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Scurvy in the Tropics: Evidence for increasing non-adult micronutrient deficiency with the transition to agriculture in northern Vietnam

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Objective: Scurvy in non-adults was assessed at the Pre-Neolithic site of Con Co Ngua and the Neolithic site of Man Bac in northern Vietnam to investigate nutritional stress during the agricultural transition in Mainland Southeast Asia (MSEA).

Materials: 104 human skeletons under the age of 20 years old were assessed.

Methods: Lesions were recorded macroscopically and radiographically. Differential diagnosis using prior established paleopathological diagnostic criteria for scurvy was conducted.

Results: There was no clear evidence for scurvy at Con Co Ngua and a high burden of scurvy was present at Man Bac (>79% diagnosed with probable scurvy). Scurvy levels were high across all non-adult ages at Man Bac indicating significant burden throughout childhood and adolescence.

Conclusions: No scurvy at Con Co Ngua is consistent with widely available food sources at the peak of the Holocene Thermal Maximum. High levels of scurvy at Man Bac corresponds with decreased dietary diversity, high pathogen load, and increased population stress with the transition to agriculture around the time of the 4.2ka desertification event.

Significance: This is the first systemic population-level non-adult investigation of specific nutritional disease in MSEA and demonstrates an increase in nutritional stress during the Neolithic transition in northern Vietnam.

Limitations: Subperiosteal new bone deposits can be due to normal growth in infants and young children, therefore, identification of scurvy in children under the age of 4 years needs to be considered critically.

Suggestions for further research: Further work in diagnosing specific nutritional disease in other non-adult cohorts throughout MSEA is required.

Keywords: health, agriculture, nutritional disease, MSEA, diet, Neolithic

1. Introduction

It is now well established in bioarchaeological research that the agricultural transition had variable consequences to human health in the past (Bocquet-Appel, Naji, & Bandy, 2008; Eshed, Gopher, Pinhasi, & Hershkovitz, 2010; Oxenham, 2006; Snoddy, Halcrow, Buckley, Standen, & Arriaza, 2017; Temple & Larsen, 2013). In Mainland Southeast Asia (MSEA) there has been extensive bioarchaeological work focused on the agricultural transition. The research has demonstrated a pattern of fewer negative health impacts compared to the Eurasian and American continents where paleopathological works of the last half century have primarily focused (Buikstra, Konigsberg, & Bullington, 1986; Clark Spencer Larsen, 2006; Larsen et al., 2015). Work by Tayles, Domett, and Nelsen (2000), Halcrow, Harris, Tayles, Ikehara-Quebral, and Pietrusewsky (2013), Oxenham (2006) and Oxenham, Trinh, Willis, Jones, Domett, Castillo, Wood, Bellwood, Tromp, and Kells (2018) argued that the reliance on domesticated rice, millet and pigs, was a gradual transition and that subsistence strategies were dominated by mixed foraging farming-practices rather than single crops. Thus, the agriculture transition was not associated with a distinct ‘decline’ in health. This previous research has primarily focused on non-specific stress markers as evidence of physiological stress rather than the systematic study of specific diseases during the agricultural transition. New research has questioned a simplified definition of ‘decline’ in health and revealed a level of epidemiological complexity only visible through the diagnosis of specific infectious diseases. For example, Vlok et al. (2020) and Vlok et al. (2022) demonstrated a shift from environmentally driven to human driven infectious diseases with the adoption of agriculture in northern Vietnam. This region is a geographical friction zone between forager groups from MSEA and farmers from modern day South China, eventually leading to both demographic and technological change (P. Bellwood & M. F. Oxenham, 2008; C. Higham, Guangmao, & Qiang, 2011). However, Vlok et al. (2021) have also presented skeletal evidence for the presence of malaria in hunter-gather communities of northern Vietnam at least 2,500 years before the adoption of agriculture. Malaria was previously thought to have been introduced with agriculture and worsened with the intensification of wet rice farming (see King, Halcrow, Tayles, & Shkrum, 2017; Tayles, 1996), in Pre-Neolithic hunter-gather communities of northern Vietnam (see Table 1 for time periods in MSEA).

***Table 1**: Approximate dates for time periods in MSEA. Note that there is considerable intraregional variation in the timing of these periods.*

Time Period	Approximate Dates	References
Pre-Neolithic	Before 2300 BC	(Oxenham, Trinh, Willis, Jones, Domett, Castillo, Wood, Bellwood, Tromp, & Kells, 2018)
Neolithic	2300-1000 BC	(Bellwood et al., 2011; C. Higham, Higham, & Douka, 2019; T. Higham et al., in press; Vlok et al., 2020)
Bronze Age (Metal Age)	1000-500BC	(C. Higham, Higham, & Kijngam, 2011; C. Higham, Higham, et al., 2019; T. Higham et al., in press)
Iron Age (Metal Age)	500BC-500AD	(C. Higham, Higham, et al., 2019; C. Higham, Manly, et al., 2019)

1.1 Nutritional deficiency with the introduction of agricultural foods

A reliance on domesticated cereals with poor dietary diversity to meet the energy requirements of large agricultural populations appears to have also led to deficiencies of many micronutrients (M. B. Brickley, R. Ives, & S. Mays, 2020; C.S Larsen, 2006). Depending on the cereal, insufficient levels of micronutrients such as iron, zinc, calcium, Vitamin A, B12, B3, B9 and C may have caused associated clinical deficiencies (Bouis & Welch, 2010; C.S Larsen, 2006; Pettifor, 2004; Snoddy et al., 2017). For example, Snoddy et al. (2017) identified evidence of Vitamin C deficiency causing scurvy in the early agricultural transition period in the Atacama desert, northern Chile. No such research on specific nutritional disease yet exists focusing on populations living during the adoption and intensification of agriculture in MSEA. Therefore, it is largely unknown to what degree this transition had directly on the nutrition of these ancient groups.

Only a certain number of micronutrient deficiencies affect the skeleton macroscopically. These include scurvy (Vitamin C deficiency), rickets (Vitamin D, calcium, or phosphate deficiency), hypovitaminosis A (Vitamin A deficiency), pellagra (Vitamin B3 deficiency) as well as the iron, folate and B12 deficiency anemias. Scurvy has well established methods for diagnosis in paleopathology (Brickley & Ives, 2010; M. Brickley, R. Ives, & S. Mays, 2020;

Ortner, 2003; Ortner & Ericksen, 1997; Snoddy et al., 2018), can be directly linked to dietary deficiency, and is therefore useful for investigating the impact of micronutrient deficiency during periods of subsistence change. Thus, evidence of scurvy is used in this research as a proxy for dietary deficiency.

1.2 Pathophysiology of Skeletal Scurvy

A biological approach for diagnosis is the predominant basis for identification of scurvy in the skeletal record. This approach was first employed by Ortner and Ericksen (1997) and is based on biological inference of skeletal lesion patterning through an understanding of anatomical implications of disease. Mays (2018) argued that this approach is elemental to scientific rigor when diagnosing disease from skeletal lesions. Skeletal changes in non-adult scurvy result from both direct and indirect impacts of malproduction of collagen on skeletal tissue (Fain, 2005). Regions of association between blood vessels in contact with bone, and underlying habitually used muscles, that cause repeated episodes of weakened vessel rupture, have been identified as eliciting subperiosteal new bone (SPNB) as an inflammatory response (Brickley & Ives, 2010; M. Brickley et al., 2020). Abnormal cortical porosity occurs due to increased capillary formation as a consequence of the repeated microtrauma to weakened blood vessels in connective tissues (Ortner & Ericksen, 1997). The external greater wing of the sphenoid bone and ectocranial temporal bone are regions known to express pathological porosity related to scurvy due to the habitual use of the *temporalis* muscles in the chewing of food (Ortner & Ericksen, 1997). Similarly, movement of the *supraspinatus* and *infraspinatus* muscles result in pooling of blood leading to SPNB deposits and abnormal cortical porosity in the supraspinous and infraspinous fossae of the scapula that form in response to the hematomas (Snoddy et al., 2018). As the actions of these muscles occur bilaterally, scorbutic subperiosteal hemorrhagic lesions (and associated new bone response) tend to be symmetrical and bilateral (Ortner & Ericksen, 1997; Snoddy et al., 2018). Lesions can also be asymmetrical, particularly if the individual is ambulatory, as they are dependent on the hemorrhaging from microtrauma due to activity of weightbearing bones (M. Brickley et al., 2020; Maat, 2004). However, asymmetric lesions may be difficult to distinguish from other microtraumas due to muscle strain. As ascorbic acid is essential in osteoid formation, for SPNB to form, some reintroduction of Vitamin C in the diet is required. Therefore, evidence of SPNB in scurvy indicates periods of Vitamin C recovery, although likely only small amounts are necessary to elicit new bone formation (Brickley & Ives, 2006; Geber & Murphy, 2012; Klaus, 2017; Snoddy et al., 2018).

Lower limb changes are common in infants and children with a predilection for the femur, tibia and fibula and lateral bulging of the legs often observed in affected infants due to subperiosteal hemorrhaging (Jaffe, 1972, p. 450). Pain is less common in the upper extremities suggesting lesion expression of the upper limb is likely to be less common than the lower limb (Jaffe, 1972, p. 450). Enlargement at the costochondral junction of the ribs due to subperiosteal hemorrhage, known as scorbutic rosary, is also a frequent clinical finding in infants (Jaffe, 1972, p. 453).

The skeletal indicators of scurvy-related bone growth disruption can be observed both macroscopically and radiographically. Porosity extending from the metaphyseal plate is a normal occurrence in growing juveniles as osteoclastic activity resorbs bone at the metaphyseal plate to allow for continued longitudinal growth (Ortner, Butler, Cafarella, & Milligan, 2001). However, in children with scurvy, the porosity exceeds beyond that of normal growth. Currently, porosity observed more than 10mm from the metaphyseal plate is arbitrarily considered to be abnormal by Ortner et al. (2001). Radiographically, this disturbance presents as a translucent zone in the metaphyses called a 'Trümmerfeld zone' or 'Scurvy' line (Jaffe, 1972; Resnick, 1995). This area of radiolucency is often accompanied by a radio dense metaphyseal plate due to poor resorption of calcified cartilage, termed a 'White line of Fraenkel'. A similar radio dense line around the epiphyseal plate (Wimberger ring sign) can also occur (Snoddy et al., 2018). Given the disruption to osteoid formation, the structural integrity of the bone is compromised and fractures at the corners of the metaphyseal plates (Pelkan spurs) are clinically reported (Snoddy et al., 2018). Radiographic signs of 'ground glass' osteopenia of the trabeculae is also another suggestive indicator of scurvy as a result of poor osteoid formation but is observed in many metabolic conditions (M. Brickley et al., 2020). Radiographic signs tend to be observed bilaterally and across multiple bones representing signs of systemic growth disruption.

This paper aims to explore the nutritional impact of the initial adoption of farming in northern Vietnam by assessing the skeletal evidence of scurvy in the non-adult cohort of Con Co Ngua, a pre-agricultural forager community (ca. 7-6500 BP; n=60). Results will be compared with the early agricultural site of Man Bac (ca. 4-3500 BP; n=44) which marks the initial adoption of domesticated rice and pigs in the region. Our research questions are: a) was there a change in nutritional disease levels with the agricultural transition? And if so, b) what were the health consequences for non-adults through infancy and childhood? Ultimately, by answering these research questions we can address the boarder issue: what does the findings at Man Bac and Con Co Ngua mean for the non-adults and overall populations during the transition of agriculture in MSEA?

2. Methods and Materials

The two sites for this study lie within 15km of each other on the coast of northern Vietnam (Figure 1). Their proximity to each other and the high representation of infants and children in both assemblages make these sites particularly suitable to meet the objectives of this study. Con Co Ngua dates to the height of the Holocene Thermal Maximum in northern Southeast Asia and southern China, whereas Man Bac directly postdates the 4.2ka desertification event.

2.1 The Unique Context of the Agricultural Transition in Southeast Asia

Prior to the agricultural revolution, forager communities descended from the first populations out of Africa and into Asia, benefitted greatly from the warmer climate of the Holocene Thermal Maximum (HTM) which reached its peak in MSEA by approximately 8-6kya (Renssen, Seppä, Crosta, Goosse, & Roche, 2012). During the HTM there was approximately 1°C mean annual temperature higher compared to industrial period temperatures in the region, and intensification of summer monsoon precipitation encouraged significant tropical floral and faunal diversity (Maher & Hu, 2006; Renssen et al., 2012). A consequence of this high resource abundance meant mobile foraging groups in northern Vietnam and southern China were capable of reorganizing into large sedentary settlements (Oxenham, Trinh, Willis, Jones, Domett, Castillo, Wood, Bellwood, Tromp, Kells, et al., 2018). A post-HTM drying and a desertification event, known as the 4.2ka event, likely significantly altered the resource returns of these large sedentary groups of foragers, possibly becoming unsustainable (Oxenham, Trinh, Willis, Jones, Domett, Castillo, Wood, Bellwood, Tromp, Kells, et al., 2018; Renssen, 2022). From approximately 4kya, farmers from southern China migrated to MSEA and interacted with local indigenous foragers (P. Bellwood & M. Oxenham, 2008). This migration prompted a subsistence transition with the introduction of domesticated pigs and dogs, and rice and/or millet farming (Castillo, 2011; Jones et al., 2019; Piper et al., 2014; Weber, Lehman, Barela, Hawks, & Harriman, 2010). However, variation within MSEA as to the degree of adoption and intensification of agricultural foods led to a heterogenous impact on health (King et al., 2017; Oxenham & Tayles, 2006). Foraging supplemented farming at many, if not all, sites in the region, which may have provided a buffer from nutritional deficiencies caused by a reliance on a single staple (Castillo, Fuller, Piper, Bellwood, & Oxenham, 2018; C. Higham & Thosarat, 2005; Jones et al., 2019; Oxenham, 2015; Oxenham, Matsumura, & Kim Dung, 2011). Indeed, full agricultural dependence did not perhaps occur until the Late Iron Age (500BC to 500AD; Table 1) with the intensification of wet rice agriculture and the construction of moated settlements (Halcrow, Tayles, & King, 2016; C. Higham, 2007; C. Higham et al., 2014; King et al., 2014; McGrath & Boyd, 2001).

Figure 1: *Location of Man Bac and Con Co Ngua. The present-day capital city of Hanoi is provided for comparison.*

2.2 The Pre-Agricultural site: Con Co Ngua (ca. 7-6500BP)

Con Co Ngua is a habitation and burial site in the Thanh Hoa province, dating to the early seventh millennium BP. The site was excavated in 1979-1980 and again 2013. During its occupation, at the height of the Holocene Thermal Maximum (HTM) the site was likely situated on an estuary (Oxenham, Trinh, Willis, Jones, Domett, Castillo, Wood, Bellwood, Tromp, & Kells, 2018). The climate was warmer and wetter than present day, and the indigenous food resources were more abundant. For this reason, the inhabitants of Con Co Ngua settled as sedentary hunter-gatherers, managing wild buffalo and potentially other large fauna, in contrast to the rice growing agricultural groups who occupied areas of southern China further north (Oxenham, Trinh, Willis, Jones, Domett, Castillo, Wood, Bellwood, Tromp, & Kells, 2018; Scott et al., 2019; Vlok et al., 2021). Foraging of a wide range of abundant terrestrial, riverine, estuarine, and marine resources allowed for the development of a large sedentary community (Jones, 2017b; Jones et al., 2019; Oxenham, Trinh, Willis, Jones, Domett, Castillo, Wood, Bellwood, Tromp, & Kells, 2018). The Con Co Ngua assemblage includes a total number of 155 individuals representing 60 non-adults under 20 (39%), and 95 adults (61%) (see table 3).

2.3 The Agricultural site: Man Bac

Man Bac is a habitation and burial site just north of Con Co Ngua in the Ninh Binh province, dating to 3906-3523 cal BP, excavated in 1999, 2005, and 2007 (Oxenham et al., 2011; Vlok et al., 2020). In the past, the surrounding ecology included riverine, coastal and estuarine flora and fauna (Tanabe et al., 2006). The site is associated with the Phung Ngyuen period known for early agriculture, distinct pottery designs, and interactions with farmers in what is now geo-politically southern China (Hiep & Phung, 2004; Oxenham et al., 2011). Long grain rice phytoliths were found within the cultural layers of Man Bac, similarly, identified at other Phung Nguyen sites (P. Bellwood & M. Oxenham, 2008; Jones et al., 2019; Mai Huong, 2013, 2016; Willis & Oxenham, 2013). The remains of domesticated pigs and a considerably lower diversity of faunal taxa when compared to Con Co Ngua, have been noted (Jones et al., 2019; Oxenham, Trinh, Willis, Jones, Domett, Castillo, Wood, Bellwood, Tromp, & Kells, 2018; Sawada, Thuy, & Tuan, 2011). Preliminary carbon isotope results suggest a lower reliance on C3 plants, such as rice, than subsequent Bronze and Iron Age assemblages in Vietnam, supporting a gradual intensification of agriculture over time (Oxenham et al., 2011; Yoneda, 2008). Isotopic and faunal evidence demonstrate a continued exploitation of marine, freshwater, estuarine and terrestrial resources, a mixed subsistence base of foraging and farming is proposed for Man Bac (Jones, 2017a; Jones et al., 2019; Sawada et al., 2011; Toizumi, Thuy, & Sawada, 2011; Yoneda, 2008). The Man Bac assemblage comprises a total of 70 individuals with 44 non-adults under 20 (63%) and 26 adults (37%) (see table 3). The high proportion of non-adults in the Man Bac assemblage is indicative of an increase in fertility and population growth compared to Con Co Ngua (McFadden, Buckley, Halcrow, & Oxenham, 2018).

2.4 Skeletal Preservation

The non-adult bones from Con Co Ngua can be predominantly described as having poor preservation. The bones were fragmented and most non-adults, particularly infants were represented by less than 50% of their total skeleton. Skeletal surfaces exhibited moderate surface erosion (Grade 3 to 4 of McKinley (2004)).

However, Man Bac displayed excellent non-adult preservation. More than half of the assemblage had a minimum of 75% completeness of the skeleton. Skeletal surfaces exhibited minimal to slight surface erosion (Grade 0 to 1 of McKinley (2004)). Beetle chewing and rodent gnawing was identified in one individual, and concretions of solidified soil matrix were present in some individuals but had minimal impact on pathological observations. Infrequently, endocranial surfaces were unobservable due to concretions inside the cranium. It is recognized that significant differentiation in the preservation of the non-adults in the two assemblages is a confounding factor, but as later discussed non-specific new bone lesion distributions indicate real difference in disease patterns regardless of the poor preservation of some elements in the Con Co Ngua assemblage.

2.5 Age and Sex Estimation

Dental eruption and calcification methods were used and compared to standards presented by Moorrees, Fanning, and Hunt (1963) and Ubelaker (1989) published in Buikstra and Ubelaker (1994) and White, Black, and Folkens (2000). Where dentition was not available, long bone diaphyseal lengths were compared to other children within the assemblage with a recorded dental age. For individuals over the age of approximately 12 years, standards for epiphyseal fusion methods were used based on Scheuer and Black (2000). As most individuals are pre-pubertal, sex was not assessed in this investigation. Frequencies for infants were separated in 6-month categories, and post-infancy, 5-year categories.

2.6 Lesion Recording and Diagnostic Protocol

All cranial and postcranial non-articular lesions were recorded macroscopically, and long bones were radiographed for each non-adult with macroscopic evidence of scurvy. Standardized methods for scurvy diagnosis by Snoddy et al. (2018) was employed for this analysis (Table 2). The Snoddy et al. (2018) threshold approach presents weighted diagnostic criteria to objectively standardize diagnosis of scurvy. The weighted criteria give greater diagnostic value to lesions that are clinically described in the medical literature and/or anatomically intuitive, with reported lesions in the paleopathological literature given lesser diagnostic weight. Lesions are considered as 'diagnostic' when there are clinically reported or anatomically intuitive with strong paleopathological literature backing. Lesions considered 'suggestive' of scurvy are associated with cases of scurvy in the clinical or paleopathological literature, but can also be found in other diseases, such as other metabolic disorders. The approach is conservative in that it does not allow for a definite diagnosis, recognizing the uncertainties associated with scurvy diagnosis in dry bone, such as confounding factors of growth in infancy and porosity due to normal human variation. The Snoddy criteria is derived from a comprehensive synthesis of the prior paleopathological and medical literature on scurvy diagnosis, and each lesion is justified through literature review and/or statistical testing of its designated diagnostic value. It is arguably a more transparent approach from critical review of cases in the archaeological record and allows for consistency in diagnosis which is potentially useful for estimating prevalence in population-based approaches in paleopathology.

Application of Snoddy et al. (2018) criteria require rigorous differential diagnosis of lesions. While it is a quantitative approach attempting to standardize criteria for determining *possible* versus *probable* cases, each lesion is considered within a biological diagnostic approach. It is expected that researchers critically engage with a differential diagnosis of similar etiologies such as rickets and pellagra when considering the contribution of each lesion to the diagnosis of scurvy. It is also expected that the researcher understands the etiology of the lesion contributing to diagnosis and how pathophysiological processes of other diseases can lead to the same expression in dry bone. Mays (2018) argues that quantitative approaches such as the Snoddy et al. (2018) criteria require comparison to more traditional approaches. Therefore, in this study, a 'traditional' differential diagnosis is carried out alongside the Snoddy et al. (2018) criteria.

Following the Snoddy et al. (2018) criteria, diagnosis of disease was determined as consistent with a *possible* or a *probable* diagnosis following these standards. A minimum of one *diagnostic* or two *suggestive* lesions was required for a possible diagnosis, with a probable diagnosis requiring at minimum two diagnostic lesions. SPNB deposits on long bones have been considered by Snoddy et al. (2018) as diagnostic for scurvy when cranial SPNB is present. However, the presence of treponemal disease in non-adults at Man Bac (11.4% of the non-adult assemblage) suggests possible co-morbidity (Vlok et al., 2020) and thalassemia occurred at both sites (Vlok et al., 2021). Therefore, diaphyseal SPNB was excluded from the diagnostic criteria for scurvy as these bone changes are a common occurrence in both diseases. Additionally, as scorbutic lesions are most commonly symmetrical, unilateral lesions were not considered diagnostic for scurvy. Abnormal endochondral porosity exceeding 10mm from the proximal or distal metaphyseal plates were also considered here as a diagnostic lesion for scurvy following Ortner's standards (Ortner et al., 2001; Snoddy et al., 2017). Lastly, active scurvy was recorded as follows. 'Active' scurvy was identified through the presence of at least one diagnostic SPNB lesion exhibiting no signs of remodeling (woven bone present only), indicative of recent scurvy-related skeletal activity. There remain challenges to identifying clear boundaries between active, healing, healed and recurrent episodes of scurvy (Schattmann, Bertrand, Vatteoni, & Brickley, 2016). Therefore, active only lesions provide a proxy to assess the most recent cases where in the child was still or had recently suffered a case of Vitamin C deficiency and had yet to recover when they died. Complete remodeling is observed where lesions present as lamellar bone only, but the original margins of the lesion have not yet been reduced to the contour of normal bone.

Due to the availability of radiographs, and continued debates in the literature about diagnostic issues in infants, we have further separated the classification of disease diagnosis into:

1. Probable case (corroborated by radiographs)
2. Probable case (macroscopic signs only)
3. Possible case

***Table 2**: Diagnostic lesions of scurvy. One diagnostic lesion is consistent with a possible case. Two or more diagnostic lesions are consistent with a probable case. Suggestive lesions that supplement diagnoses are provided in Supplementary Table S1.*

Pathology	**Differential Diagnosis**
Macroscopic Signs	
Abnormal cortical porosity/ subperiosteal new bone (SPNB) on: Ectocranial Parietal/Squamous Temporal bones	Trauma, infection, anemia
External Greater Wing of Sphenoid	Trauma, infection
Foramen Rotundum	Appositional growth (juveniles)
Pterygoid Fossae and/or Plates	Appositional growth (juveniles)
Anterior Surface of Maxillae/ Infraorbital Foramina	Trauma, infection
Posterior Surface of Maxillae	Alveolar resorption
Palatal Surface of Maxillae	Infection, trauma
Medial surfaces of Coronoid Processes of Mandible	Infection, trauma
Supraspinous Fossae of the Scapula	Trauma, appositional growth
Infraspinous Fossae of the Scapula	Trauma, appositional growth
Orbital roof	Trauma, anemia
Abnormal endochondral porosity extending >10mm from the distal metaphyseal plate of long bones	Rickets, longitudinal growth
Radiographic Signs	
White Line of Fraenkel	Normal variation, lead toxicity, rickets
Trümmerfeld Zone	Osteopenia, trauma, amaemia
Wimberger Ring Sign	Normal variation
Corner Fracture at position of dense zone of calcification (Pelkan's spur) Can also be observed macroscopically.	Trauma

(Brickley & Ives, 2010, p. 65; Geber & Murphy, 2012; Ortner et al., 2001; Schattmann et al., 2016; Snoddy et al., 2018; Snoddy et al., 2017)

2.7 Statistical Analysis

Fisher's exact tests were applied to test whether there was a:

1. Significant difference in the prevalence of scurvy across time periods
2. Significant difference in the prevalence of scurvy between children over the age of 5 in each site.
3. Significant difference in the prevalence of *active* scurvy between children over the age of 5 in each site

The "under-five" morbidity and mortality rate is a common epidemiological age comparator, with children under the age of 5 years recognized to be more susceptible to diseases than their older counterparts (World Health Organization, 2016). Significance was considered at p<0.05. Where a cell was '0', a score of '0.5' was inputted as is standard for Fisher's exact test.

Odds ratio analyses were also applied to test the size of the effect in the prevalence of scurvy across time periods (see Smith (2020) on discussion of importance for size of effect in bioanthropological data).

3. Results

3.1 Lesion Distribution and Radiographic Outcome

Con Co Ngua

The infants all exhibited diffuse active new bone. However, the layered and uniform distribution indicated these were due to normal growth and were remarkably different to the new bone identified as abnormal in the Man Bac assemblage (Figure 2). While there are differences in the preservation between the sites, the differences in pathological versus non-pathological new bone in infants can be determined. One adolescent exhibited abnormal porosity and new bone of the temporal bones. While the porosity is bilateral it is not symmetrical and does not follow any of the predictable anatomical locations observed in cases of scurvy, such as the of the *temporalis* muscle attachments on the cranium and mandible.

Man Bac

The general lesion pattern observed in the Man Bac non-adults was symmetrical discrete subperiosteal new bone with abnormal cortical porosity of the facial bones, sphenoid bones, and temporal bones, diffuse new bone across the long bones, and abnormal endochondral porosity of the metaphyses of long bones associated with zones of radiolucency, and radio dense metaphyseal plates (Figure 2). The Man Bac perinates and neonates present with distinct regions of cortical porosity that are absent in the Con Co Ngua perinates and neonates clearly indicating these lesions are not due to normal growth (Figures 2 and 3; Supplementary Text S1).

Over ninety-five percent (95.4%; n=42/44) of the assemblage had lesions in two or more skeletal elements, suggesting a pattern of systemic disease as defined by Ortner (1992) and Buckley and Tayles (2003). The lesions were predominantly bilateral and symmetrical islands of SPNB, with association of abnormal cortical porosity, particularly in the cranium. Ninety-three (n=40/43) percent had lesions on the crania, and 88.6% had lesions on the postcranial bones (n=39/44). While not considered here as diagnostic in their own right, vascular impressions in association with symmetrical discrete SPNB and abnormal cortical porosity suggests hematoma formation (Klaus, 2017). Vascular impressions were observed particularly in children under the age of five years on the anterior and posterior zygomatic bones and maxillae of children with subperiosteal lesions. Abnormal deep endochondral porosity of the long bones, extending more than 10mm from the metaphyseal plates, was evident in 52.3% (n=23/44) of the assemblage. Fifty percent (n=22/44) of the nonadults also presented with a White line of Fraenkel, Trümmerfeld zone and/ or Pelkan spurs (corner fractures of metaphyses) in conjunction with macroscopic lesions.

Figure 2: Comparisons of normal porosity and new bone in infants from Con Co Ngua (CCN), and pathological porosity and new bone in infants from Man Bac (MB). (A) difference in appositional new bone vs. porous pathological new bone in the orbits. (B) Cortical porosity perpendicular to bone surface of the posterior zygoma in the MB infants is absent in the CCN infant. (C) Porosity and new bone in the MB infant cover a region extending far beyond the margins of the growing frontal bone. Normal new bone at the fontanelle margins is observed in the CCN infant without evidence of cortical porosity.

Figure 3: Further comparisons of normal porosity and new bone in infants from Con Co Ngua (CCN), and pathological porosity and new bone in infants from Man Bac (MB). (A) Posterior aspect of distal femora displayed. The MB individuals exhibit abnormal endochondral porosity extending beyond that observed at CCN. Note the linear striated formation of the metaphyseal region in the MB infants indicating defect in bone deposition. (B) Clustered deposits of perpendicular porosity are present in the MB infants and absent in the CCN infant.

3.3 Diagnosis of Scurvy

There were no lesions diagnostic for scurvy present in the Con Co Ngua non-adults. The new bone (and the associated porosity) on the skull of an adolescent, appeared asymmetrical, more consistent with an inflammatory response to systemic infection than metabolic disorder. In contrast the lesions at Man Bac were highly consistent with metabolic disease and/or intrinsic disorders demonstrating a wide distribution of symmetrical lesions across the skeleton. Caffey's disease, rickets, hypophosphatemia, pellagra, and scurvy were included in the traditional differential diagnosis for non-adults from Man Bac (Supplementary Text S2). Scurvy was the most likely candidate at Man Bac, with some pathological overlap with rickets. Caffey's disease, hypophosphatemia and pellagra were ruled out based on clinical and contextual grounds. Co-occurrence of scurvy with rickets is common (Schattmann et al., 2016), and was observed in some of the non-adults in the assemblage (Vlok et al. forthcoming).

The application of Snoddy et al. (2018)'s criteria for diagnosis of scurvy identified that 79.5% (n=35/44) of the assemblage met the minimum threshold criteria for diagnosis of probable scurvy and 95.5% (n=42/44) met the threshold criteria for, at minimum, possible scurvy (see Figure 4; Table 3). However, given radiographs were available, and the prevalence for scurvy at Man Bac is uniquely high, the evidence for scurvy was further divided into three diagnostic classifications to investigate the validity of the prevalence generated by the Snoddy et al. (2018) method. Almost 60% (n=25/42) of the individuals exhibited active only lesions related to scurvy. No scorbutic non-adult lesions were completely remodeled.

Table 3: Con Co Ngua (CCN) and Man Bac (MB) non-adult scurvy prevalence.

	Possible *Affected/ Observed (%)*		**Probable** *Affected/Observed (%)*		**Probable (Corroborated)** *Affected/Observed (%)*	
Age Cohort	***CCN***	***MB***	***CCN***	***MB***	***CCN***	***MB***
0 to 6 months	0/9 (0)	3/8 (37.5)	0/9 (0)	5/8 (62.5)	0/9 (0)	3/8 (37.5)
6 months to 1 year	0/4 (0)	0/6 (0)	0/4 (0)	6/6 (100)	0/4 (0)	6/6 (100)
1 to 5 years	0/10 (0)	3/20 (15)	0/10 (0)	16/20 (80)	0/10 (0)	10/20 (50)
5 to 10 years	0/8 (0)	0/4 (0)	0/8 (0)	4/4 (100)	0/8 (0)	4/4 (100)
10 to 15 years	0/6 (0)	1/3 (33.3)	0/6 (0)	2/3 (66.7)	0/6 (0)	0/3 (0)
15 to 20 years	0/17 (0)	0/4 (0)	0/17 (0)	3/4 (75)	0/17 (0)	0/4 (0)
Total	**0/60 (0)**	**7/44 (16) ***	**0/60 (0)**	**35/44 (79.5) ***	**0/60 (0)**	**23/44 (52.3) ***

**=* statistically significant ($p<0.05$)* Supplementary Table S1 provides a detailed scurvy diagnosis outcome for all non-adults at both sites.

Figure 4: Lesions diagnostic for scurvy in Man Bac non-adults. SPNB and cortical porosity of the palate (A), anterior maxilla (B, C and J), coronoid process of the mandible (D), lateral greater wings (E) and pterygoid processes of the sphenoid bone (G). These lesions were all symmetrical. Abnormal deep endochondral porosity of the distal femur twice extending twice as long as what is considered normal (<10mm) (H). White lines of Fraenkel and Trümmerfeld zones observed in the radiographs of the long bones (I).

Evidence for Probable Scurvy Corroborated by Radiographs (Man Bac)

Out of the 35 individuals who met the criteria for a probable diagnosis of scurvy, 23 individuals had long bones exhibiting radiographic signs for scurvy. Therefore, a total of 52.3% (n=23/44) of the assemblage could be confidently diagnosed with probable scurvy with both macroscopic and radiographic evidence for the disease. Macroscopic *and* radiographic features for scurvy were identified in all age groups including the perinates (Figure 5).

Figure 5: Macroscopic and Radiographic diagnostic features for scurvy in a Man Bac perinate (MB05M7). Porosity and new bone of the (A) posterior zygoma, (B) coronoid process of mandible, (C) incisive fossa of mandible, (D) greater wing and around foramen rotundum of the sphenoid, (E) radiograph showing White lines of Fraenkel and Trümmerfeld zones.

Evidence for Probable Scurvy by Macroscopic Evidence Only (Man Bac)

Only 12 individuals had macroscopic evidence consistent with a probable case of scurvy who lacked radiographic signs of scurvy. Most of these cases were 10 years of age or older at time of death during a period of slower long bone growth than in early childhood. Therefore, it is unlikely radiographic signs would be valuable for diagnosis at this age (Figure 6a). For children under the age of 2 years old at death, the 6-months to under 1 year of age-at-death presented with the highest prevalence for scurvy. This pattern is observed when considering only macroscopic signs as well as a combination of macroscopic *and* radiographic signs (Figure 6b).

Figure 6: Prevalence of total probable scurvy vs. probable scurvy corroborated by radiographs in Man Bac age groups (A) throughout the whole non-adult assemblage, and (B) under 2 years of age.

Evidence for Possible Scurvy (Man Bac)

Only 18.2% (n=8/44) of the Man Bac non-adult assemblage presented evidence of possible scurvy. Diagnosis for possible cases appear to be predominantly due to poor preservation, especially poor representation of the skull, as more weight in diagnosis is given to lesions of the face and cranium (Supplementary Table S1). However, when all lesions that are considered diagnostic and suggestive for scurvy are represented within a skeletal distribution diagram, the lesion distribution from possible cases is similar to that of probable cases (Figure 7; Supplementary Table S1).

The disparity observed between the diagnosis of possible and probable cases is due to the absence of diagnostic lesions of the fragile facial bones in the possible cases. That is, the diagnosis of possible cases was a product of poor preservation inhibiting confidence in diagnosis. The most frequently observed evidence for scurvy at Man Bac were abnormal endochondral porosity of long bone metaphyses, and new bone lesions with cortical porosity of the mandible, scapula, zygomatics and the sphenoid bone, followed by lesions of the cranium and maxilla, regardless of age of the individuals.

It is important to note that these possible cases identified at Man Bac, even with poor preservation, further distinguishes the pathological findings from the non-adults from Con Co Ngua. Despite similarly poor preservation of Con Co Ngua non-adults to those of possible cases at Man Bac, the older site presents no clear evidence for scurvy.

Figure 7: Distribution of diagnostic and suggestive macroscopic lesions for scurvy in the Man Bac non-adults. Individual data for each lesion prevalence per bone (NISP) can be found in Supplementary Table S1.

3.4 Statistical Analysis

Across Time Periods

The Fisher's exact test demonstrates a statistically significant difference between the prevalence of probable scurvy at Con Co Ngua versus Man Bac ($p<0.0001$). Given the significance of the Fisher's exact test, the size of the effect was tested with odd ratio analysis. An odds ratio of 452.2 (95%CI: 25.5-8005.9; $p<0.0001$) supports an exceptionally high effect size. The outcome is expected given remarkably no clear evidence for scurvy at Con Co Ngua, and exceptionally high prevalence at Man Bac.

Across Age Groups by Site (Man Bac)

Given the considerable evidence for scurvy at Man Bac, statistical analysis across different age-at-death cohorts was completed. There were no statistical differences in the prevalence of probable only ($p=0.6$) or combined possible/probable scurvy ($p=0.4$), under and over 5 years of age. Therefore, age does not appear to play a significant role in the overall presence of scurvy at Man Bac. However, most non-adults (69.7%; n=23/33) under the age of 5 years exhibited active scurvy, and only 22% of individuals 5 years and over presented with active scurvy (n=2/9; Table 4). This difference was statistically significant ($p=0.015$). Given the significance, the size of the effect was tested with odd ratio analysis. An odds ratio of 8

(95%CI: 1.4-45.8; p=0.019) supports a great effect size. The greater effect size adds weight to the confidence to a significant outcome.

***Table 4**: Prevalence of active scurvy at Man Bac across age-at-death cohorts*

Age Cohort	*Active/ Observed (%)*
0 to 6 months	7/8 (87.5)
6 months to 1 year	5/6 (83.3)
1 to 5 years	11/19 (57.9)
5 to 10 years	0/3 (0)
10 to 15 years	1/3 (33)
15 to 20 years	1/3 (33)
Total	25/42 (59.5)

*only cases where pathology was observed is included in the analysis

4.1 Discussion

Our results demonstrate a significant increase of non-adult scurvy from the Pre-Neolithic to early Neolithic periods in northern Vietnam. No clear evidence was found in the non-adults at Con Co Ngua, whereas almost 80% of the Man Bac assemblage exhibited pathology consistent with a diagnosis of probable scurvy.

4.1 The use of radiographs to strengthen diagnosis in scurvy

The Snoddy criteria provided a useful standard for assessing diagnosis of scurvy across a large non-adult assemblage. However, as demonstrated in this paper, the use of radiographs is further useful in increasing the confidence in diagnosis. While in the older children at Man Bac (>4 years of age) lesions related to scurvy were easy to discern macroscopically from underlying normal bone, the challenge of diagnosis remains in infants still undergoing rapid subperiosteal bone growth, particularly in those under 6 months of age (see discussion in M. E. Lewis, 2017). The Snoddy criteria (as well as other previous criteria for diagnosis of scurvy) does not provide clear definitions for differentiating lesions of normal growth from those due to pathological bone change in response to Vitamin C deficiency. In this research, we confronted this problem with comparisons of bone surfaces amongst two different groups with biosocial, environmental, and genetic affinities.

4.2 Revisiting diagnosis of scurvy in infants under 1-years-of-age

Prior research has previously identified cases of scurvy in perinatal and neonatal skeletal remains (see Buckley et al., 2014; Kinaston et al., 2009; Snoddy et al., 2017). Attention to diagnosis of scurvy in infants is essential given the high proportion of this age cohort represented in the Man Bac non-adult assemblage. The benefit of such research is that diagnosis of scurvy in this cohort facilitates discussion of Vitamin C deficiency of the expecting or breastfeeding mother. At Man Bac all infants under 6 months of age (100%; n=8/8) presented with possible or probable scurvy with 62.5% (n=5/8) having probable scurvy. While it is possible that growth is playing some role in the bone changes observed in the young infants at Man Bac, the frequency of all individuals under the age of 6 months with probable scurvy was not higher than other age cohort, which would be expected if the SPNB observed was strictly due to growth. Furthermore, White lines of Fraenkel associated with Trümmerfeld lines were present in 60% (n=3/5) of these infants diagnosed with probable scurvy. These radiographic signs indicate disruptions to osteoid formation and do not share the same confounding factor of growth associated with macroscopic observations of SPNB. We argue here that the infant cohort of a skeletal assemblage can be assessed for scurvy and should not be excluded from paleopathological analyses based on age alone. This is particularly important in assemblages such as Man Bac with high fertility indices and therefore a greater proportion of the assemblage being represented by infants.

4.3 Causes of scurvy at Man Bac

Even in the absence of any other systematic study of nutritional diseases in the region, the levels of scurvy in Man Bac non-adults is exceptionally high, but the presence of scurvy in a tropical context is not entirely unexpected given prior reports in tropical countries. Halcrow, Harris, Beavan, and Buckley (2014) report a case of scurvy in a non-adult from historical period Cambodia and a high prevalence of the disease was reported from a population in subsistence transition from the Pacific islands (Buckley et al., 2014). The excellent preservation of bone surfaces at Man Bac may also have contributed to this high rate, as active SPNB can be lost through a range of taphonomic factors (Roberts & Connell, 2004). The excellent preservation of crania at Man Bac may also have contributed to this high observable prevalence (Brickley & Ives, 2010; Snoddy et al., 2018). It is also conceivable that the frequencies of possible cases of scurvy is an overrepresentation of individuals with clinical scurvy. As previously mentioned, treponemal disease has been identified in the Man Bac assemblage, possibly contributing to the SPNB recorded in the non-adult assemblage (Vlok et al., 2020). However, regarding probable cases, 84.1% (n=37/44) of Man Bac non-adults had more than three diagnostic lesions for scurvy, and 56.8% (n=25/44) also presented with radiographic signs of scurvy, further strengthening the argument for high levels of non-adult scurvy at Man Bac.

Man Bac inhabitants had a broad-based diet. It is currently not known to what degree rice was relied on or to what degree indigenous plants supplemented the diet at Man Bac. Evidence for fruits and nuts of a wide variety have been found in Pre-Neolithic sites in northern Vietnam (Mai Huong, 2013; Oxenham, Trinh, Willis, Jones, Domett, Castillo, Wood, Bellwood, Tromp, & Kells, 2018) and the diverse ecologies exploited by the Man Bac community may have provided a range of available fruits and nuts. However, following climate cooling after the HTM decline in at approximately 5kya, the ecology of the region would have changed significantly. Globally, dietary diversity decreased with the transition to agriculture, and this pattern is also present at Man Bac with a decrease in faunal taxa exploitation around the introduction of agriculture (Jones et al., 2019). It is possible a similar reduction in floral diversity also occurred with the introduction of rice and concurrent climate change, that may partly explain the high levels of scurvy identified at Man Bac. Both wild and cultivated food sources may have been occasionally disrupted by frequent tropical storms, potentially increasing the nutritional stress already experienced with the decrease in dietary diversity (Oxenham, 2006), an interpretive point also used in the Pacific (Buckley et al., 2014).

Although at Man Bac there was a high reliance on various species from marine, freshwater, and brackish environments, all fish types provided inadequate levels of Vitamin C. Similarly, the terrestrial faunal assemblage would not have yielded sufficient levels of Vitamin C (Sawada et al., 2011). The cooking and processing of these foods would have further depleted the bioavailable Vitamin C (Mays, 2013; Rumm-Kreuter & Demmel, 1990). The interaction between local foragers and migrant farmers was also likely to have had an impact on nutritional stress. The migrants may have needed to adapt the process of growing domesticated crops in this new environment, and locals likely needed to navigate the change of their environment by the agricultural efforts from this new migrant group. The process of teaching the other group their subsistence strategies would also have been imperfect.

Finally, adequate intake of Vitamin C is essential for immune function. Man Bac has already demonstrated paleopathological evidence for an exceptional pathogen load of treponematosis and malaria (Vlok et al., 2021; Vlok et al., 2020). A high pathogen load, where phagocytes are activated in the immune response, consequently, increases oxidative stress and increases the demand for Vitamin C, an antioxidant, in the body (Hemilä, 2017; Khaw & Woodhouse, 1995; Rokkas et al., 1995). Indeed, in a subtropical climate a high pathogen load from many infectious diseases is expected. Hookworm, roundworm, *Shigella* sp., *Salmonella* sp., schistosomiasis, malaria and *Escherichia coli* are all possible causes for infectious diarrhea which decrease the absorption of vitamin C (King et al., 2017; Oxenham, 2016). Weanling diarrhea, associated with the introduction of foods to supplement breast feeding may have also increased the dietary requirement for Vitamin C in infants. This synergy is possibly driving the high frequencies of scurvy identified in the Man Bac infants and has been argued to be a contributing factor in other tropical environments (Buckley, 2000). To date, no isotopic research has identified the terminal age of weaning at Man Bac, but passive immunity from the maternal intrauterine environment is known to be reduced by 3 months of age (M. E. Lewis, 2017). Furthermore, the high levels of fertility at Man Bac indicate shorter birth intervals which may have been facilitated by the early introduction of weaning foods (Buikstra et al., 1986; McFadden & Oxenham, 2018; Oxenham & Willis, 2017). It is possible the increased frequency of probable scurvy after 6 months of age is related to the decreased efficacy of passive immunity from the intrauterine environment combined with the introduction of weaning foods and increasing susceptibility of pathogens and the requirements for Vitamin C deficiency in these infants. In sum, a combination of restricted dietary diversity possibly due to environmental factors, combined with transition to agricultural subsistence, and high pathogen loads are likely underlying the outcome of high levels of non-adult scurvy at Man Bac.

4.4 Epidemiology of scurvy at Man Bac

Active scurvy cases were highest under 1 year of age. Additionally, active cases of scurvy were significantly higher in individuals under the age of 5 years than those over the age of 5 years. Selective mortality is most likely at play regarding the presentation of scurvy in infants and young children. Children under the age of 5 were likely more susceptible to risk of death from scurvy than those over the age of 5 years who more commonly presented with patterns of healing. However, the increase in prevalence following the 6-month mark indicate other factors beyond the mortality profile influencing the age-at-death distribution of scurvy. Potential impacts include weaning, the changing growth demands of an infant at this age, and introduction of pathogens via supplementary weaning foods. It is possible that breast milk provided some buffering to nutritional deficiency in the neonatal and early infant period. Indeed, scurvy is documented to be less common in breastfed infants. Even when not weaned, at 5 or 6 post-natal months, maternal stores of Vitamin C in breastmilk also tend to be depleted (World Health Organization, 1999). Additionally, infants between 6 months to 1 year are known to have an increased risk to nutritional disease when compared to infants under 6 months due to increased nutrient requirements (Devaney, Ziegler, Pac, Karwe, & Barr, 2004).

4.5 The Role of Vitamin C and Complications of Scurvy

Ascorbic acid (Vitamin C) is an antioxidant free radical compound with the ability to bind to aggressive oxidative compounds and make them less reactive, thereby playing a crucial role in the maintenance of the cellular membrane of intracellular organelles (Linster & Van Schaftingen, 2007). It also plays an antioxidant role in the plasma surrounding the lung, lens and retina of the eye (Bendich, Machlin, Scandurra, Burton, & Wayner, 1986). Oxidation occurs due to inflammatory immune response to pathogens, therefore Vitamin C plays an essential role in immune function (Wintergerst, Maggini, & Hornig, 2006). Vitamin C is also essential in the production of collagen formation in the body. Lysyl and prolyl (procollagen molecules) are hydroxylized by enzymes which require ascorbic acid for proper function. With prolonged Vitamin C deficiency, collagen fibers are rendered unstable, weakening collagen-based structures in the body such as blood vessels (Hirschmann & Raugi, 1999; Maat, 2004). Chronic hemorrhaging subsequently occurs in Vitamin C deficiency due to repeated rupturing of weak blood vessels causing the nutritional disease known as scurvy (Hirschmann & Raugi, 1999).

Chronic hemorrhaging subsequently occurs in Vitamin C deficiency due to repeated rupturing of weak blood vessels causing the nutritional disease known as scurvy (Hirschmann & Raugi, 1999).

At minimum 10mg a day is required to prevent clinical scurvy in an adult male, but requirements are poorly understood for non-adults (Hirschmann & Raugi, 1999). As observed in adults, within a few weeks of restricted dietary Vitamin C, fatigue develops as the first symptom (Hirschmann & Raugi, 1999). Within 90 days of deficiency, bodily stores of Vitamin C are depleted (Hirschmann & Raugi, 1999). Extended periods of scurvy over a few months can then result in hyperkeratotic papules around hair follicles, corkscrew hairs and eventually perifollicular and subperiosteal hemorrhaging as a consequence of weakened blood vessels (Hirschmann & Raugi, 1999; S. J. Lewis, Mcdowell, & Hawthorne, 1998). Hemorrhages have been reported to occur in the conjunctiva, eye lids, retrobulbar space, the sheaths of the optic nerve and in the limbs (which can cause neuropathy) (Hirschmann & Raugi, 1999; S. J. Lewis et al., 1998).

A plethora of other symptoms can occur including joint pain, joint effusions, ankle edema, mucosal ulceration, weakness, shortness of breath, tooth loss and insufficiency fractures of the spine (Hirschmann & Raugi, 1999; Keenan, Mitts, & Kurtz, 2002; S. J. Lewis et al., 1998). Pain associated with swelling of joints, movement of limbs, and bone pain predominantly due to hemorrhaging can sometimes lead to difficulty walking in adults and children (Hirschmann & Raugi, 1999; Keenan et al., 2002; Ortner & Ericksen, 1997). Infantile scurvy usually presents as tenderness of the limbs, pseudoparalysis (paralysis caused by pain and not nerve damage), irritability, cessation of sitting or standing, the drawing up of legs into a frog position, pain of the chest resulting in difficulty breathing, and bleeding gums with erupting teeth (Woodruff, 1956).

The production of abnormal type X collagen in children can cause metaphyseal deformities in growing limb bones (Keenan et al., 2002). As Vitamin C plays a role in osteoid production, calcified cartilage at the provisional zone of calcification of the metaphyseal plates lacks this vital component of growing bone (Keenan et al., 2002). Deficiency also results in thinning trabeculae in the metaphyses and an increased occurrence of microfractures (Keenan et al., 2002). Lastly, death can occur due to pulmonary hypertension, myocardial hemorrhaging, pericardial hemorrhaging, and most commonly fatal shock due to internal blood loss and impaired vasoconstriction (Hirschmann & Raugi, 1999). Reintroduction of Vitamin C into the diet is curative. The high prevalence of scurvy in the Man Bac children suggests that a suite of the above signs and symptoms likely occurred amongst them, providing a significant care burden on the community. In conjunction with other non-specific signs of stress, it is clear these children required significant care beyond what is standard for infants (Oxenham & Willis, 2017).

4.6 Non-adult health and the Neolithic transition in Southeast Asia

Non-adults are the most sensitive indicators of health in a population where due to their rapid bone development and overall fragility, disease is likely to be more visible in this cohort than in adults (Halcrow et al., 2016; M. E. Lewis, 2017). Much of the recent findings such as by Vlok and colleagues (2020, 2021) have been contingent on the identification of diseases in non-adults. Other paleopathological works in the region further demonstrate the importance this cohort has had on revealing details of health in MSEA's past (Halcrow et al., 2013; Halcrow et al., 2016; Oxenham et al., 2008; Tayles, 1996, 1999). For example, the research by Halcrow and colleagues (2013, 2016) have distinctly demonstrated a significant impact on the health of the younger individuals in Thailand from the Iron Age onwards with the rise of hierarchical urban proto states.

The adoption of agriculture in MSEA, and the degree of interactions between farmers and foragers were complex and non-linear, therefore variations in the impact to health is expected (Oxenham & Buckley, 2016). Indeed, subsistence, population interaction, population density and sedentism vary throughout Neolithic sites in MSEA. Therefore, Man Bac and Con Co Ngua do not reflect the overall impact of the Neolithic transition on health in the region. To date no other MSEA Neolithic site presents with non-adult SPNB levels as high as Man Bac (Halcrow et al., 2016; Pietrusewsky & Douglas, 2002; Tayles, 1999), further indicating Man Bac may be a unique case in the overall transition to agriculture in the region. Additionally, scurvy has to date not been identified in other prehistoric sites in

MSEA. Interestingly, the skeletal evidence of non-specific stress at Man Bac, particularly in children is comparative to that of Khok Phanom Di (Halcrow et al., 2016; Oxenham & Domett, 2011), possibly indicating that the initial adoption of agriculture may have had a detrimental impact on health. However, to fully appreciate shifts in health with the adoption of agriculture, further paleopathological work on Pre-Neolithic sites is required beyond that of Con Co Ngua, the only systematically studied Pre-Neolithic site in MSEA to date. In other parts of MSEA such as modern day Thailand, Pre-Neolithic forager groups were smaller and more mobile, and a different transitional epidemiological pattern could be expected for these regions when agriculture was introduced (Shoocongdej, 2000).

There were very little differences in the prevalence of non-specific stress markers such as linear enamel hypoplasia and cribra orbitalia at Man Bac and Con Co Ngua (Oxenham & Domett, 2011; Oxenham, Trinh, Willis, Jones, Domett, Castillo, Wood, Bellwood, Tromp, & Kells, 2018). We now know that the inhabitants of Con Co Ngua greatly suffered high infectious disease burdens including malaria, hydatid disease, as well as genetic anemia (Vlok et al., 2022; Vlok et al., 2021), which would have obscured the differing nutritional trends contributing to non-specific stress, and now revealed through investigation for evidence of scurvy in the assemblages. That is, while the morbidity of general physiological stress was similar, the contribution of nutritional and infectious diseases to these stressors differed greatly among Con Co Ngua and Man Bac.

This trend in high burdens of disease revealed through specific and non-specific disease at Man Bac and Con Co Ngua is not observed in later Bronze and Iron Age sites that mark the intensification of agriculture (Halcrow et al., 2016). It is likely that factors not directly related to the dietary effects of rice, rather secondary impacts of initial agricultural adoption, such as a significant increase in fertility, and climatic decline of wild resource returns, are the drivers for an increase in nutritional stress at Man Bac. A reappraisal of prehistoric MSEA sites, employing recent approaches to identifying specific nutritional diseases is warranted to further investigate if this is a consistent (albeit generalized) temporal trend. Ultimately, the impact of agricultural transition on health should be investigated at a site level, and various lines of paleopathological study involving assessment of non-specific markers of stress *and* the diagnosis of specific diseases should be incorporated in the analysis of changes of health with the agricultural transition in this region.

5. Conclusion

We document here paleopathological evidence for an exceptional increase in nutritional stress from the Pre-Neolithic to Neolithic of northern Vietnam. Between the conditions of the Holocene Thermal Maximum experienced by the inhabitants of Con Co Ngua and the 4.2ka event which affected the Man Bac inhabitants, the extremes of ecological, social, and biological change created a scenario wherein dramatic shifts in nutritional disease could be observed over time. Ultimately, a large climatic shift whereby a subsistence change to farming was likely necessary for survival, enacted a plethora of flow on effects with consequences to health. Increased sedentism, a higher juvenile to adult ratio, a greater burden of infectious disease, increased food demands, diminishing wild resource returns, and renegotiation of kinship and social structure would have all contributed to the most vulnerable in the population dying with scurvy (and all the other diseases that interact to exacerbate the effects of scurvy) prior to achieving adulthood. We conclude that it is not necessary for significant agricultural efforts (especially agricultural dependence) to occur for there to be potentially significant deleterious consequences to health, particularly in the context of climate change, as was the case at Man Bac.

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7. Data Availability Statement

Data is provided in the supplementary material.

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Figure 1: Location of Man Bac and Con Co Ngua. The present-day capital city of Hanoi is provided for comparison.

596x315mm (300 x 300 DPI)

Figure 2: Comparisons of normal porosity and new bone in infants from Con Co Ngua (CCN), and pathological porosity and new bone in infants from Man Bac (MB). (A) difference in appositional new bone vs. porous pathological new bone in the orbits. (B) Cortical porosity perpendicular to bone surface of the posterior zygoma in the MB infants is absent in the CCN infant. (C) Porosity and new bone in the MB infant cover a region extending far beyond the margins of the growing frontal bone. Normal new bone at the fontanelle margins is observed in the CCN infant without evidence of cortical porosity.

470x283mm (300 x 300 DPI)

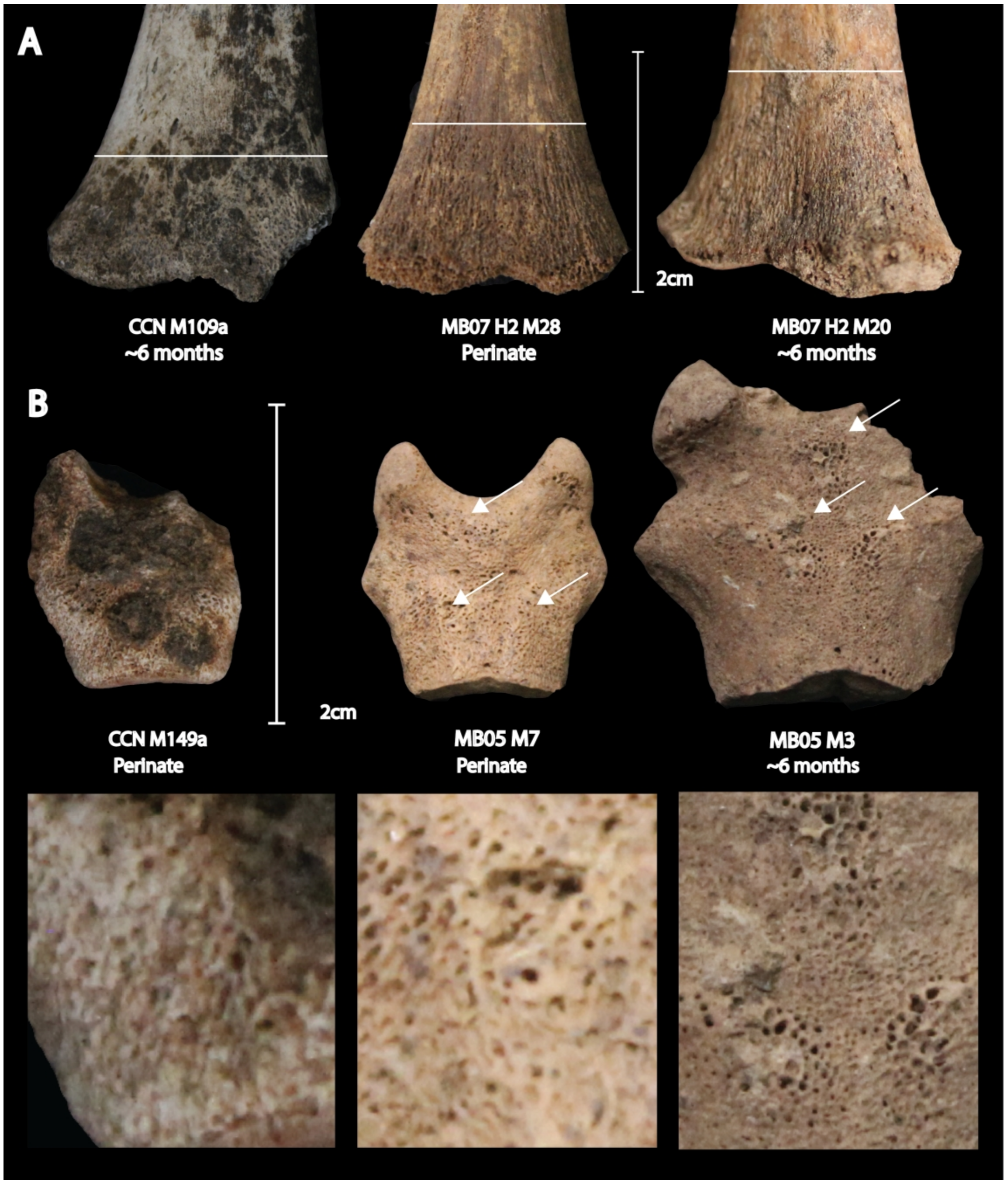

Figure 3: Further comparisons of normal porosity and new bone in infants from Con Co Ngua (CCN), and pathological porosity and new bone in infants from Man Bac (MB). (A) Posterior aspect of distal femora displayed. The MB individuals exhibit abnormal endochondral porosity extending beyond that observed at CCN. Note the linear striated formation of the metaphyseal region in the MB infants indicating defect in bone deposition. (B) Clustered deposits of perpendicular porosity are present in the MB infants and absent in the CCN infant.

259x304mm (300 x 300 DPI)

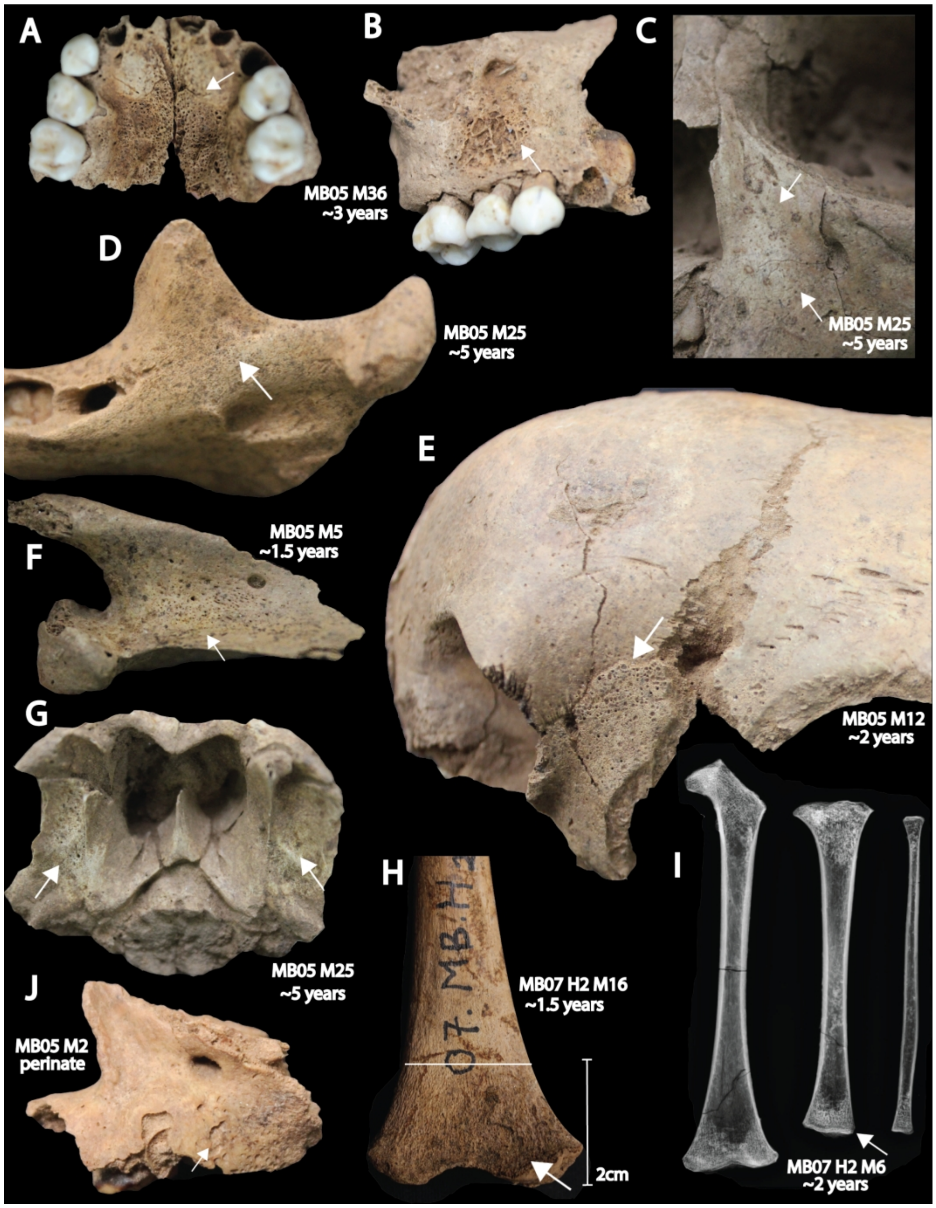

Figure 4: Lesions diagnostic for scurvy in Man Bac non-adults. SPNB and cortical porosity of the palate (A), anterior maxilla (B, C and J), coronoid process of the mandible (D), lateral greater wings (E) and pterygoid processes of the sphenoid bone (G). These lesions were all symmetrical. Abnormal deep endochondral porosity of the distal femur twice extending twice as long as what is considered normal (<10mm) (H). White lines of Fraenkel and Trümmerfeld zones observed in the radiographs of the long bones (I).

215x278mm (300 x 300 DPI)

Figure 5: Macroscopic and Radiographic diagnostic features for scurvy in a Man Bac perinate (MB05M7). Porosity and new bone of the (A) posterior zygoma, (B) coronoid process of mandible, (C) incisive fossa of mandible, (D) greater wing and around foramen rotundum of the sphenoid, (E) radiograph showing White lines of Fraenkel and Trümmerfeld zones.

520x558mm (300 x 300 DPI)

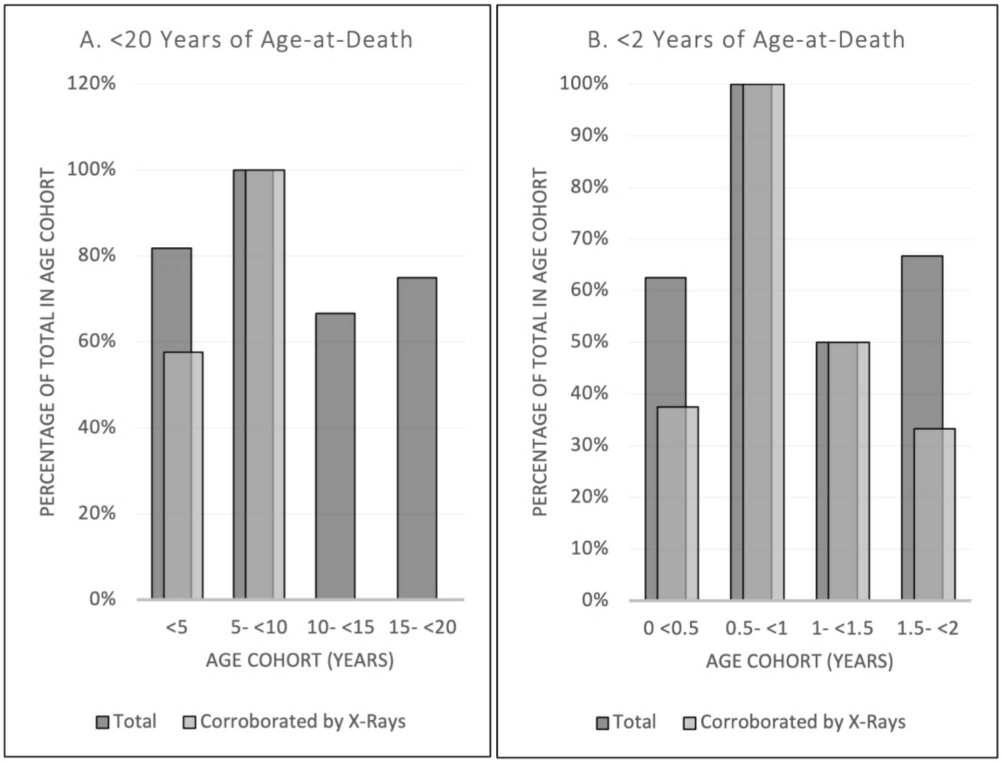

Figure 6: Prevalence of total probable scurvy vs. probable scurvy corroborated by radiographs in Man Bac age groups (A) throughout the whole non-adult assemblage, and (B) under 2 years of age.

148x112mm (300 x 300 DPI)

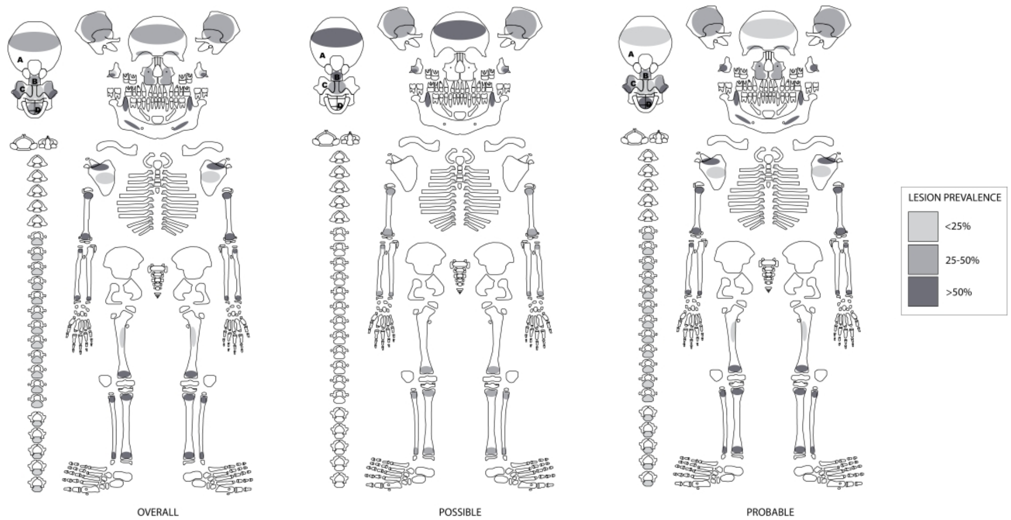

Figure 7: Distribution of diagnostic and suggestive macroscopic lesions for scurvy in the Man Bac non-adults. Individual data for each lesion prevalence per bone (NISP) can be found in Supplementary Table S1.

654x335mm (300 x 300 DPI)