were often characterized as 'other'. For example, the monk Felix recorded that St. Guthlac, who lived in the Lincolnshire marshes in the 8th century AD, was forced to ward off supernatural attacks upon his

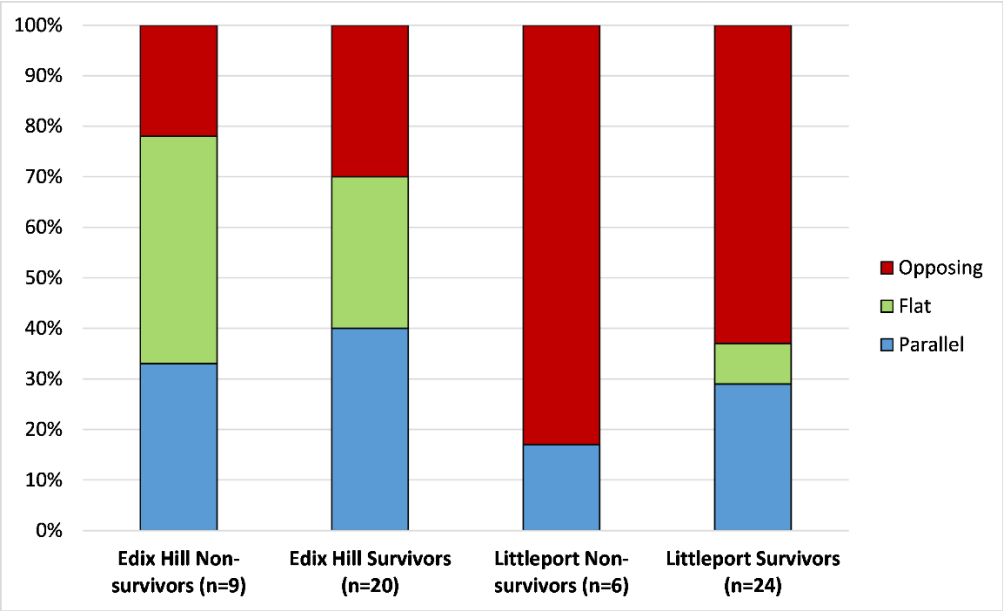

Figure 2: Opposing covariance in the δ13 carbon and δ15 nitrogen isotope values from Littleport (malarial) and Edix Hill (non-malarial) (copyright Ellen Kendall).

person (Colgrave 1985). These 'attacks' involved extremes of bodily temperature, which could possibly represent fever-induced hallucinations associated with malaria. As Felix records "*No settler had been able to dwell alone in this place…on account of the phantoms of demons which haunted it"* (Colgrave, 1985: 89).

The specificity of local knowledge and skills required to successfully exploit the wetland areas, in combination with local disease ecologies, including malaria, likely contributed to this 'othering' of Fenlanders (Kendall and Kendall 2021). It is worthwhile considering the entanglement of local biologies and the marginalization of Fenlander identities in these uniquely challenging environments. Gowland et al. (2018) argued that these marginal environments forged distinctive cultural identities that manifested as localized variations in the material culture assemblages associated with the early medieval period in the Fens. This marginal view of Fenlanders persists in numerous historical records, most notably in first-hand accounts by authors such as Daniel Defoe

in the early 18th century, and is an attitude that continues to this day (Kendall and Kendall 2021). Such 'othered' identities are important to consider within a syndemic framework as social isolation and constrained social capital are significant in creating a cluster of risk factors, which in this instance are derived from the unique environmental, cultural and biological milieu. This is evidenced in 19th century medical accounts of Fenlanders, which allude not only to malaria but also the inadequate diet, parasites and general poor health of the inhabitants (Nicholls 2000).

Vivax malaria has widely been considered a non-lethal form of malaria, with a current fatality rate of approximately 0.01% (Phyo et al. 2022). The fatality of vivax malaria in Britain is well-attested from mortality records (Dobson 1994) and early clinical studies. For example, James (1929) suggests a fatality as high as 10-12% for malaria in the late 19th century wetlands, based on his direct experience treating patients with the disease. It is worth noting that this figure was likely higher for the preceding period, because malaria was already in decline during the time of James' work. The lethality of this condition in the Fens have led others to suggest that the cause of death was instead more likely to be gastrointestinal in origin rather than malarial (Hutchinson and Lindsay 2006). Clinically, the synergistic interaction between malaria and nutritional insufficiencies, helminths and *Giardia* infections, as well as other infectious diseases, have been observed to thrive in the type of basic housing and unsanitary conditions that were present in the medieval and post-medieval fenlands (Chang and Stevenson, 2004; Anstey *et al*., 2009). The syndemic interaction between malaria and other comorbidities for the Fenland region are likely to have had an additive impact on the lethality of this disease, particularly within the context of poor living conditions and social exclusion.

Crucial to the syndemic interpretation in the early medieval Fenlands is that both helminth and malaria infections were driven by social determinants, including nutritional insufficiency, living conditions and subsistence patterns. Strong parallels can be drawn with the hookworm/malaria described in British Malaya discussed above (Webb 2020). Infection with *Plasmodium vivax*, whilst not necessarily fatal on its own, would have presented as relapsing fevers that would have been debilitating for several years. If contracted alongside existing gastrointestinal parasite infections, then the chance of fatality is much higher, and this likely contributed to the increased mortality in the

malaria endemic parts of the wetlands recorded by Dobson (1997) in post-medieval England.

Another relevant factor to consider in relation to malaria syndemics is the Developmental Origins of Health and Disease hypothesis. Pregnant women are more susceptible to malaria infection, particularly during the first half of pregnancy. Pregnant women and young children are also especially vulnerable to harmful clinical impacts of the disease (Singer 2013, Phyo et al. 2022). Infection during pregnancy adversely affects developing infants, resulting in higher mortality and infants born small for gestational age (SGA) (Chang and Stevenson 2004, Lindsay et al. 2000, Levy et al. 2005, Singer 2013). The impact of malaria on mortality in infancy and early childhood has been noted in a number of bioarchaeological studies. For example, Sallares and colleagues' (2004) describe the 5th century infant cemetery at Poggio Gramignano, Umbria, where the aDNA of *P. falciparum* was retrieved from skeletal remains: of the 47 infants recovered, 22 were thought to have been either premature or SGA. Kendall and Kendall (2021) likewise discuss the anomalously high levels of infant mortality in the post-medieval Fenlands, arguing that this was likely due to the risk of being born SGA to a mother infected with malaria and/or direct infection via the *anopheles* vector. The effects of comorbidities in pregnancy, such as between helminths and malaria, provide additional challenges for the mother and her infant. In Africa, malaria and helminths are considered infectious syndemics, with particular susceptibility and risks for pregnant women (Jepkogei et al. 2016). The early and post-medieval Fenlands provide likely environments for this to likewise have been the case.

The impact of local disease ecologies can therefore affect health even prior to birth, contributing to the very high levels of infant and child mortality recorded historically for the Fenland region and inherent frailties in those who survived to adulthood (Dobson 1997). Slagboom et al. (2022) discuss the intergenerational impacts of 'syndemic vulnerability' in a former fishing village in the Netherlands through a combination of shared exposure to social inequities and the clustering of interactive diseases and health conditions. In the Netherlands, these conditions led to early onset of disease and significantly lower life expectancy and increased disease risk, even in offspring removed from the direct effects of historical adversity experienced by their grandparents.

Slagboom et al. (2022, pg. 7) define syndemic vulnerability as “a predisposition to the development of clustering and interacting diseases or health conditions that results from shared exposure to a set of adverse social conditions”. These observations align with the Developmental Origins hypothesis, and can readily be applied to the historical data from the Fenlands. Here, the impacts of malaria and gastrointestinal parasite exposure, in concert with social marginalization, created intergenerational vulnerabilities that resulted in markedly higher mortality, as noted in historical documents for the post-medieval period (Dobson 1997). Research by Kendall et al. (2020) strongly suggests that similar health stresses were felt during the early medieval period too, evidenced both in terms of skeletal pathologies and opposing covariance in the Nitrogen and Carbon isotope data.

The impact of the social and ecological determinants of health within the Fenland regions, and the resulting syndemic interaction between these and various gastrointestinal parasitic infections, likely contributed to the cribra orbitalia hotspots observed by Gowland and Western (2012). It is helpful to reflect on the skeletal evidence as more than just the outcome of comorbidities, but instead as a malaria/helminth syndemic, closely tied to the specific societal and ecological constraints of those living within these unique environments. A syndemic perspective in this context has facilitated a deeper understanding of the likely role of helminths and giardiasis in terms of both general health stress and the lethality of the *Plasmodium. vivax* malaria endemic. Through the incorporation of a DOHaD perspective the syndemic vulnerability of the local population and intergenerational adversity in health can be more easily understood. This unique socio-ecological niche served to forge particularized Fenland identities, which compounded the marginalization of these inhabitants. This, in turn, contributed to the persistence of conditions which exacerbated the impact of this clustering of diseases. The decrease in lethality of vivax from the late 19th century may well illustrate what happens when some of the syndemic drivers are removed. The improvement in land management/drainage and living conditions in the Fenland areas at this time, resulted in a documented reduction in both the prevalence and mortality risk from malaria (Dobson 1997). Bioarchaeological studies, therefore,

have the potential to provide longer-term insights into syndemics when one or more of the contributing factors are ameliorated.

4.1 Conclusions

Paleopathological and bioarchaeological research is primed to adopt a syndemic approach, as noted by Crespo and Larsen (2022) and Robbins Schug and Halcrow (2022). Methodological (e.g. paleogenomic and immunological studies) and theoretical (e.g. DOHaD, intersectional and local biologies/disease ecologies) developments have created a more grounded and contextualized paleopathology that goes beyond diagnosis to explore how diseases emerge and are maintained in ancient communities. Singer and colleagues (2021) note a critical yet often missing factor of syndemic applications is the lack of clearly establishing a true relationship between the diseases and understanding *how* they interact. In other words, what would happen to the syndemic if one of the elements was alleviated or resolved? Bioarchaeological studies have an advantage, as they can provide a longer-term perspective to view how disease prevalence alters when specific social or environmental factors change (e.g. improved drainage of the wetlands and better housing led to a drastic reduction in deaths from the malaria syndemic). Singer and colleagues (2021) also argue for the importance of establishing syndemic pathways beyond just identifying co-occurrence or the presence of deleterious social or economic variables. Likewise, a deeper time perspective may help to illuminate such pathways in some instances.

The empirical-based understanding of synergism and interaction between disease and social factors in many ancient contexts may in some situations be limited to a theoretical construct. However, paleopathologists have the tools to identify many of the synergistic elements of past syndemics, and this approach has the potential to provide new perspectives on past health, whilst also informing present-day syndemic interactions. The syndemic approach delves deeper into the lived experiences of people in the past, how their quality of life is impacted by the environmental and political-economic change, and perhaps how and whether a past syndemic ever ended. The embedded nature of the syndemic concept provides a complementary framework for

paleopathologists working within a biocultural theoretical approach. It provides an approach that encourages the more seamless integration of the pathophysiology of diseases and comorbidities with a deeper understanding of the social determinants of health. Information on the social lives of these communities and their lived experiences become re-centered alongside, not superseded by the scientific study of their biology, as recommended by Lans (2021).

SARS-Cov-2 laid bare the embedded inequalities that exist in seemingly egalitarian epidemic situations and how this manifests biologically and socially in humans. Syndemic elements might not all manifest in one individual, however, their endemic presence can rupture a community and create instability that reverberates inter-generationally. The syndemic framework helps us better understand the heterogeneity of disease through human history and how local biologies are entrenched in wider power structures, and why those who are most marginalized suffer such adverse health outcomes.

References Cited:

Adegnika A.A., Kremsner P.G. 2012. Epidemiology of malaria and helminth interaction: a review from 2001 to 2011. Curr Opin HIV AIDS 7(3):221-4.

Ahmad, T., Drummond, R., Bosworth, M., 2022. Updating ethnic contrasts in deaths involving the coronaviruses (COVID-19), England: 10 January 2022 to 16 February 2022. Office for National Statistics, United Kingdom.

Aibana, O., Huang, C.-C., Aboud, S., Arnedo-Pena, A., Becerra, M.C., Bellido-Blasco, J.B., Bhosale, R., Calderon, R., Chiang, S., Contreras, C., Davaasambuu, G., Fawzi, W.W., Franke, M.F., Galea, J.T., Garcia-Ferrer, D., Gil-Fortuño, M., Gomila-Sard, B., Gupta, A., Gupte, N., Hussain, R., Iborra-Millet, J., Iqbal, N.T., Juan-Cerdán, J.V., Kinikar, A., Lecca, L., Mave, V., Meseguer-Ferrer, N., Montepiedra, G., Mugusi, F.M., Owolabi, O.A., Parsonnet, J., Roach-Poblete, F., Romeu-García, M.A., Spector, S.A., Sudfeld, C.R., Tenforde, M.W., Togun, T.O., Yataco, R., Zhang, Z., Murray, M.B., 2019. Vitamin D status and risk of incident tuberculosis disease: A nested case-control study, systematic review, and individual-participant data meta-analysis. PLOS Medicine 16, e1002907. https://doi.org/10.1371/journal.pmed.1002907

Annweiler C, Beaudenon M, Gautier J, Gonsard J, Boucher S, Chapelet G, et al. (2022) High-dose versus standard-dose vitamin D supplementation in older adults with COVID-19 (COVIT-TRIAL): A multicenter, open-label, randomized controlled superiority trial. PLoS Med 19(5): e1003999. https://doi.org/10.1371/journal.pmed.1003999

Anstey, N.M., Russell, B., Yeo, T.W., Price, R.N. 2009. The Pathophysiology of vivax malaria. Trends in Parasitology 25 (5): 220-227.

Appleby, J. 2019. Osteobiographies: Local Biologies, Embedded Bodies, and Relational Persons. Bioarchaeology International 3 (1): 32–43

Agarwal, S. C. 2016. Bone morphologies and histories: Life course approaches in bioarchaeology. *American Journal of Physical Anthropology*, *159*(Suppl 61), S130–S149.

Baer, H.A., Singer, M., Johnsen, J.H., 1986. Toward a critical medical anthropology. Social Science & Medicine 23, 95–98. https://doi.org/10.1016/0277-9536(86)90358-8

Baker, B. J., & Agarwal, S. C. 2017. Stronger together: Advancing a global bioarchaeology. *Bioarchaeology International*, *1*(1-2), 1–18.

Bambra, C., Lynch, J., Smith, K.E., Pickett, K., 2021. Pale rider, in: The Unequal Pandemic, COVID-19 and Health Inequalities. Bristol University Press, pp. 13–34. https://doi.org/10.2307/j.ctv1qp9gnf.9

Bambra, C., Riordan, R., Ford, J., Matthews, F., 2020. The COVID-19 pandemic and health inequalities. J Epidemiol Community Health 74, 964. https://doi.org/10.1136/jech-2020-214401

Bankoff, G. 2018. Malaria, water management, and identity in the English lowlands. Environmental History, 23(3), 470-494. https://doi.org/10.1093/envhis/emx137

Barker, D. J. P. 2007. “The Origins of the Developmental Origins Theory.” Journal of Internal Medicine 261 (5): 412–17.

Barker, D.J.P. 2012. Developmental origins of chronic disease Public Health, 126 (3), 185-189. https://doi.org/10.1016/j.puhe.2011.11.014.

Battles, H.T., Gilmour, R.J., 2022. Beyond mortality: survivors of epidemic infections and the bioarchaeology of impairment and disability. Bioarchaeology International 6, 23–40.

Beaumont, J. and Montgomery, J. 2016 The Great Irish Famine: Identifying Starvation in the Tissues of Victims Using Stable Isotope Analysis of Bone and Incremental Dentine Collagen, *PloS one*, 11(8), p. e0160065.

Bitzan, M., Goodyer, P.R., 2019. Hypophosphatemic Rickets. Pediatric Clinics of North America 66, 179–207. https://doi.org/10.1016/j.pcl.2018.09.004

Bivins, R., 2014. Ideology and disease identity: the politics of rickets, 1929-1982. Medical Humanities 40, 3–10.

Blakey, M.L., 2001. Bioarchaeology of the African Diaspora in the Americas: Its Origins and Scope. Annu. Rev. Anthropol. 30, 387–422. https://doi.org/10.1146/annurev.anthro.30.1.387

Brickley, M.B., Ives, R., Mays, S., 2020. Bioarchaeology of Metabolic Disease, 2nd edition. ed. Academic Press, San Diego. https://doi.org/10.1016/B978-0-08-101020-4.00016-1

Brown, H., Nading, A.M., 2019. Introduction: Human Animal Health in Medical Anthropology. Medical Anthropology Quarterly 33, 5–23.

Brown, P.J., Inhorn, M.C., Smith, D.J., 1990. Disease, ecology, and human behavior, in: Sargent, C.F., Johnson, T.M. (Eds.), Medical Anthropology: Contemporary Theory and Method. Praeger, Westport, CT, pp. 183–218.

Bruce-Chwatt L J. 1976. Ague as malaria. The Journal of Tropical Medicine and Hygiene 79: 168-176.

Bulled, N., Singer, M., Ostrach, B., 2022. Syndemics and intersectionality: A response commentary. Social Science & Medicine 295, 114743. https://doi.org/10.1016/j.socscimed.2022.114743

Cameron ML. 1993. Anglo-Saxon Medicine. Cambridge: Cambridge University Press.

Centers for Disease Control, 2022. Risk for COVID-19 Infection, Hospitalization, and Death by Race/Ethnicity [WWW Document]. Risk for COVID-19 Infection, Hospitalization, and Death By Race/Ethnicity. URL https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/hospitalization-death-by-race-ethnicity.html (accessed 4.8.22).

Chanchlani, R., Nemer, P., Sinha, R., Nemer, L., Krishnappa, V., Sochett, E., Safadi, F., Raina, R., 2020. An Overview of Rickets in Children. Kidney International Reports 5, 980–990. https://doi.org/10.1016/j.ekir.2020.03.025

Chang K-H, Stevenson MM. 2004. Malarial anemia: mechanisms and implications of insufficient erythropoiesis during blood stage malaria. *International Journal for Parasitology* 13-14: 1501-1516, 1572.

Chocano-Bedoya, P., Ronnenberg, A.G., 2009. Vitamin D and tuberculosis. Nutrition Reviews 67, 289–293. https://doi.org/10.1111/j.1753-4887.2009.00195.

Colgrave, B. 1985. Felix's Life of Saint Guthlac: Texts, Translation and Notes: Cambridge University Press.

Craddock, S., Hinchliffe, S., 2015. One world, one health? Social science engagements with the one health agenda. Social Science & Medicine 129, 1–4. https://doi.org/10.1016/j.socscimed.2014.11.016

Cracknell, B. 2005. *Outrageous Waves: Global Warming and Coastal Change in Britain through Two Thousand Years.* The Cromwell Press, Wiltshire.

Crenshaw, K., 1989. Demarginalizing the intersection of race and sex: a Black feminist critique of antidiscimination doctrine, feminist theory and antiracist politics. The University pf Chicago Legal Forum 1989, 139–167.

Crespo, F.A., 2021. Reconstructing immune competence in skeletal samples, in: Cheverko, C.M., Prince-Buitenhuys, J., R., Hubbe, M. (Eds.), Theoretical Approaches in Bioarchaeology. Routledge, London, pp. 75–92.

Davies, R.P.O., Tocque, K., Bellis, M.A., Rimmington, T., Davies, P.D.O., 1999. Historical declines in tuberculosis in England and Wales: improving social conditions or natural selection? [Unresolved Issues]. The International Journal of Tuberculosis and Lung Disease 3, 1051–1054.

DeWitte, S., Slavin, P., 2013. Between Famine and Death: England on the Eve of the Black Death—Evidence from Paleoepidemiology and Manorial Accounts. The Journal of Interdisciplinary History 44, 37–60.

DeWitte, S.N., 2014. Health in post-Black Death London (1350–1538): Age patterns of periosteal new bone formation in a post-epidemic population. American Journal of Physical Anthropology 155, 260–267. https://doi.org/10.1002/ajpa.22510

DeWitte S.N. 2018. Stress, sex, and plague: Patterns of developmental stress and survival in pre- and post-Black Death London. Am J Hum Biol, 30(1). doi: 10.1002/ajhb.23073. Epub 2017 Oct 26. PMID: 29071763.

DeWitte, Sharon N., and Christopher M. Stojanowski. 2015. “The Osteological Paradox 20 Years Later: Past Perspectives, Future Directions.” Journal of Archaeological Research 23 (4): 397–450.

DeWitte, S.N., Yaussy, S.L., 2021. Bioarchaeological applications of intersectionality, in: Cheverko, C.M., Prince-Buitenhuys, J., R., Hubbe, M. (Eds.), Theoretical Approaches in Bioarchaeology. Routledge, Abingdon, UK, pp. 45–58.

Dick, T.A., Nelson, P.A., and Choudhury, A. 2001. Diphyllobothriasis: update on human cases, foci patterns and sources of human infections and future considerations. Southeast Asian Journal of Tropical Medicine and Public Health 32: 59-76.

Dobson MJ. 1994. Malaria in England: A Geographical and Historical Perspective. Parassitologia 36: 35-50.

Dobson MJ. 1997. Contours of Death and Disease in Early Modern England. Cambridge: Cambridge University Press.

Donoghue, H.D., 2017. Insights gained from ancient biomolecules into past and present tuberculosis—a personal perspective. International Journal of Infectious Diseases 56, 176–180. https://doi.org/10.1016/j.ijid.2016.11.413

Douglas NM, Anstey NM, Buffet PA, Poespoprodjo JR, Yeo TW, White NJ, Price RN. 2012. The anaemia of Plasmodium vivax malaria. Malar J,11:135. doi: 10.1186/1475-2875-11-135.

Dror AA, Morozov N, Daoud A, Namir Y, Yakir O, Shachar Y, Lifshitz M, Segal E, Fisher L, Mizrachi M, Eisenbach N, Rayan D, Gruber M, Bashkin A, Kaykov E, Barhoum M, Edelstein M, Sela E. 2022. Pre-infection 25-hydroxyvitamin D3 levels and association with severity of COVID-19 illness. PLoS One, 17(2):e0263069. doi: 10.1371/journal.pone.0263069.

Echeverri M, Tobon A, Alvarez G, Carmona J, Blair S. 2003. Clinical and Laboratory Findings of Plasmodium vivax Malaria in Colombia, 2001. Rev. Inst. Med. Trop. S. Paulo 45(1): 29-3.

Feleke, B.E., Feleke, T.E., Biadglegne, F., 2019. Nutritional status of tuberculosis patients, a comparative cross-sectional study. BMC Pulmonary Medicine 19, 182. https://doi.org/10.1186/s12890-019-0953-0

Fernandez J, Idrovo A, Cucunuba Z, Reyes P. 2008. Validity of studies on the association between soil-transmitted helminths and the incidence of malaria: Should it impact on health policies? Rev Bras Epidemiol 11(3): 1-13.

Flores, J.A., Coit, J., Mendoza, M., Leon, S.R., Konda, K., Lecca, L., Franke, M.F., 2021. Is exclusive breastfeeding for six-months protective against pediatric tuberculosis? Glob Health Action 14, 1861922–1861922. https://doi.org/10.1080/16549716.2020.1861922

Franklin, M., Wilson, S.M., 2020. A Bioarchaeological Study of African American Health and Mortality in the Post-Emancipation U.S. South. American Antiquity 85, 652–675. https://doi.org/10.1017/aaq.2020.58

Freeman, J., 2020. Something Old, Something New: The Syndemic of Racism and COVID-19 and Its Implications for Medical Education. Family Medicine 52, 623–625. https://doi.org/10.22454/FamMed.2020.140670

Geller, P. L. (2021). *Theorizing Bioarchaeology*. Springer International Publishing.

Geus D, Sifft KC, Habarugira F, Mugisha JC, Mukampunga C, Ndoli J, Bayingana C, Sendegeya A, Martus P, Fraundorfer K, von Samson-Himmelstjerna G, Gahutu

JB, Klotz C, Aebischer A, Mockenhaupt FP. Co-infections with Plasmodium, Ascaris and Giardia among Rwandan schoolchildren. Trop Med Int Health. 2019 Apr;24(4):409-420. doi: 10.1111/tmi.13206. Epub 2019 Feb 3. PMID: 30659700.

Gluckman, P., Cutfield, W., Hofman, P., Hanson, M., 2005. The fetal, neonatal, and infant environments—the long-term consequences for disease risk. Early Human Development 81, 51–59.

Gluckman, Peter D., Mark A. Hanson, and Alan S. Beedle. 2007. “Early Life Events and Their Consequences for Later Disease: A Life History and Evolutionary Perspective.” American Journal of Human Biology: The Official Journal of the Human Biology Council 19 (1): 1–19.

Gluckman, P.D., Hanson, M.A., Buklijas, T., 2010. A conceptual framework for the developmental origins of health and disease. Journal of Developmental Origins of Health and Disease 1, 6–18. https://doi.org/10.1017/S2040174409990171

Gluckman, P.D., Hanson, M.A., Cooper, C., Thornburg, K.L., 2008. Effect of In Utero and Early-Life Conditions on Adult Health and Disease. N Engl J Med 359, 61–73. https://doi.org/10.1056/NEJMra0708473

Goodman, A.H., Leatherman, T.L., 1998. Traversing the chasm between biology and culture: an introduction, in: Goodman, A.H., Leatherman, T.L. (Eds.), Building a New Biocultural Synthesis: Political-Economic Perspectives on Human Biology. University of Michigan Press, Ann Arbor, pp. 3–41.

Gowland, R.L., 2015. Entangled lives: Implications of the developmental origins and health and disease hypothesis for bioarchaeology and the life course. American Journal of Physical Anthropology 158, 530–540.

Gowland RL, Garnsey P. 2010. Skeletal evidence for health, nutritional status and malaria in Roman and the empire. Journal of Roman Archaeology, supplementary series 78: 131-156.

Gowland, R. L.. and Western, A.G. 2012. Morbidity in the marshes: Using spatial epidemiology to investigate skeletal evidence for malaria in Anglo-Saxon England (AD 410–1050). Am. J. Phys. Anthropol., 147: 301-311. https://doi.org/10.1002/ajpa.21648

Gowland, R.L., Brundle, L., Western, A.G. 2018. 'Ague', 'Spring Ill' and 'Fever Terciane': Vivax Malaria and Social Constructions of 'Otherness' in the Anglo-Saxon Fens of England (AD 500-900). Poster presented at the AAPA, 2018, Austin, Texas.

Grange, J.M., Gandy, M., Farmer, P., Zumla, A., 2001. Historical declines in tuberculosis: nature, nurture and the biosocial model [Counterpoint]. The International Journal of Tuberculosis and Lung Disease 5, 208–212.

Gravlee, C.C., 2020. Systemic racism, chronic health inequities, and COVID-19: A syndemic in the making? American Journal of Human Biology 32, e23482. https://doi.org/10.1002/ajhb.23482

Gravlee, C.C., 2009. How race becomes biology: Embodiment of social inequality. American Journal of Physical Anthropology 139, 47–57. https://doi.org/10.1002/ajpa.20983

Hardy, A., 2003. Commentary: Bread and alum, syphilis and sunlight: rickets in the nineteenth century. International Journal of Epidemiology 32, 337–340. https://doi.org/10.1093/ije/dyg175

Harkins, K.M., Buikstra, J.E., Campbell, T., Bos, K.I., Johnson, E.D., Krause, J., Stone, A.C., 2015. Screening ancient tuberculosis with qPCR: challenges and opportunities. Philos Trans R Soc Lond B Biol Sci 370, 20130622–20130622. https://doi.org/10.1098/rstb.2013.0622

Hartgers, F.C. and Yazdanbakhsh, M. 2006. Co-infection of helminths and malaria: modulation of the immune responses to malaria. Parasite Immunology, 28: 497-506. https://doi.org/10.1111/j.1365-3024.2006.00901.x

Higham, N. 2010. The Landscape Archaeology of Anglo-Saxon England: An Introduction. In Higham, N. J. and Ryan, M. J. (eds), Landscape Archaeology of Anglo-Saxon England. The Boydell Press, Woodbridge.

Hmama, Z., Sendide, K., Talal, A., Garcia, R., Dobos, K., Reiner, N.E., 2004. Quantitative analysis of phagolysosome fusion in intact cells: inhibition by mycobacterial lipoarabinomannan and rescue by an 1α,25-dihydroxyvitamin D3–phosphoinositide 3-kinase pathway. J. Cell Sci. 117, 2131. https://doi.org/10.1242/jcs.01072

Holick, M.F., 2007. Vitamin D Deficiency. N Engl J Med 357, 266–281. https://doi.org/10.1056/NEJMra070553

Holick, M.F., 2005. The Vitamin D Epidemic and its Health Consequences. The Journal of Nutrition 135, 2739S-2748S. https://doi.org/10.1093/jn/135.11.2739S

Hollis, B.W., Wagner, C.L., 2017. New insights into the vitamin D requirements during pregnancy. Bone Research 5, 17030. https://doi.org/10.1038/boneres.2017.30

Horton, R., 2020. Offline: COVID-19 is not a pandemic. The Lancet 396, 874. https://doi.org/10.1016/S0140-6736(20)32000-6

Houben, E.N., Nguyen, L., Pieters, J., 2006. Interaction of pathogenic mycobacteria with the host immune system. Current Opinion in Microbiology 9, 76–85. https://doi.org/10.1016/j.mib.2005.12.014

Huldén L, Huldén L, Heliövaara K. 2005. Endemic Malaria: an indoor disease in northern Europe. Historical data analysed. Malaria Journal 4(19) Published online http://www.malariajournal.com/content/4/1/19.

Hutchinson R A, Lindsay SW. 2006. Malaria in the English marshes. Lancet 367: 1947-1952.

Ideraabdullah, F.Y., Belenchia, A.M., Rosenfeld, C.S., Kullman, S.W., Knuth, M., Mahapatra, D., Bereman, M., Levin, E.D., Peterson, C.A., 2019. Maternal vitamin D deficiency and developmental origins of health and disease (DOHaD). Journal of Endocrinology 241, R65–R80. https://doi.org/10.1530/JOE-18-0541

Inhorn, M.C., Brown, P.J., 1990. The Anthropology of Infectious Disease. Annu. Rev. Anthropol. 19, 89–117. https://doi.org/10.1146/annurev.an.19.100190.000513

Ives, R., 2018. Rare paleopathological insights into vitamin D deficiency rickets, co-occurring illnesses, and documented cause of death in mid-19th century London, UK. International Journal of Paleopathology 23, 76–87. https://doi.org/10.1016/j.ijpp.2017.11.004

Jaffe, H.L., 1972. Metabolic degenerative, and inflammatory diseases of bones and joints. Lea and Febiger, Philadelphia.

Jaimni, V., Shasty, B.A., Madhyastha, S.P., Shetty, G.V., Acharya, R.V., Bekur, R., Doddamani, A., 2021. Association of Vitamin D Deficiency and Newly Diagnosed

Pulmonary Tuberculosis. Pulm Med 2021, 5285841–5285841. https://doi.org/10.1155/2021/5285841

James SP. 1929. The disappearance of malaria from England. Proceedings of the Royal Society for Medicine 23 (1): 71-87.

Javaid, M., Crozier, S., Harvey, N., Gale, C., Dennison, E., Boucher, B., Arden, N., Godfrey, K., Cooper, C., 2006. Maternal vitamin D status during pregnancy and childhood bone mass at age 9 years: a longitudinal study. The Lancet 367, 36–43. https://doi.org/10.1016/S0140-6736(06)67922-1

Jeavans, C., 2021. Dying too young: maps show little has changed in 170 years [WWW Document]. URL https://www.bbc.com/news/health-57730353 (accessed 6.11.22).

Jensen, C., Lundqvist, M., Sorensen, T., Heitmann, B., 2017. Neonatal vitamin D levels in relation to risk of overweight at 7 years in the Danish D-Tect case-cohort study. Obesity Facts 10, 273–283. https://doi.org/10.1159/000471881

Jepkogei MR, Ngeiywa M, Makwali J. 2016 Sociodemographic factors associated with malaria-geohelminth co-infection and syndemics in pregnancy: A cross-sectional study of pregnant women attending ante-natal care at Nandi Hills Sub County Hospital, Kenya. Journal of Biology, Agriculture and Healthcare 6(14).

Jolliffe, D.A., Camargo, C.A., Jr, Sluyter, J.D., Aglipay, M., Aloia, J.F., Ganmaa, D., Bergman, P., Bischoff-Ferrari, H.A., Borzutzky, A., Damsgaard, C.T., Dubnov-Raz, G., Esposito, S., Gilham, C., Ginde, A.A., Golan-Tripto, I., Goodall, E.C., Grant, C.C., Griffiths, C.J., Hibbs, A.M., Janssens, W., Khadilkar, A.V., Laaksi, I., Lee, M.T., Loeb, M., Maguire, J.L., Majak, P., Mauger, D.T., Manaseki-Holland, S., Murdoch, D.R., Nakashima, A., Neale, R.E., Pham, H., Rake, C., Rees, J.R., Rosendahl, J., Scragg, R., Shah, D., Shimizu, Y., Simpson-Yap, S., Trilok-Kumar, G., Urashima, M., Martineau, A.R., 2017. Vitamin D supplementation to prevent acute respiratory infections: a systematic review and meta-analysis of aggregate data from randomised controlled trials. The Lancet Diabetes & Endocrinology. https://doi.org/10.1016/S2213-8587(21)00051-6

Kelmelis, S. and DeWitte, S.N. 2021. Urban and rural survivorship in Pre- and Post-Black Death Denmark. Journal of Archaeological Science: Reports 38, 103089, https://doi.org/10.1016/j.jasrep.2021.103089.

Kendall, E.J., Millard A., Beaumont, J., Gowland, R. L., Gorton, M., Gledhill, A. 2020. ‘What doesn’t kill you’: Early life health and nutrition in early Anglo-Saxon east Anglia’, in R.L. Gowland and S. Halcrow (eds), The Mother-Infant Nexus in Anthropology. Cham: Springer International Publishing, pp. 103–123.

Kerudin, A., Müller, R., Buckberry, J., Knüsel, C.J., Brown, T.A., 2019. Ancient Mycobacterium leprae genomes from the mediaeval sites of Chichester and Raunds in England. Journal of Archaeological Science 112, 105035. https://doi.org/10.1016/j.jas.2019.105035

Kline, N., 2022. Intersectionality and Syndemics: A Reply to Sangaramoorthy and Benton. Social Science & Medicine 295, 113786. https://doi.org/10.1016/j.socscimed.2021.113786

Kohrt, B.A., Carruth, L., 2022. Syndemic effects in complex humanitarian emergencies: A framework for understanding political violence and improving multi-morbidity

health outcomes. Social Science & Medicine 295, 113378. https://doi.org/10.1016/j.socscimed.2020.113378

Kuhn KG, Campbell-Lindrum D, Armstrong B, Davies R. 2003. Malaria in Britain: past, present and future. Proceedings of the National Academy of Sciences of the USA 100(17): 9997-10001.

Lans, A.M., 2021. Decolonize this collection: Integrating black feminism and art to re-examine human skeletal remains in museums. Feminist Anthropology 2, 130–142. https://doi.org/10.1002/fea2.12027

Larsen, C.S., Crespo, F.A., 2022. Paleosyndemics: A bioarchaeological and biosocial approach to study infectious diseases in the past. Centaurus: Journal of the European Society for the History of Science 1. https://dx.doi.org/10.1484/J.CNT.5.130031

Leatherman, T., Goodman, A., 2020. Building on the biocultural syntheses: 20 years and still expanding. American Journal of Human Biology 32, e23360. https://doi.org/10.1002/ajhb.23360

Leatherman, T.L., Goodman, A.H., 1997. Expanding the biocultural synthesis toward a biology of poverty. American Journal of Physical Anthropology 102, 1–3.

Lee, J.M., Smith, J.R., Philipp, B.L., Chen, T.C., Mathieu, J., Holick, M.F., 2007. Vitamin D Deficiency in a Healthy Group of Mothers and Newborn Infants. Clin Pediatr (Phila) 46, 42–44. https://doi.org/10.1177/0009922806289311

Levy, A., Fraser, D., Katz, M., Mazor, M. and Sheiner, E. 2005. Maternal anemia during pregnancy is an independent risk factor for low birthweight and preterm delivery. European Journal of Obstetrics & Gynecology and Reproductive Biology, 122(2), pp. 182-186.

Lewis, M., 2018. Paleopathology of Children, 1st edition. ed. Academic Press, London.

Lewontin, R. (2000). The Triple Helix — Gene, Organism and Environment. Harvard University Press, Cambridge, MA.

Liberman, U.A., 2007. Vitamin D–Resistant Diseases. Journal of Bone and Mineral Research 22, V105–V107. https://doi.org/10.1359/jbmr.07s210

Lindsay, S., Ansell, J., Selman, C., Cox, V., Hamilton, K. and Walraven, G. 2000. Effect of pregnancy on exposure to malaria mosquitoes. The Lancet, 355(9219), pp. 1972.

Lindsay SW, Hole DG, Hutchinson RA, Richards SA, Willis SG. 2010. Assessing the future threat from vivax malaria in the United Kingdom using two markedly different modelling approaches. Malaria Journal 9: 70.

Liu, P.T., Stenger, S., Tang, D.H., Modlin, R.L., 2007. Cutting Edge: Vitamin D-Mediated Human Antimicrobial Activity against Mycobacterium tuberculosis Is Dependent on the Induction of Cathelicidin. J. Immunol. 179, 2060. https://doi.org/10.4049/jimmunol.179.4.2060

Lock, M. (1993). Encounters with Aging: Mythologies of Menopause in Japan and North America. Berkeley, CA: University of California Press.

Lönnroth, K., Jaramillo, E., Williams, B.G., Dye, C., Raviglione, M., 2009. Drivers of tuberculosis epidemics: The role of risk factors and social determinants. Social Science & Medicine 68, 2240–2246. https://doi.org/10.1016/j.socscimed.2009.03.041

Loufouma Mbouaka, A., Gamble, M., Wurst, C. *et al.* The elusive parasite: comparing macroscopic, immunological, and genomic approaches to identifying malaria in human skeletal remains from Sayala, Egypt (third to sixth centuries AD). *Archaeol Anthropol Sci* **13**, 115 (2021). https://doi.org/10.1007/s12520-021-01350-z

Lucas, R.M., Ponsonby, A.-L., Pasco, J.A., Morley, R., 2008. Future health implications of prenatal and early-life vitamin D status. Nutrition Reviews 66, 710–720. https://doi.org/10.1111/j.1753-4887.2008.00126.x

Mant, M., de la Cova, C., & Brickley, M. B. (2021). Intersectionality and trauma analysis in bioarchaeology. *American Journal of Physical Anthropology*, *174*(4), 583–594.

Marciniak, S., Prowse, T.L., Herring, D.A. Klunk, J., Kuch, M., Duggan, A.T., Bondioli, L., Holmes, E.C., Poinar, H.N. 2016. Plasmodium falciparum malaria in 1st–2nd century CE southern Italy. Current Biology, 26 (23), R1220-R1222, https://doi.org/10.1016/j.cub.2016.10.016.

Marciniak, S., Herring, D.A., Sperduti, A., Poinar, H.N., Prowse, T.L. 2018. A multi-faceted anthropological and genomic approach to framing Plasmodium falciparum malaria in Imperial period central-southern Italy (1st–4th c. CE), Journal of Anthropological Archaeology, 49, 210-224, https://doi.org/10.1016/j.jaa.2018.01.004.

Martinez, L., Ncayiyana, J.R., Goddard, E., Botha, M., Workman, L., Burd, T., Myer, L., Nicol, M.P., Zar, H.J., 2022. Vitamin D Concentrations in Infancy and the Risk of Tuberculosis Disease in Childhood: A Prospective Birth Cohort in Cape Town, South Africa. Clinical Infectious Diseases 74, 2036–2043. https://doi.org/10.1093/cid/ciab735

Mathur, R., Rentsch, C.T., Morton, C.E., Hulme, W.J., Schultze, A., MacKenna, B., Eggo, R.M., Bhaskaran, K., Wong, A.Y.S., Williamson, E.J., Forbes, H., Wing, K., McDonald, H.I., Bates, C., Bacon, S., Walker, A.J., Evans, D., Inglesby, P., Mehrkar, A., Curtis, H.J., DeVito, N.J., Croker, R., Drysdale, H., Cockburn, J., Parry, J., Hester, F., Harper, S., Douglas, I.J., Tomlinson, L., Evans, S.J.W., Grieve, R., Harrison, D., Rowan, K., Khunti, K., Chaturvedi, N., Smeeth, L., Goldacre, B., 2021. Ethnic differences in SARS-CoV-2 infection and COVID-19-related hospitalisation, intensive care unit admission, and death in 17 million adults in England: an observational cohort study using the OpenSAFELY platform. The Lancet 397, 1711–1724. https://doi.org/10.1016/S0140-6736(21)00634-6

Mays, S., 2018. The epidemiology of rickets in the 17th–19th centuries: Some contributions from documentary sources and their value to palaeopathologists. International Journal of Paleopathology 23, 88–95. https://doi.org/10.1016/j.ijpp.2017.10.011

Mays, S., Brickley, M., Ives, R., 2009. Growth and vitamin D deficiency in a population from 19th century Birmingham, England. International Journal of Osteoarchaeology 19, 406–415. https://doi.org/10.1002/oa.976

McDade Thomas W., 2012. Early environments and the ecology of inflammation. Proceedings of the National Academy of Sciences 109, 17281–17288. https://doi.org/10.1073/pnas.1202244109

McDade, T.W., Rutherford, J., Adair, L., Kuzawa, C.W., 2010. Early origins of inflammation: microbial exposures in infancy predict lower levels of C-reactive protein in adulthood. Proc Biol Sci 277, 1129–1137. https://doi.org/10.1098/rspb.2009.1795

McFarlane, N., 1989. Hospitals, Housing, and Tuberculosis in Glasgow, 1911–51. Social History of Medicine 2, 59–85. https://doi.org/10.1093/shm/2.1.59

McKeown, T., Record, R.G., 1962. Reasons for the decline of mortality in England and Wales during the nineteenth century. Population Studies 16, 94–122. https://doi.org/10.1080/00324728.1962.10414870

McKerracher, Luseadra, Ruby Fried, Andrew W. Kim, Tina Moffat, Deborah M. Sloboda, and Tracey Galloway. 2020. “Synergies between the Developmental Origins of Health and Disease Framework and Multiple Branches of Evolutionary Anthropology.” Evolutionary Anthropology 29 (5): 214–19.

Mendenhall, E., 2020. The COVID-19 syndemic is not global: context matters. The Lancet 396, 1731. https://doi.org/10.1016/S0140-6736(20)32218-2

Mendenhall, E., 2012. Syndemic Suffering: Social Distress, Depression, and Diabetes among Mexican Immigrant Women. Left Coast Press, Walnut Creek, CA.

Mendenhall, E., Kohrt, B.A., Norris, S.A., Ndetei, D., Prabhakaran, D., 2017. Non-communicable disease syndemics: poverty, depression, and diabetes among low-income populations. The Lancet 389, 951–963. https://doi.org/10.1016/S0140-6736(17)30402-6

Mendenhall, E., Newfield, T., Tsai, A.C., 2022. Syndemic theory, methods, and data. Social Science & Medicine 295, 114656. https://doi.org/10.1016/j.socscimed.2021.114656

Miele, K., Bamrah Morris, S., Tepper, N.K., 2020. Tuberculosis in Pregnancy. Obstetrics & Gynecology 135.

Mishra, P.K., Palma, M., Bleich, D., Loke, P., Gause, W.C., 2014. Systemic impact of intestinal helminth infections. Mucosal Immunology 7, 753–762. https://doi.org/10.1038/mi.2014.23

Moloney, D.P., Chawke, L., Crowley, M.T., O’Connor, T.M., 2018. Fluctuating hypercalcaemia caused by cavitary Mycobacterium bovis pulmonary infection. BMJ Case Reports 2018, bcr-2017-222351. https://doi.org/10.1136/bcr-2017-222351

Müller, R., Roberts, C.A., Brown, T.A., 2014. Biomolecular identification of ancient Mycobacterium tuberculosis complex DNA in human remains from Britain and continental Europe. American Journal of Physical Anthropology 153, 178–189. https://doi.org/10.1002/ajpa.22417

Munns, C.F., Shaw, N., Kiely, M., Specker, B.L., Thacher, T.D., Ozono, K., Michigami, T., Tiosano, D., Mughal, M.Z., Mäkitie, O., Ramos-Abad, L., Ward, L., DiMeglio, L.A., Atapattu, N., Cassinelli, H., Braegger, C., Pettifor, J.M., Seth, A., Idris, H.W., Bhatia, V., Fu, J., Goldberg, G., Sävendahl, L., Khadgawat, R., Pludowski, P., Maddock, J., Hyppönen, E., Oduwole, A., Frew, E., Aguiar, M., Tulchinsky, T., Butler, G., Högler, W., 2016. Global Consensus Recommendations on Prevention and Management of Nutritional Rickets. J Clin Endocrinol Metab 101, 394–415. https://doi.org/10.1210/jc.2015-2175

Newfield, T.P., 2022. Syndemics and the history of disease: Towards a new engagement. Social Science & Medicine 295, 114454. https://doi.org/10.1016/j.socscimed.2021.114454

Nicholls A. 2000. Fenland ague in the Nineteenth century. Medical History 44: 523-550.

Niewöhner, Jörg, and Margaret Lock. 2018. “Situating Local Biologies: Anthropological Perspectives on Environment/human Entanglements.” BioSocieties 13 (4): 681–97.

Nuttall GHF, Cobbett L, Strangeways-Pigg T. 1901. Studies in relation to malaria 1. The Geographical distribution of anopheles in relation to the former distribution of ague in England. Journal of Hygiene 1: 1-44.

Parry, J.S., 1872. ART. I.--Remarks on the Pathological Anatomy, Causes, and Treatment of Rickets. The American Journal of the Medical Sciences (1827-1924) 305.

Pealing, L., Moore, D., Zenner, D., 2013. The resurgence of tuberculosis and the implications for primary care. Br J Gen Pract 63, 344–345. https://doi.org/10.3399/bjgp13X669077

Peduzzi R, Boucher-Rodoni R. 2001. Resurgence of human bothriocephalosis (Diphyllobothrium latum) in the subalpine lake region. J. Limnol. 60(1): 41-44.

Pettifor, J.M., Prentice, A., 2011. The role of vitamin D in paediatric bone health. Best Practice & Research Clinical Endocrinology & Metabolism 25, 573–584. https://doi.org/10.1016/j.beem.2011.06.010

Pettifor, J.M., Thandrayen, K., Thacher, T.D., 2018. Chapter 67 - Vitamin D Deficiency and Nutritional Rickets in Children, in: Feldman, D. (Ed.), Vitamin D (Fourth Edition). Academic Press, pp. 179–201. https://doi.org/10.1016/B978-0-12-809963-6.00067-5

Phyo AP, Dahal P, Mayxay M, Ashley EA (2022) Clinical impact of vivax malaria: A collection review. PLoS Med 19(1): e1003890.

Prietl, B., Treiber, G., Pieber, T.R., Amrein, K., 2013. Vitamin D and Immune Function. Nutrients 5. https://doi.org/10.3390/nu5072502

Rajendra, A., Mishra, A.K., Francis, N.R., Carey, R.A.B., 2016. Severe hypercalcemia in a patient with pulmonary tuberculosis. J Family Med Prim Care 5, 509–511. https://doi.org/10.4103/2249-4863.192327

Redfern, R.C., DeWitte, S.N., Pearce, J., Hamlin, C., Dinwiddy, K.E., 2015. Urban–rural differences in Roman Dorset, England: A bioarchaeological perspective on Roman settlements. American Journal of Physical Anthropology 157, 107–120. https://doi.org/10.1002/ajpa.22693

Reichetzeder, C., Chen, H., Föller, M., Slowinski, T., Li, J., Chen, Y.-P., Lang, F., Hocher, B., 2014. Maternal Vitamin D Deficiency and Fetal Programming - Lessons Learned from Humans and Mice. Kidney and Blood Pressure Research 39, 315–329. https://doi.org/10.1159/000355809

Reiter P. 2000. From Shakespeare to Defoe: Malaria in England in the Little Ice Age. Emerging Infectious Diseases 6: 1-11.

Rippon, S. 2000. The Transformation of the Coastal Wetlands: Exploitation and Management of the Marshland Landscapes in North West Europe during the Roman and Medieval Periods. Oxford University Press, Oxford.

Rippon, S. 2002. Infield and Outfield: The Early Stages of Marshland Colonisation and

the Evolution of Medieval Field System. In Lane, T. and Coles. J. (eds). Through Wet and Dry: Essays in Honour of David Hall. Heritage Trust of Lincolnshire/WARP Occasional Paper 17: 54-70.

Rippon, S. 2010. Landscape Change during the 'Long Eighth Century' in Southern England. In Higham, N. J. and Ryan, M. J. (eds), *Landscape Archaeology of Anglo-Saxon England.* The Boydell Press, Woodbridge.

Robbins Schug, G., 2021. The Routledge Handbook of the Bioarchaeology of Climate and Environmental Change. Routledge, London.

Robbins Schug, G., Halcrow, S.E., 2022. Building a bioarchaeology of pandemic, epidemic, and syndemic diseases: lessons for understanding COVID-19. Bioarchaeology International 6, 1–22.

Roberts, C.A., Brickley, M.B., 2019. Infectious and metabolic diseases: a synergistic relationship, in: Biological Anthropology of the Human Skeleton. Wiley & Sons, New York, pp. 415–446.

Roberts, C.A., Buikstra, J.E., 2019. Chapter 11 - Bacterial Infections, in: Buikstra, J.E. (Ed.), Ortner's Identification of Pathological Conditions in Human Skeletal Remains (Third Edition). Academic Press, San Diego, pp. 321–439. https://doi.org/10.1016/B978-0-12-809738-0.00011-9

Roberts, C.A., Buikstra, J.E., 2003. The Bioarchaeology of Tuberculosis: A global view on a reemerging disease. University Press of Florida, Gainesville, FL.

Roberts, C.A., Caffell, A., Filipek-Ogden, K.L., Gowland, R., Jakob, T., 2016. 'Til Poison Phosphorous Brought them Death': A potentially occupationally-related disease in a post-medieval skeleton from north-east England. International Journal of Paleopathology 13, 39–48. https://doi.org/10.1016/j.ijpp.2015.12.001

Rodriguez-Morales, A.J., Sanchez, E., Vargas, M., Piccolo, C., Colina, R., Arria, M., Franco-Paredes, C. 2006. Is Anemia in Plasmodium vivax Malaria More Frequent and Severe than in Plasmodium falciparum? The American Journal of Medicine, Volume 119, Issue 11, e9 - e10

Sabin, S., Herbig, A., Vågene, Å.J., Ahlström, T., Bozovic, G., Arcini, C., Kühnert, D., Bos, K.I., 2020. A seventeenth-century Mycobacterium tuberculosis genome supports a Neolithic emergence of the Mycobacterium tuberculosis complex. Genome Biology 21, 201. https://doi.org/10.1186/s13059-020-02112-1

Sallares R. 2002. Malaria and Rome. Oxford: Oxford University Press.

Sallares R, Bouwman A, Anderung C. 2004. The spread of malaria to Southern Europe in antiquity: new approaches to old problems. Medical History 48: 311-328

Sallares R., Gomzi, S. 2001. Biomolecular archaeology of malaria. Ancient Biomolecules 3: 195-213.

Sangaramoorthy, T., Benton, A., 2022. Intersectionality and syndemics: A commentary. Social Science & Medicine 295, 113783. https://doi.org/10.1016/j.socscimed.2021.113783

Sawchuk, L.A., Tripp, L., Samakaroon, M., 2022. Assessing a syndemic: Gibraltar in the time of cholera. Social Science & Medicine 295, 112956. https://doi.org/10.1016/j.socscimed.2020.112956

Sérandour J, Girel J, Boyer S, Ravanel P, Lemperière G, Raveton M. 2007. How human practices have affected vector-borne diseases in the past: a study of malaria transmission in Alpine valleys. Malaria Journal 6: 115-125.

Scheidel, W. 1994. Libetina's bitter gains: seasonal mortality and endemic disease in the ancient city of Rome. Ancient Society, 25: 151-175.

Shankar AH. 2000. Nutritional modulation of malaria morbidity and mortality. The Journal of Infectious Diseases 182: s37-s53.

Sharma, O.P., 2000. Hypercalcemia in granulomatous disorders: a clinical review. Current Opinion in Pulmonary Medicine 6.

Shi, B., Zheng, J., Xia, S., Lin, S., Wang, X, Liu, Y., Zhou, X-N, & Liu, J., 2021. Accessing the syndemic of COVID-19 and malaria intervention in Africa. *Infect Dis Poverty* 10, 5 https://doi.org/10.1186/s40249-020-00788-y

Shute PG, Maryon M. 1974. Malaria in England, past, present and future. The Journal of the Royal Society for the Promotion of Health 94: 23-29.

Singer, M., 2015. Anthropology of Infectious Disease. Left Coast Press, Walnut Creek, CA.

Singer, M., 1996. A Dose of Drugs, A Touch of Violence, A Case of AIDS: Conceptualizing the SAVA Syndemic. Free Inquiry in Creative Sociology 24, 99–110.

Singer, M., 1994. Aids and the health crisis of the U.S. urban poor; the perspective of critical medical anthropology. Social Science & Medicine 39, 931–948. https://doi.org/10.1016/0277-9536(94)90205-4

Singer, Merrill. 2009. Introduction to Syndemics: A Critical Systems Approach to Public and Community Health. John Wiley & Sons.

Singer, M., Baer, H.A., 1995. Critical Medical Anthropology, 2nd edition. ed. Routledge, New York.

Singer, Merrill, Nicola Bulled, and Bayla Ostrach. 2020. "Whither Syndemics?: Trends in Syndemics Research, a Review 2015–2019." Global Public Health. https://doi.org/10.1080/17441692.2020.1724317.

Singer, M., Bulled, N., Ostrach, B., Lerman Ginzburg, S., 2021. Syndemics: A Cross-Disciplinary Approach to Complex Epidemic Events Like COVID-19. Annu. Rev. Anthropol. 50, 41–58. https://doi.org/10.1146/annurev-anthro-100919-121009

Singer, M., Bulled, N., Ostrach, B., Mendenhall, E., 2017. Syndemics and the biosocial conception of health. The Lancet 389, 941–950. https://doi.org/10.1016/S0140-6736(17)30003-X

Singer, M., Clair, S., 2003. Syndemics and Public Health: Reconceptualizing Disease in Bio-Social Context. Medical Anthropology Quarterly 17, 423–441. https://doi.org/10.1525/maq.2003.17.4.423

Slagboom, M.N., Crone, M.R., Reis, R. 2022. Exploring syndemic vulnerability across generations: A case study of a former fishing village in the Netherlands. Social Science & Medicine, 295, 113122, https://doi.org/10.1016/j.socscimed.2020.113122.

Smith-Guzmán, Nicole E. 2015. The Skeletal Manifestation of Malaria: An Epidemiological Approach Using Documented Skeletal Collections. American Journal of Physical Anthropology 158 (4): 624–35.

Smith-Guzmán, Nicole E., Heidi S. Davis, and Jerome C. Rose. 2016. Malaria at Amarna, Egypt: Evidence from the South Tombs Cemetery. American Journal of Physical Anthropology 159: 296–97.

Snoddy, A.M.E., Buckley, H.R., Halcrow, S.E., 2016. More than metabolic: Considering the broader paleoepidemiological impact of vitamin D deficiency in bioarchaeology. American Journal of Physical Anthropology 160, 183–196. https://doi.org/10.1002/ajpa.22968

Soren, HD. 2003. Can archaeologists excavate evidence of malaria? World Archaeology 35, 193-205.

Stall, R., Mills, T.C., Williamson, J., Hart, T., Greenwood, G., Paul, J., Pollack, L., Binson, D., Osmond, D., Catania, J.A., 2003. Association of Co-Occurring Psychosocial Health Problems and Increased Vulnerability to HIV/AIDS Among Urban Men Who Have Sex With Men. Am J Public Health 93, 939–942. https://doi.org/10.2105/AJPH.93.6.939

Stuart JM, Orr HJ, Warburton FG, Jeyakanth S, Pugh C, Morris I, Sarangi J, Nichols G. 2003. Risk factors for sporadic giardiasis: a case-control study in southwestern England. Emerging Infectious Diseases 9(2):229-33.

Talat, N., Perry, S., Parsonnet, J., Dawood, G., Hussain, R., 2010. Vitamin D deficiency and tuberculosis progression. Emerg Infect Dis 16, 853–855. https://doi.org/10.3201/eid1605.091693

Tomori, C., McFall, A.M., Solomon, S.S., Srikrishnan, A.K., Anand, S., Balakrishnan, P., Mehta, S.H., Celentano, D.D., 2018. Is there synergy in syndemics? Psychosocial conditions and sexual risk among men who have sex with men in India. Social Science & Medicine 206, 110–116. https://doi.org/10.1016/j.socscimed.2018.03.032

Tsai, A.C., 2018. Syndemics: A theory in search of data or data in search of a theory? Social Science & Medicine 206, 117–122. https://doi.org/10.1016/j.socscimed.2018.03.040

Tsai, A.C., 2015. Home Foreclosure, Health, and Mental Health: A Systematic Review of Individual, Aggregate, and Contextual Associations. PLOS ONE 10, e0123182. https://doi.org/10.1371/journal.pone.0123182

Tsai, A.C., Mendenhall, E., Trostle, J.A., Kawachi, I., 2017. Co-occurring epidemics, syndemics, and population health. The Lancet 389, 978–982. https://doi.org/10.1016/S0140-6736(17)30403-8

Velavan, T.P., Meyer, C.G., Esen, M., Kremser, P.G., Ntoumi, F. 2021. COVID-19 and syndemic challenges in ‘Battling the Big Three’: HIV, TB and Malaria. International Journal of Infectious Diseases, 106, 29-32.

Veselka, B., Brickley, M.B., Waters-Rist, A.L., 2021. A joint medico-historical and paleopathological perspective on vitamin D deficiency prevalence in post-Medieval Netherlands. International Journal of Paleopathology 32, 41–49. https://doi.org/10.1016/j.ijpp.2020.10.010

Veselka, B., Hoogland, M.L.P., Waters-Rist, A.L., 2015. Rural Rickets: Vitamin D Deficiency in a Post-Medieval Farming Community from the Netherlands. International Journal of Osteoarchaeology 25, 665–675. https://doi.org/10.1002/oa.2329

við Streym, S., Kristine Moller, U., Rejnmark, L., Heickendorff, L., Mosekilde, L., Vestergaard, P., 2013. Maternal and infant vitamin D status during the first 9 months of infant life—a cohort study. European Journal of Clinical Nutrition 67, 1022–1028. https://doi.org/10.1038/ejcn.2013.152

Viljakainen, H.T., Korhonen, T., Hytinantti, T., Laitinen, E.K.A., Andersson, S., Mäkitie, O., Lamberg-Allardt, C., 2011. Maternal vitamin D status affects bone growth in early childhood—a prospective cohort study. Osteoporosis International 22, 883–891. https://doi.org/10.1007/s00198-010-1499-4

Wade, L., 2020. An unequal blow. Science 368, 700–703. https://doi.org/10.1126/science.368.6492.700

Walker, P.L., Bathurst, R.R., Richman, R., Gjerdrum, T., Andrushko, V.A. 2009. The causes of porotic hyperostosis and cribra orbitalia: a reappraisal of the iron deficiency-anemia hypothesis. American Journal of Physical Anthropology 139: 109-125.

Watkins, R., 2012. Variation in health and socioeconomic status within the W. Montague Cobb skeletal collection: Degenerative joint disease, trauma and cause of death. International Journal of Osteoarchaeology 22, 22–44. https://doi.org/10.1002/oa.1178

Watkins, R.J., 2020. An Alter(ed)native Perspective on Historical Bioarchaeology. Historical Archaeology 54, 17–33. https://doi.org/10.1007/s41636-019-00224-5

Webb, J. 2020. Syndemic anemia in British Malaya: An early global health encounter with hookworm and malaria Co-infections in plantation workers. Social science & medicine: 113555.

Wells, J.C.K., 2010. Maternal capital and the metabolic ghetto: An evolutionary perspective on the transgenerational basis of health inequalities. American Journal of Human Biology 22, 1–17. https://doi.org/10.1002/ajhb.20994

WHO Malaria Program, 2021. World Malaria Report 2021. World Health Organization, Geneva.

Wiley, A.S., Cullin, J.M., 2016. What Do Anthropologists Mean When They Use the Term Biocultural? American Anthropologist 118, 554–569. https://doi.org/10.1111/aman.12608

Williamson, E.J., Walker, A.J., Bhaskaran, K., Bacon, S., Bates, C., Morton, C.E., Curtis, H.J., Mehrkar, A., Evans, D., Inglesby, P., Cockburn, J., McDonald, H.I., MacKenna, B., Tomlinson, L., Douglas, I.J., Rentsch, C.T., Mathur, R., Wong, A.Y.S., Grieve, R., Harrison, D., Forbes, H., Schultze, A., Croker, R., Parry, J., Hester, F., Harper, S., Perera, R., Evans, S.J.W., Smeeth, L., Goldacre, B., 2020. Factors associated with COVID-19-related death using OpenSAFELY. Nature 584, 430–436. https://doi.org/10.1038/s41586-020-2521-4

Wilson, J.L., Mayr, H.K., Weichhart, T., 2019. Metabolic Programming of Macrophages: Implications in the Pathogenesis of Granulomatous Disease. Frontiers in Immunology 10, 2265. https://doi.org/10.3389/fimmu.2019.02265

Woldehanna, S., Zimicki, S., 2015. An expanded One Health model: Integrating social science and One Health to inform study of the human-animal interface. Social Science & Medicine 129, 87–95. https://doi.org/10.1016/j.socscimed.2014.10.059

Wolf, M., 2015. Is there really such a thing as “one health”? Thinking about a more than human world from the perspective of cultural anthropology. Social Science & Medicine 129, 5–11. https://doi.org/10.1016/j.socscimed.2014.06.018

Wood, J.W., Milner, G.R., Harpending, H.C., Weiss, K.M., 1992. The osteological paradox: problems in inferring prehistoric health from skeletal samples. Current Anthropology 33, 343–58.

Wu, B., Wang, O., Jiang, Y., Li, M., Xing, X., Xia, W., 2017. Atypical skeletal manifestations of rickets in a familial hypocalciuric hypercalcemia patient. Bone Research 5, 17001. https://doi.org/10.1038/boneres.2017.1

Yaussy, S. (2022). Intersectionality and the interpretation of past pandemics. *Bioarchaeology International*. https://doi.org/10.5744/bi.2020.0028

Zhang, M., Shen, F., Petryk, A., Tang, J., Chen, X., Sergi, C., 2016. “English Disease”: Historical Notes on Rickets, the Bone-Lung Link and Child Neglect Issues. Nutrients 8, 722. https://doi.org/10.3390/nu8110722

Zhu, H., Bhagatwala, J., Huang, Y., Pollock, N.K., Parikh, S., Raed, A., Gutin, B., Harshfield, G.A., Dong, Y., 2016. Race/Ethnicity-Specific Association of Vitamin D and Global DNA Methylation: Cross-Sectional and Interventional Findings. PLOS ONE 11, e0152849. https://doi.org/10.1371/journal.pone.0152849

Zhu, K., Whitehouse, A.J., Hart, P.H., Kusel, M., Mountain, J., Lye, S., Pennell, C., Walsh, J.P., 2014. Maternal Vitamin D Status During Pregnancy and Bone Mass in Offspring at 20 Years of Age: A Prospective Cohort Study. Journal of Bone and Mineral Research 29, 1088–1095. https://doi.org/10.1002/jbmr.2138

Zink, A.R., Grabner, W., Reischl, U., Wolf, H., Nerlich, A.G., 2003. Molecular study on human tuberculosis in three geographically distinct and time delineated populations from ancient Egypt. Epidemiol Infect 130, 239–249. https://doi.org/10.1017/s0950268802008257

Zuckerman, M.K., Martin, D.L., 2016. Introduction: the development of biocultural perspectives in anthropology, in: Zuckerman, M.K., Martin, D.L. (Eds.), New Directions in Biocultural Anthropology. John Wiley & Sons, New York, pp. 7–26.

Zvelebil, M., Weber, A.W., 2013. Human bioarchaeology: Group identity and individual life histories – Introduction. Journal of Anthropological Archaeology 32, 275–279. https://doi.org/10.1016/j.jaa.2012.01.003