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RESEARCH ARTICLE

Hypomineralization disorder in tropical Southeast Asia during the agricultural revolution: Analysis of morbidity and mortality

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Abstract

This paper presents evidence for hypomineralization disorders (rickets and osteomalacia) in non-adults at Man Bac, a Neolithic site from northern Vietnam dated to 4000–3500BP, contributing to the well-described disease burden at the site that includes scurvy, treponemal disease, thalassemia, and malaria. Forty-four non-adults (<20 years of age-at-death) were assessed for macroscopic and radiographic evidence for hypomineralization disorders. Differential diagnosis was completed using traditional methods and three-level standardized criteria to combat the challenges of overlapping pathological features between hypomineralization disorder and the other diseases already diagnosed at the site. In addition, a diagnostic certainty approach was applied to investigate the impact of lesion ambiguity on our findings. Kaplan–Meier and Fishers exact tests were applied to assess age-at-death-related epidemiological patterns of hypomineralization disorder and co-morbid relationships with scurvy, thalassemia, and treponemal disease. Almost 50% of the non-adult assemblage presented with evidence for hypomineralization disorder, which was associated with decreased survivorship in childhood. Potential epidemiological relationships between scurvy and hypomineralization disorders, and thalassemia and hypomineralization disorders are described. The former relationship may be due to the likelihood of the introduction of rice resulting in multi-micronutrient deficiency, including vitamin C and calcium deficiency, and cultural attitudes to sunlight. The latter relationship may relate to the pathophysiology of thalassemia that can result in secondary osteomalacia possibly contributing to the development of hypomineralization disorder in the thalassemic non-adults. The findings are significant as they present possible approaches for diagnosis of disease embedded within complex disease burdens where individuals are likely suffering from co-morbidities.

KEYWORDS

frailty, micronutrient, MSEA, nutritional disease, prehistory, survivorship, tropics, Vietnam

1 | INTRODUCTION

Rickets is a skeletal childhood condition caused by hypomineralization of osteoid and reduced apoptosis of endochondral cartilage before epiphyseal fusion is complete (Wharton & Bishop, 2003). Hypomineralization of osteoid also causes a condition called osteomalacia that results in the softening of bones that are prone to bending and fracturing. Although rickets does not occur in adults, osteomalacia does. In non-adults, rickets and osteomalacia occur in tandem. For shorthand purposes in this paper, we shall refer to the condition of both rickets and osteomalacia that occur in non-adults as hypomineralization disorder. The causes of hypomineralization disorder are complex but deficiency of vitamin D and/or calcium are the common causes of this disease (Munns et al., 2016).

Gross skeletal changes, observable in dry bone and due to metabolic disturbance, include fraying/porosity, flaring, and cupping of the metaphyses, and long bone bending deformities (Brickley, Ives, & Mays, 2020). Hypomineralization disorders in tropical and desert regions are rarely reported in the paleopathological literature but are frequently reported in the clinical literature (see Vlok, Snoddy, et al., 2023). This dearth in the paleopathological literature is due to the emphasis on investigation for hypomineralization disorders in assemblages where poor UV rays, particularly in wintertime, likely contributed to the development of vitamin D deficiency. For example, a significant number of cases of hypomineralization disorder documented in the paleopathological literature are related to historical periods of Europe where urbanization in high latitude areas, crowding, and pollution significantly reduced the access to sufficient sunlight in order to prevent vitamin D deficiency (Giuffra et al., 2015; Ives, 2018; Lamer et al., 2023; Mays et al., 2006; Schattmann et al., 2016; Veselka et al., 2021).

Although contested by Mays and Brickley (2022), there is both consensus among the clinical community (Munns et al., 2016) and strong evidence for the presence of calcium deficiency-predominant hypomineralization disorder in countries closer to the equator with high sunlight hours. Therefore, assemblages in these sunlit countries should not be ignored in investigations of this disease. In these circumstances, vitamin D deficiency plays a secondary albeit still an essential role in the development of clinically observable "nutritional rickets" (hypomineralization disorder not associated with genetic or renal origins). The presence of hypomineralization disorder in an assemblage enables consideration of dietary and behavioral factors that restricted calcium and vitamin D bioavailability. Additionally, the presence of these deficiencies marks unseen systemic effects on the individual's organ and cognitive function, immuno-sufficiency to cancers and infectious diseases, normal endocrine function, growth and development, and musculoskeletal development (Snoddy et al., 2016; Vlok, Snoddy, et al., 2023). Where multitudes of individuals within an assemblage present skeletal evidence for hypomineralization disorder, a population burden on economic and domestic production of food and resources, cognitive impacts on decision making in changing environments, high infant and maternal mortality, and high burdens of care related to disabled and sick individuals can therefore be inferred (Arshad et al., 2022; Grant et al., 2009; Morales-Suárez-Varela et al., 2022; Snoddy et al., 2016; Zittermann et al., 2009).

The aim of this paper is to explore diagnostic approaches and assess epidemiological patterns of hypomineralization disorder in the Neolithic assemblage of Man Bac, northern Vietnam. Prior paleopathological research at the site (dated to 4-3500BP) identified a uniquely heavy burden of scurvy (almost 80%) prolific throughout the non-adult assemblage ($n = 44$) (Vlok, Oxenham, et al., 2023). However, some pathological features that were identified in the differential diagnosis were not consistent with scurvy, but rather more consistent with hypomineralization disorder.

Given hypomineralization disorder is predominantly observed via the presentation of musculoskeletal clinical signs, the disease has had a significant focus in the paleopathological literature both in terms of representation throughout space and time in archeological assemblages (Brickley & Ives, 2010; Brickley, Ives, & Mays, 2020; Ortner & Mays, 1998). However, the non-adult assemblage at Man Bac presents a challenge in the identification of skeletal lesions specific to hypomineralization disorder because of the presence of a great number of co-morbidities previously described and overlapping pathological features. Specifically, the identification of thalassemia, scurvy, and treponemal disease at Man Bac contributed greatly to the ambiguity of lesions potentially related to hypomineralization disorder in the site. This site is markedly unique both spatially and temporally in the Southeast Asian region, and no other site to date displays remotely similar disease burdens.

Although features consistent with hypomineralization disorder were identified in Vlok, Oxenham, et al. (2023), the focus of that particular paper was on the diagnosis of scurvy. The research by Vlok, Oxenham, et al. (2023) attributed the presence of scurvy in the non-adults at Man Bac to a combination of climate change, the initiation of rice agriculture, an intense infectious disease burden, and rapid population growth. Given the role that calcium can have in the development of hypomineralization disorder, there may be shared etiologies between these two diseases as both micronutrients may have been lacking in the diet in tandem. However, interpretation of etiology requires a full diagnosis of the pathological features of hypomineralization disorder and an epidemiological analysis of the relationship between the two diseases.

Scurvy is well recognized to co-occur with hypomineralization disorder (Ives, 2018; Klaus, 2014; Schattmann et al., 2016). However, scurvy and hypomineralization disorder can have overlapping pathological features because of their impact on bone modeling and remodeling requiring a detailed differential diagnosis between the two diseases. New bone deposits and endochondral porosity of long bone ends can be differentiated between the conditions (Schattmann et al., 2016; Vlok, Oxenham, et al., 2023). For example, porosity of the metaphyseal plate itself is characteristic of rickets rather than scurvy (Brickley, Ives, & Mays, 2020). However, variation of severities of the two conditions results in overlapping macroscopically and radiographically observable features, especially regarding porosity on the bone surfaces. Schattmann et al. (2016) have previously described

macroscopic and radiographic overlapping features for scurvy and hypomineralization disorder. The authors similarly recognized that "porosity" particularly of the cranial vault and orbits, ribs, and metaphyses of long bones was difficult to distinguish between the two diseases. Ortner and Mays (1998) originally argued that hypomineralization disorder can co-occur with scurvy in cases where sick and disabled scorbutic infants and children were kept in doors for prolonged periods of time away from sunlight. However, in agricultural contexts as well as in the case of both the rural and urban poor, the co-occurrence may have been concurrently driven by the over-reliance on micronutrient-poor crops causing deficiency in both vitamin C and calcium, with vitamin D insufficiency or deficiency as a complicating factor. A case of co-morbidity of hypomineralization disorder and scurvy in a 1.5-month-old infant from the early agricultural period of the Atacama desert, Chile has been identified and described (Sohler, 2017; Vlok, Snoddy, et al., 2023). Radiographic features useful in the diagnosis of scurvy such as white lines of Fraenkel, Trümmerfeld zones, and cortical thinning appear similar to the radiodensity of metaphyseal plates observed in healed rickets. However, radiodense metaphyseal plates associated with healed rickets are discernible based on their relative thickness due to the mineralization of excessive deposit of osteoid in comparison with the case of scurvy where the white line of Fraenkel represents a provisional zone of calcification where osteoid is again being deposited and mineralized. A white line of Fraenkel should always be observed in relation to a Trümmerfeld zone. Without this zone, which represents a region of continued bone osteolysis in the absence of the typical bone deposit and mineralization process during bone modeling, an expanded provisional zone of calcification as an adaptation for the disturbance during vitamin C deficiency would not exist (Pelkan, 1925). Radiographic signs in less severe cases can, however, overlap if the features are not distinctly observable. It is important that radiographic and macroscopic features be observed in tandem to minimize the potential for misattribution of the feature to one of the two diseases. The radiographic features in vitamin C deficiency represent advanced scurvy, meaning vitamin C deficiency has been occurring long term (Agarwal et al., 2015). Therefore, where radiographic features exist, it is expected that macroscopic signs of scurvy should also be apparent. The presence of a Pelkan spur directly associated with the Trümmerfeld zone and Fraenkel line further provides confidence the radiographic features are due to scurvy.

Like hypomineralization disorder, treponemal disease (a bacterial disease caused by *Treponema pallidum*, responsible for diseases including syphilis (*T.p. pallidum*) and yaws (*T.p. pertenue*) is associated with generalized long bone hypertrophy (Vlok et al., 2020). This disease was identified in up to 11% (5/44) of the non-adults at Man Bac (Vlok et al., 2020). In hypomineralization disorder, the lesion forms due to healing following the excessive deposit of unmineralized osteoid on the cortical surfaces, and in treponemal disease due to inflammatory cortical enlargement in response to secondary and tertiary infection (Baker et al., 2020; Hackett, 1976; Harper et al., 2011; Vlok et al., 2020). In many circumstances, these pathological signs are discernible from each other as the long bone hypertrophy in hypomineralization disorder is associated with poor organization of the new bone from the lack of osteoid mineralization. For example, MB05M5, an 18-month-old child at Man Bac exhibited clear signs of cortical enlargement of the tibiae (in the form of "nodes" as described by Hackett, 1976), without any evidence for poor mineralization, clearly not consistent with hypomineralization disorder, and more suggestive of treponemal disease (see Vlok et al., 2020). However, at Man Bac, the prolific burden of scurvy causes further ambiguity between the distinction of long bone hypertrophy in hypomineralization disorder versus treponemal disease.

Almost 11% (5/44) of the Man Bac non-adult assemblage exhibited evidence for clinical signs of thalassemia (Vlok et al., 2021). The clinical signs of thalassemia that are strongly diagnostic for this disease include radiographic rib-within-rib signs and gross marrow expansion leading to macroscopic deformity of the mandible and maxilla (Lewis, 2012; Vlok et al., 2021). In Southeast Asia, a high burden of thalassemia, a genetic disease, has emerged over the millennia because of the advantage it provides to the host against malarial mortality (Weatherall, 1997). Those who have a combination of normal and thalassemic alleles present minimal to moderate clinical consequence from the genetic anemia while also having protection against malarial mortality. Stabilizing selection leads to generational persistence of both thalassemic and non-thalassemic alleles within malarial areas. As over 10% of the Man Bac non-adult assemblage had clinical signs that indicated fatal thalassemia, a greater proportion of the overall Man Bac assemblage (adults and non-adults) could be expected to have minor clinical changes related to thalassemia. Clinical signs of thalassemia that overlap with hypomineralization disorder include flaring of the metaphyseal plates and porosity of the metaphyseal and diaphyseal regions due to extramedullary hematopoiesis, but thalassemia distinctly does not cause cupping or fraying of the metaphyseal plates. In the minor cases, the porosity (albeit extending from the medullary canal) may be indistinguishable or indeed coincide with porosity of the metaphyses and flaring of the long bone ends. Additionally, focal osteomalacia from iron overload appears to be a sequela of thalassemia (Mahachoklertwattana et al., 2003). Whether the same occurs in endochondral cartilage causing hypomineralization disorder is poorly documented but has been mentioned in passing in the literature potentially due to hepatic impairment (Pollak et al., 2000; Soliman et al., 1998), but the hypomineralization disorder observed in clinical cases may be related to iron chelation treatment instead of the disease itself, clouding the picture (Orzincolo et al., 1990). In addition, many thalassemic individuals are clinically reported to have deficient levels of vitamin D and calcium (Pollak et al., 2000; Soliman et al., 2013; Vichinsky, 1998; Voskaridou & Terpos, 2004). As such, the individuals diagnosed with thalassemia at Man Bac cannot be disregarded from the analysis of hypomineralization disorder, as thalassemia may be a contributor to the epidemiology of this disease.

In addition to thalassemia, the presence of a high malarial burden itself likely added to the prolific evidence of general anemia at Man Bac. Thirty-four percent (12/35) of the non-adult assemblage exhibited moderate or severe cribra orbitalia and/or porotic hyperostosis (Vlok, 2020), and over 90% (29/32) exhibited some form of

pathological orbital porosity or porous new bone (Oxenham & Domett, 2011; see Wang et al., 2023, for similar circumstances hypothesized for Con Co Ngua, a forager site in northern Vietnam with evidence of thalassemia; Vlok et al., 2021). Cortical thinning of long bones is similarly observed in anemia and in active hypomineralization disorder. Both conditions in healing or in the process of chronic long-term pathology also lead to the coarsening of trabeculae observed radiologically (Aksoy et al., 1966; Schattmann et al., 2016). The trabecular coarsening develops as a result of compromised and eventual loss of smaller trabeculae (Mays et al., 2007; Shore & Chesney, 2013). In anemia, the response is due to medullary hyperplasia and increased osteolysis, and in hypomineralization disorder, it is due to hypomineralization of osteoid in the process of normal remodeling often accompanied by thick osteoid in living tissue (Oppenheimer & Snodgrass, 1980; Pithon, 2011; Sanger et al., 1977).

Work by Lewis (2010, 2011, 2012) has similarly identified scurvy, thalassemia, and hypomineralization disorder in the non-adults at Romano-British Poundbury Camp. Thalassaemia was identified in three individuals (<1%), and 11.2% presented with scurvy and/or hypomineralization disorder. In addition, tuberculosis was also prevalent in 4.2% of non-adults (Lewis, 2010, 2011, 2012). Lewis' findings indicate that complex disease interactions could be contributing not only to the intensity of the disease prevalence but also provide a diagnostic challenge in a number of archeological contexts.

Considering these challenges in achieving the aim of diagnosing hypomineralization disorder at Man Bac, this paper investigates whether lesions consistent with hypomineralization disorder can be identified separately from lesions caused by other conditions the community suffered. Additionally, we will investigate the impact of hypomineralization disorder on morbidity and mortality and recontextualize the overall disease burden at Man Bac in relation to our findings.

2 | MATERIALS

Man Bac is a habitation and mortuary site dated approximately between 4000 and 3500BP during the early agricultural transition in

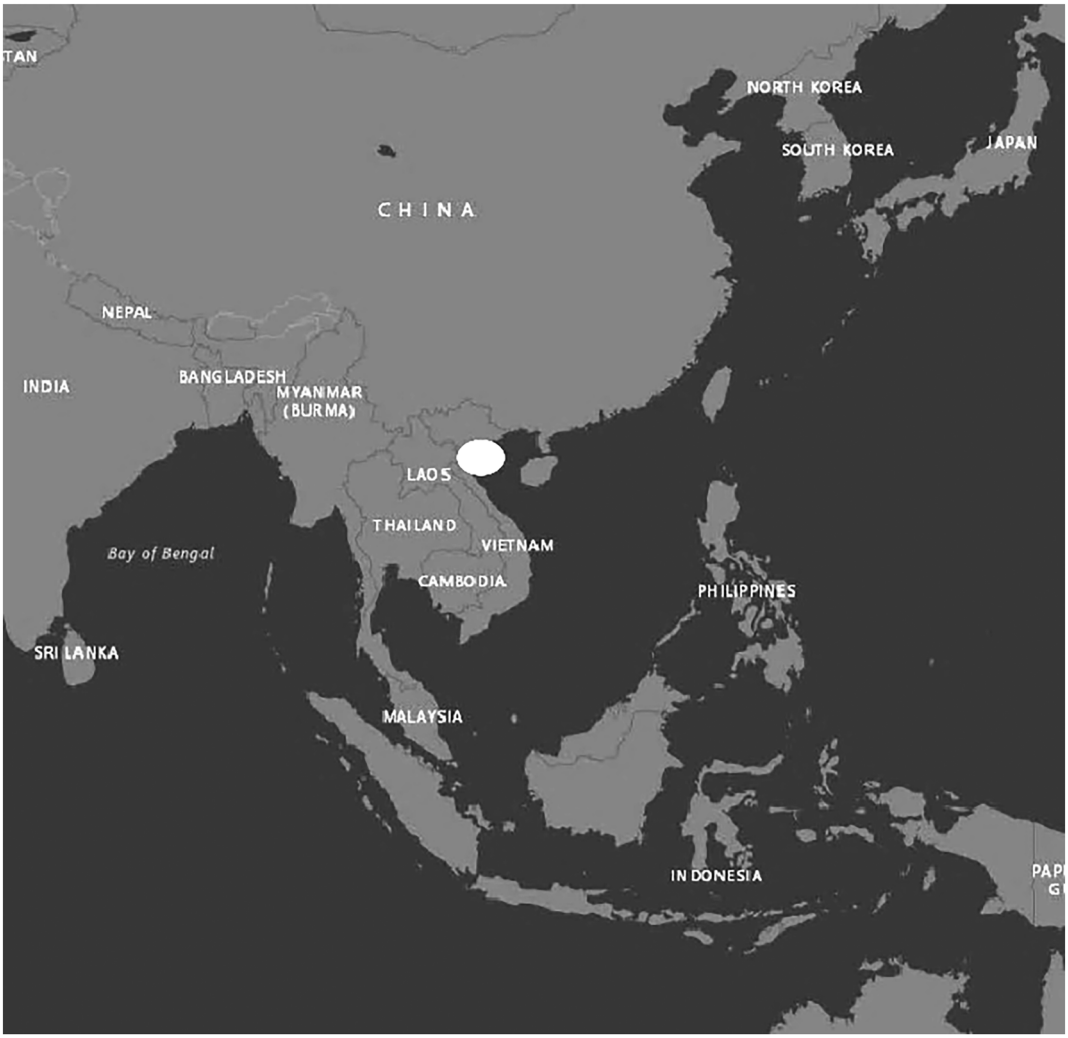

FIGURE 1 Location of Man Bac (white ellipse).

northern Vietnam (Figure 1). During this time, a significant population-scale migration of farmers expanded from what is currently geo-politically southern China into northern Vietnam, which had up until this point resisted the adoption of agriculture in favor of large sedentary foraging communities. These indigenous communities were instead sustained by the productive food returns from multiple accessible environments including aquatic, marine, forest, grassland, and wetland zones, as well as the likely management of wild buffalo and possibly deer (Jones et al., 2019; Oxenham et al., 2018; Vlok, Buckley, et al., 2022). The combination of biological and archeological evidence demonstrates that the Man Bac community consisted of a group of recently migrated farmers cohabitating with indigenous foragers. Their main subsistence base continued to be primarily the exploitation of natural resources, supplemented by the consumption of domesticated pigs and rice (Jones, 2017; Jones et al., 2019; Oxenham et al., 2011). Compared with most other Southeast Asian sites in prehistory, Man Bac has high fertility levels, a high rate of natural population increase (higher number of births versus deaths), and as outlined above, a high burden of infectious and nutritional diseases (McFadden et al., 2018). The distinct epidemiological pattern of Man Bac may be attributed to a unique set of spatio-temporal characteristics including an extreme climate drying event (4.2 ka event), introduction of agriculture, increased sedentary residence, and a high level of interpopulation interaction (as defined by Vlok & Buckley, 2022).

Forty-four non-adults (individuals under the age of 20 years) presented with at least two skeletal elements that have the potential to display diagnostic lesions for hypomineralization disorder and therefore were selected for this analysis. These skeletal elements include bones of the crania, long bones, and ribs. All these individuals also presented with the minimum skeletal preservation required to be assessed for scurvy (crania and long bones) (Vlok, Oxenham, et al., 2023), which provides a valuable cross-analysis for scurvy and hypomineralization disorder co-occurrence at the site.

2.1 | Age-at-death estimation

The age-at-death estimation was completed by Domett and Oxenham (2011), and the methods used are summarized as follows:

Where teeth were available, a combination of dental mineralization and dental eruption standards was applied as the primary age-at-death estimation techniques until adolescence (Moorrees et al., 1963; Ubelaker, 1989). Radiographs were taken of the maxillae and mandibles to enable recording of dental mineralization within the tooth beds. Where teeth had yet to be developed or were absent due to lack of preservation, diaphyseal long bone standards were compared with the long bone lengths (Fazekas & Kosa, 1978; Maresh, 1970). Standards for the primary and secondary fusion of elements were also applied following Scheuer and Black (2000). For adolescents, secondary fusion (epiphyseal fusion) was the primary method used for age-at-death estimation. Biological sex estimation was not included in this analysis as the sample size of non-adults with secondary sex characteristics was too small ($n = 4$).

2.2 | Lesion identification and hypomineralization disorder diagnosis

All osteoblastic, osteolytic, and bone shape deformity lesions of the skeletons were recorded, and the long bones of all the non-adults were radiographed. A traditional differential diagnosis including hypomineralization disorder and scurvy was completed previously and identified that hypomineralization disorder was the most likely cause for certain long bone and cranial features (Vlok, Oxenham, et al., 2023). Cupping, flaring, and fraying/porosity of metaphyseal plates and poorly mineralized new bone on the crania observed in this study were inconsistent with a diagnosis of scurvy.

Core lesions for diagnosis by Brickley and Mays (2019) were adapted to the special considerations of the overall Man Bac disease environment and to standardize diagnosis within the assemblage for statistical purposes. The clinical diagnostic signs include porosity, flaring, and cupping of metaphyses of long bones, porosity of rib ends and endochondral plates, and poorly mineralized porous new bone on the orbits and cranium. Unlike in scurvy, radiographic signs for hypomineralization disorder (such as coarsening of trabeculae) only support a diagnosis and are not "diagnostic" (after Vlok, 2023), although macroscopically observable porosity of the endochondral ends is also identifiable on radiographs as "fraying," and the

TABLE 1 Diagnostic framework for hypomineralization disorder adapted from Brickley, Ives, and Mays (2020).

Diagnostic confidence	Skeletal sign
Diagnostic (non-overlapping features)	Poorly mineralized new bone of the cranial vault (A) Alteration in rib neck angle Enlargement/porosity (A) of costochondral junction Bending deformities of the limbs *Coxa Vara*: depression of the femoral neck with reduced angulation Porosity of the metaphyseal plate (A) Metaphyseal cupping Superior flattening of the femoral head Ilium bending/angulation deformity. Mandibular ramus bending/angulation deformity
Diagnostic (overlapping features)	Flaring of the distal metaphyses Severe porosity of the metaphysis (A) Long bone hypertrophy (H) Thin cranial bones (A) Cortical hypertrophy of cranial bones (H) Poorly mineralized new bone deposit of the orbits: Easily misclassified as orbital porosity or hemorrhage (A)
Suggestive features	Kyphosis or scoliosis (mainly T9-L3) Porosity on the concave side of deformed bones (H) *Radiographic sign*: Trabecular coarsening *Radiographic sign*: Generalized osteopenia

Note: Because of the metabolic nature of the disease, features are expected to be bilateral. (A) = active feature, (H) = healed feature.

combination of both methods increases confidence that the feature is not pseudopathological (caused by post-mortem damage to the endochondral plate). For the purposes of this study, the lesions were categorized into three levels of diagnostic confidence (see Tables 1 and 2). The terms "diagnostic" and "suggestive" were standardized following Vlok (2023). In addition, diagnostic probability was also sorted into three levels:

Level 1: Probable

- Two or more diagnostic features that do not overlap with scurvy, thalassemia, or treponemal disease are present.

Level 2: Probable (including overlapping features)

- Two or more diagnostic features including those that overlap with scurvy, thalassemia, or treponemal disease are present.

Level 3: Possible

- Only one diagnostic and/or two or more suggestive features are present.

2.3 | Healing stage

Some features in hypomineralization disorder are only present when the disease is active. These features appear porotic because of the

TABLE 2 Overlapping lesions between hypomineralization disorder and other diseases diagnosed at Man Bac.

Diagnostic lesion for hypomineralization disorder (after Brickley et al., 2020)	Thalassaemia (after Vlok et al., 2021)	Scurvy (after Snoddy et al., 2018)	Treponemal disease (after Vlok et al., 2020)
Overlapping features			
Flaring of the distal metaphyses	Yes	Yes: Rarely due to severe osteoid depletion	No
Porosity of the metaphysis	Yes: Due to extramedullary hematopoiesis and cortical thinning.	Yes: Due to lack of osteoid deposit. Not typically as severe as in hypomineralization disorder, but readily misattributed.	No
Long bone hypertrophy	Yes: But appearance tends to be in adults due to secondary hypoparathyroidism and where red-yellow marrow conversion has ceased.	Yes: Due to repeated subperiosteal hemorrhaging	Yes: Due to subperiosteal inflammatory new bone response in secondary stage. The presence of "nodes" of new bone as described by Hackett can be a distinctive feature but is not always the skeletal pattern observed.
Thin cranial bones	Yes: Prior to development of medullary hyperplasia	Yes	
Cortical hypertrophy of cranial bones	No: But porotic hyperostosis can be misattributed	No: Cranial lesions tend to be discrete and associated with clear cortical porosity and vascular impressions around muscle attachment sites with underlying vessels.	Yes: Due to subperiosteal inflammatory response in secondary stage.
Poorly mineralized new bone deposit of the orbitals	No: But severe cribra orbitalia with extramedullary hyperplasia causing new bone response may be misattributed.	No: But discrete new bone and cortical porosity due to retro-orbital hematoma can be misattributed.	No
Non-overlapping diagnostic features			
See Table 1	Marrow hyperplasia of the facial bones Radiographic rib-within-a-rib appearance Poor pneumatization of the paranasal and cranial sinuses Widening of the entire rib head and neck Costal osteomas	Symmetrical discrete new bone lesions with cortical porosity and vascular impressions of muscle attachments of the cranium and mandible White line of Fraenkel and Trümmerfeld zones (note: There is overlap with radiodense metaphyseal plates of healing rickets in less distinct cases)	*Caries sicca* sequence Gummatous lesions on any skeletal element Hutchinson's incisors and Moon's molars (congenital) Osteomyelitis of the long bone ends and Wimberger's corner sign (congenital)

continued hypomineralized osteoid that has since decomposed. In contrast, a thick bone deposit develops in the healing stage, where the excessive osteoid deposits have since been mineralized. In this study, hypomineralization disorder cases were classified as active when only active lesions were present, healed when only healed lesions were present, and multiple when active and healed lesions were present indicating two or more instances or sustained/intermittent development of hypomineralization disorder (after Brickley & Mays, 2019).

TABLE 3 Scales of different diagnostic certainties by Brickley and Morgan (2023, table 3, p. 641).

Categories of diagnostic certainty	Relationship of category to diagnosis	Definitions for macroscopic and radiographic analysis
Diagnostic	Another condition could not have caused the pathology	Active rickets Clear lesions of the bone underlying a growth plate and, where relevant, the associated metaphysis arising from defective mineralization (seen clinically on radiographs and observed directly in dry bone). Other lesions of rickets should also be anticipated. Healed rickets Unambiguous evidence of biomechanical deformity of bones and/or lesions such as thickening
Highly consistent	Strong probability the pathology observed is caused by this disease	Active rickets Low-grade porosis/roughening in bone surfaces underlying a growth plate and/or other lesion(s) that have few other possible causes. Healed rickets Evidence of typical biomechanical deformity of bones indicative of previous systemic defective mineralization of bone and/or other lesion(s) observed macroscopically or radiographically that have few other possible causes.
Consistent	Pathology may be seen in the disease, but other causes cannot be excluded	Porotic lesions and/or biomechanical deformity that are consistent with rickets but have various other possible causes.

Note: There is a difference in the definition of "diagnostic" as applied in the threshold criteria approaches compared to this approach.

2.4 | Addressing issues of lesion ambiguity

The threshold criteria approach presented here has one major shortcoming, the lack of consideration of lesion ambiguity (Vlok, 2023). That is, multiple subtle lesions can be more diagnostic than fewer lesions that are more severe. Although it would be expected that in a severe case of systemic disease such as hypomineralization disorder, multiple features would be present, that is not always the case when you consider poor preservation, especially of the metaphyseal regions of long bones. Our experience indicates that researchers are particularly hesitant with a threshold of only two diagnostic lesions (as originally presented by Brickley and Ives (2010) and adapted since by Snoddy et al. (2018), Vlok et al. (2020), Vlok et al. (2021), Vlok, Buckley, et al. (2022), and Vlok, Myagmar, et al. (2022)) for various diseases. Concerns about a threshold of only two diagnostic lesions are particularly problematic when diagnosing scurvy and hypomineralization disorders, as neither disease has a lesion that is universally accepted in the field as being strongly diagnostic or pathognomonic for the disease. The limitations of this method led to the removal of a threshold diagnostic approach from the second edition of *The Bioarchaeology of Metabolic Disease* (Brickley et al., 2020). We maintain, however, that a threshold is still necessary in order to provide statistically sound standards to the inclusion or exclusion of certain cases in epidemiological analysis. Single case studies are probably best represented by a differential diagnostic approach that emphasizes the core lesions presented in Brickley, Ives, and Mays (2020) and Brickley and Mays (2019).

To combat the issue of lesion ambiguity in diagnostic certainty, Brickley and Morgan (2023) have presented definitions to delineate cases that are more defined as being pathological and highly specific for non-adult hypomineralization disorder (and also scurvy) from those who are more subtle or provide less certainty to the diagnosis. Currently, its application is challenging to apply as the authors do not provide guidance as to what is considered clear and unambiguous compared to more subtle cases (Table 3). Instead, they suggest researchers' personal experience in the matter should ultimately guide the outcome, but it is difficult for readers and reviewers to assess the experience of others, and such an approach obscures transparency of diagnosis. Lastly, the differences across the categories are also based on whether there are no other, few, or various other possible causes, which is similar to the threshold diagnostic approach, but the authors do not define which of the core lesions of hypomineralization disorder presented have alternative causes and to what degree. Although the approach is new and requires independent testing, it is clearly a promising development moving forward. Currently, combining the two approaches appears to provide the most comprehensive strategy to diagnosis.

We applied the diagnostic certainty approaches to both the Level 1 and Level 2 probable cases to assess the relationship of lesion ambiguity with our findings using the threshold diagnostic approach in order to interrogate any potential shortcomings of our method and possible impacts on our findings. This approach does not consider the specific contexts of Man Bac and the high potential for multiple co-morbidities at this site, rather we apply the approach to rank the certainty of the lesion expressions of pathology potentially related to hypomineralization disorders in non-adults on a case-by-case basis. Photographs, radiographs, pathological descriptions, and diagnostic outcomes for every individual defined as a probable case of hypomineralization disorder are presented in Data S2. We do so in recognition that there is still subjectivity and lack of a uniform approach to the diagnosis of hypomineralization disorder and to provide complete transparency in our diagnostic process. We emphasize that given the variable approaches to the diagnosis of hypomineralization disorder in the field and the deeply complex situation of co-morbidity of different diseases at Man Bac, our findings are largely exploratory and open to reinterpretation in the future. There are also recent microscopic, radiographic, and micro-computed tomography approaches available to independently assess hypomineralization of bone and dentine (Brickley, Kahlon, & D'Ortenzio, 2020; Snoddy et al., 2021; Veselka & Snoeck, 2021; Welsh et al., 2020), but these were published following the data collection for this research project that was conducted in 2018.

2.5 | Statistical analysis

Age-related differences were assessed in the entire assemblage as well as the infants only (under 1 year of age). Fisher's exact tests were applied to analyze whether there was a statistically significant difference between:

- 0 to under 5 years old and 5+ years old in accordance with the World Health Organization under-5 mortality measure.
- 0 to under 6 months old and 6 months to under 1 year old to assess the potential of weaning and maternal stores of calcium and vitamin D on the morbidity and mortality of hypomineralization disorder.
- Individuals with hypomineralization disorder only, and individuals with both scurvy and hypomineralization disorder.
- Individuals with hypomineralization disorder only, and individuals with both treponemal disease and hypomineralization disorder.
- Individuals with hypomineralization disorder only, and individuals with both thalassemia and hypomineralization disorder.

Survivorship was assessed using Kaplan–Meier analysis. This non-parametric test assesses the different relationships between survival time (age-at-death) of two cohorts. The model was used to test for differences in the age-at-death distribution between those who exhibited Level 1 confidence for hypomineralization disorder compared with those who were not. The highest level of diagnostic confidence was employed to specifically assess heterogenous frailty and selective mortality associated with hypomineralization disorder only and not potential interacting co-morbidities. Instead of applying a *p*-value cut-off, the validity of the model was interpreted via a combination of the *p*-value (via a Mantel–Cox test), and the mean 95% confidence interval to statistically evaluate the findings. If the 95% CIs of the two test groups did not overlap, the outcome was considered meaningful. As the assemblage is limited to non-adults, the cumulative survival will reach an endpoint at the age of 20. This outcome reflects the sample selection and not a true end to the sample survival time, as adults in the assemblage were excluded.

3 | RESULTS

The non-adult assemblage at Man Bac presented with multiple pathological features that could be attributed to hypomineralization disorder including deformities and porosity of the metaphyseal plates; porosity of the crania, ribs, and appendicular skeleton; and bending deformities of the long bones and ribs (Figures 2 and 3). Almost 50% ($n = 21/44$) of the assemblage exhibited multiple diagnostic signs that did not overlap with possible co-morbidities previously identified (Level 1) (Table 4 and Data S1). An additional 2.3% ($n = 1/44$) met the criteria for a probable case when overlapping diagnostic lesions were also included (Level 2). Finally, 18.4% ($n = 8/44$) of individuals were diagnosed as possible cases.

The porosity that was observed differed from the cases who were diagnosed with scurvy only (Figure 4). For those with scurvy, the porosity resembled an accentuation of the normal metaphyseal cutting zone which results from the physiological process of osteolysis in order to necessitate longitudinal bone growth at the metaphyseal plate (Scheuer & Black, 2000). This porosity was originally observed by Ortner et al. (2001), which they defined as abnormal when extending >10 mm from the metaphyseal plate. In contrast, the porosity observed as pertaining possibly to hypomineralization disorder appeared more "chaotic," and fray-like in appearance, resembling the hairs of a bristle brush. The clinical sign is described as "fraying" in the radiological literature (Uday & Högler, 2024). This porosity was observed in dry bone on the plates and the metaphyseal regions. The difference in potential appearance of porosity of the metaphyses between scurvy and hypomineralization disorder can be related to the metabolic complications of the two diseases across different stages of bone development. The lack of osteoid deposit in scurvy would result in the same appearance, albeit accentuated, as the physiologically normal cutting zone in the metaphysis where bone is removed from the cortex systematically but not deposited. In rickets, osteoid is deposited but remains either fully or partially demineralized therefore leaving spaces where unmineralized osteoid decomposed. Thus, the appearance is more erratic in nature and appears deeper. Full descriptions, photographs, radiographs, and diagnoses for each individual diagnosed with a probable case of rickets are provided in Data S2. The following sections analyze the diagnosis results in more detail.

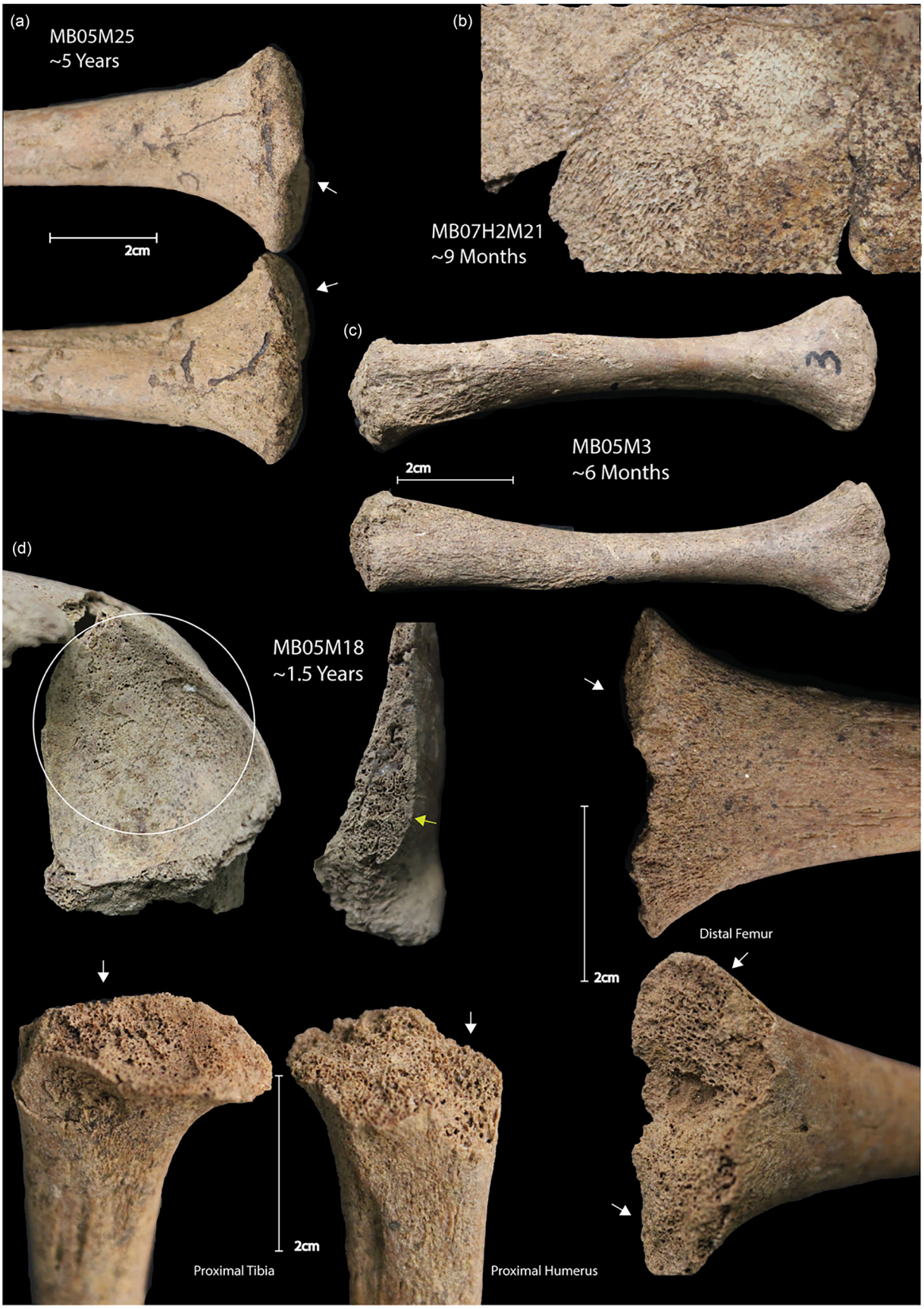

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FIGURE 2 Macroscopic signs of hypomineralization disorder at Man Bac. (a) Mild flaring and cupping of tibiae, (b) poorly mineralized new bone on the ectocranium, (c) porosity with poorly mineralized appearance of the metaphyseal plate and mild bending deformities of the humeri, and (d) a suite of lesions in one individual including poorly mineralized new bone of the orbits (circle), thick and poorly organized cortical deposit on the external cranium (yellow arrow), and porosity with poorly mineralized appearance, flaring and cupping of the long bone ends. Cupping is demonstrated by the white arrows. [Colour figure can be viewed at wileyonlinelibrary.com]

3.1 | Diagnosis (Level 1)

The most common non-overlapping pathological features that contributed to diagnosis were porosity and cupping of the metaphyseal plates, porosity and enlargement of the costochondral junction, and bending deformities of the limbs (Figure 5). Bending deformities and metaphyseal changes to the lower limbs were predominant (total prevalence of 41%), with only upper limb deformities present in infants under 6 months of age (total prevalence of 14%). On average, those diagnosed as meeting the criteria for Level 1 diagnostic confidence had three or more non-overlapping lesions and on average 10 or more pathological features diagnostic or suggestive for hypomineralization disorder including macroscopic and radiographic features. All individuals with bending deformities of the long bone ends exhibited non-overlapping features of the metaphyseal plates and presented as the most severe cases in the assemblage.

3.2 | Diagnosis (Level 2)

Only one more individual was diagnosed as Level 2 as opposed to Level 1 (MB05M7, a neonate). The Level 2 case exhibited one non-overlapping diagnostic feature for hypomineralization disorder (poorly mineralized and spiculated new bone of the cranial vault). MB05M7 only exhibited pathological features of the cranial vault (as opposed to post-cranial) consistent for hypomineralization disorder.

3.3 | Assessment of lesion ambiguity in probable cases

Under the Brickley and Morgan (2023) criteria, the lesions represented a level of certainty consistent with the highest level of diagnosis ("diagnostic") in 64% ($n = 14/22$) of the probable cases, whereas the remaining cases met the definition for cases with a strong probability ("highly consistent") of pertaining to hypomineralization disorder (36%, $n = 8/22$, see Data S2). These findings complement the use of the three-level system of diagnosis for hypomineralization disorder at Man Bac and lend supporting evidence to the high prevalence observed.

3.4 | Diagnosis (Level 3)

All individuals diagnosed with possible hypomineralization disorder presented with at least one diagnostic pathological feature including poor mineralization of new bone in the orbits, long bone hypertrophy, and hypertrophy of the cranial bones. An 18-month-old (MB05M5) was previously diagnosed as a possible case of secondary treponemal disease due to the presence of distinct nodes of new bone of the tibiae not consistent with hypomineralization disorder (Vlok et al., 2020), and their long bone hypertrophy can be attributed to this disease. The characteristic node-like enlargement is typical in the secondary stage of treponemal disease near regions of lymphatic drainage (Buckley & Dias, 2002). Therefore, this cortical hypertrophy was not considered diagnostic for hypomineralization disorder. Kyphosis has been associated with treponemal disease, but only due to tertiary destruction of the spine not seen in this child (Greenbaum, 1929). New bone in the orbits of this child does appear to be poorly mineralized; therefore, a possible diagnosis of hypomineralization disorder is not entirely ruled out.

3.5 | Epidemiology

Infants under 1 year of age were the most affected by hypomineralization disorder at Man Bac (Level 1: $n = 9/14$, 64.3%), with the highest prevalence in children between 6 months to 1 year of age (Level 1: $n = 5/6$, 83.3%). A declining trend in prevalence with increasing age is observed (Figure 6). The outcome was consistent when excluding (Level 1) and including (Level 2) overlapping pathological features. However, there were no significant differences in the prevalence of hypomineralization disorder between individuals who were under or over 5 years of age-at-death (Fishers exact: $p = 0.35$), nor was there a significant difference between infants under or over 6 months of age-at-death (Fishers exact: $p = 0.3$).

Multiple or sustained instances of hypomineralization disorder observed through the presence of a combination of active and healed features were present in 68% ($n = 17/25$) of probable cases of hypomineralization disorder (Levels 1 and 2; Figures 7 and 8). Individuals with multiple or sustained instances of hypomineralization disorder were observed in age groups under the age of 10 years at death including neonates and infants. Only two individuals (aged 1 and 2 years at death) presented with strictly active hypomineralization disorder. Healed cases were only present from 1.5 years at death and older. With increasing age (over 10 years), features specifically related to healed and active cases became difficult to discern. The features remaining may possibly represent residual hypomineralization disorder, with homeostasis of bone remodeling predominantly restored in these cases. These lesions were also more subtle in appearance.

Co-morbidity of scurvy and thalassemia was assessed alongside results from Vlok, Oxenham, et al. (2023) and Vlok et al. (2021),

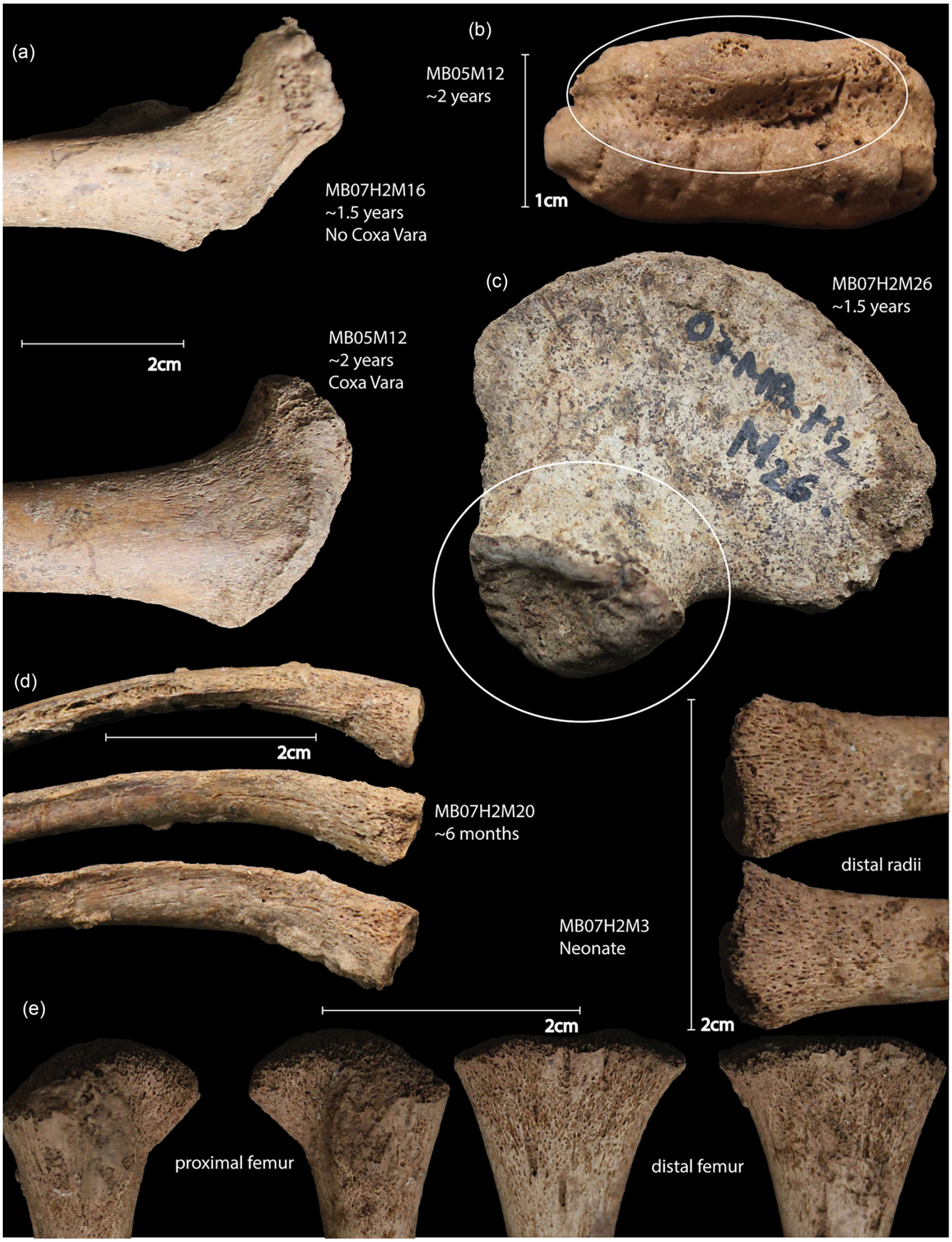

FIGURE 3 Legend on next page.

FIGURE 3 More macroscopic signs of hypomineralization disorder at Man Bac. (a) Coxa vara (compared with an individual of similar age without this deformity), (b) deformity of the anterior vertebra, (c) angulation deformity of the acetabulum, (d) costochondral porosity and enlargement (rachitic rosary), and (e) pronounced porosity of the metaphyseal region and of the metaphyseal plates. [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 4 Results of hypomineralization disorder diagnosis.

Age-at-death	Probable Level 1 (%)	Probable Level 1 and 2 (%)	Possible Level 3 (%)
0 to under 6 months	4/8 (50)	5/8 (62.5)	3/8 (37.5)
6 months to under 1 year	5/6 (83.3)	5/6 (83.3)	0/6 (0)
1 year to under 6 years	10/19 (52.6)	10/19 (52.6)	4/19 (21.1)
6 years to under 10 years	2/4 (50)	2/4 (50)	0/4 (0)
10 to under 15 years	0/3 (0)	0/3 (0)	1/3 (33.3)
15 to under 20 years	0/4 (0)	0/4 (0)	0/4 (0)
Total	**21/44 (47.7)**	**22/44 (50)**	**8/44 (18.2)**

FIGURE 4 Comparison of metaphyseal porosity at the Tsukumo site in prehistoric Japan dated to 4500 to 2300BP where only scurvy was diagnosed (Vlok et al., in press), compared with the cases of rickets and scurvy co-morbidity at Man Bac. The porosity of Man Bac individuals appears deeper, coarser, erratic, and more frayed/bristle brush in appearance. MB07H1M7 presents a case that is intermediate in appearance. In active cases of rickets, the porosity appeared overwhelmingly rachitic, and the scorbutic changes were obscured. Enlargement of the image is recommended as the changes are subtle. [Colour figure can be viewed at wileyonlinelibrary.com]

respectively. The prevalence of probable scurvy (79.5%) was higher than that of hypomineralization disorder (Level 1: 50%) at Man Bac. There was a statistically significant difference (Fishers exact: $p = 0$) between the prevalence of individuals with hypomineralization disorder only (2.3%; $n = 1/44$) and those who presented with co-morbidity of hypomineralization disorder and scurvy (45.5%; 20/44). These statistical findings were clearly associated with the fact that only one case of hypomineralization disorder was not diagnosed with scurvy. There was also a statistically significant difference between the prevalence of hypomineralization disorder only cases compared with those with hypomineralization disorder and thalassemia (Fishers exact: $p < 0.001$). However, 60% (3/5) of thalassemia cases also presented with hypomineralization disorder. No cases of probable hypomineralization disorder were identified to exhibit evidence for treponemal disease, and vice versa.

3.6 | Survivorship analysis

There was a statistically meaningful difference in survival time of those diagnosed with and without hypomineralization disorder (Level 1) both in terms of the p-value ($p = 0.008$; see Figure 9) and the upper and lower limits of the mean 95% CIs that do not overlap (Table 5). The mean survival time for those diagnosed with Level 1 hypomineralization disorder was 1.9 years, whereas for those not diagnosed was 5.9 years at death. A disparity between the 95% CIs of the mean versus the median appears to be attributed to high representation of infants in the non-adult assemblage that reduced the cumulative survival to less than 0.5 by 1.5–2 years regardless of whether diagnosis of Level 1 hypomineralization disorder was present or absent. A clearer differentiation in survival times is apparent from 2 years onwards (Figure 7).

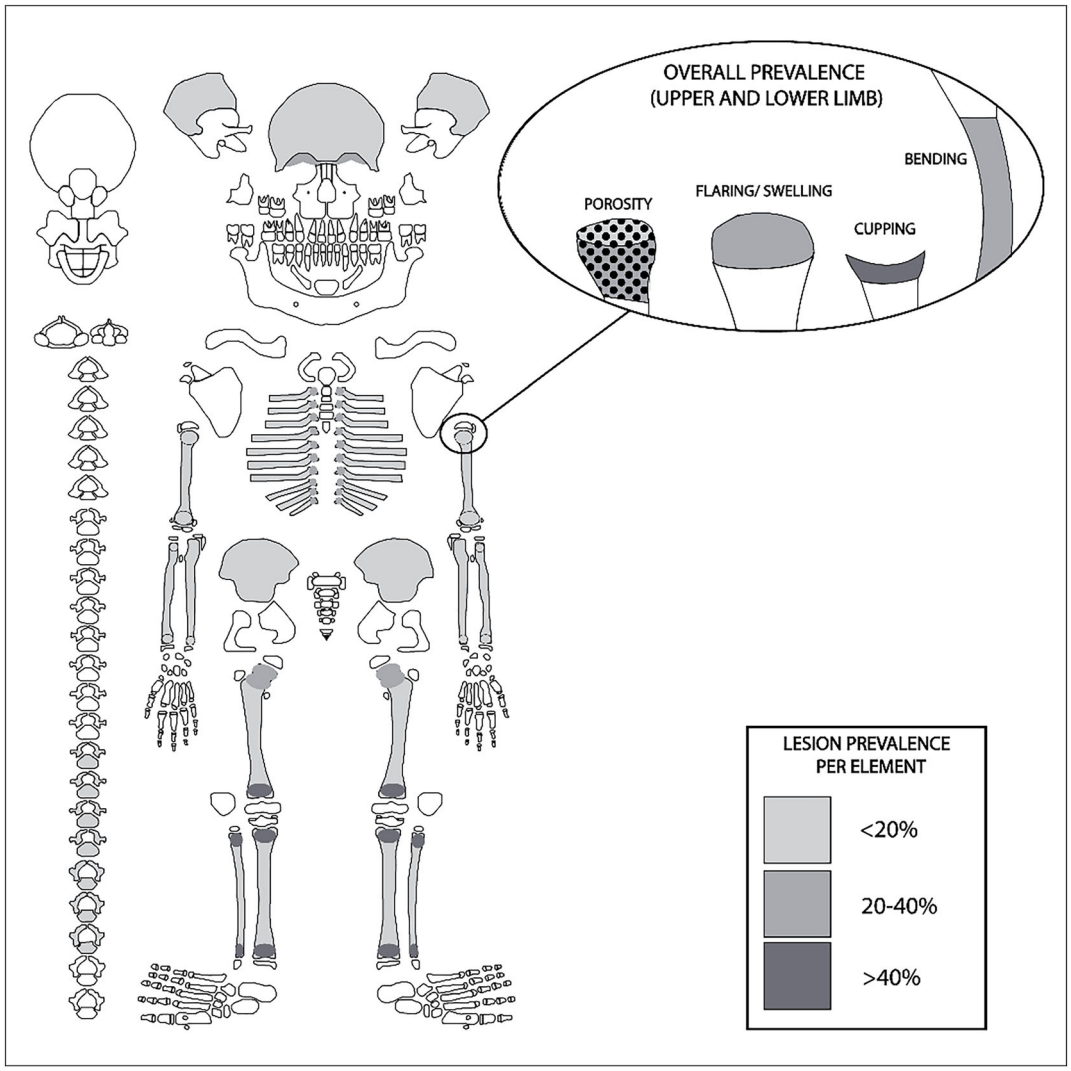

FIGURE 5 Skeletal expression and the prevalence of major lesions related to hypomineralization disorder at Man Bac.

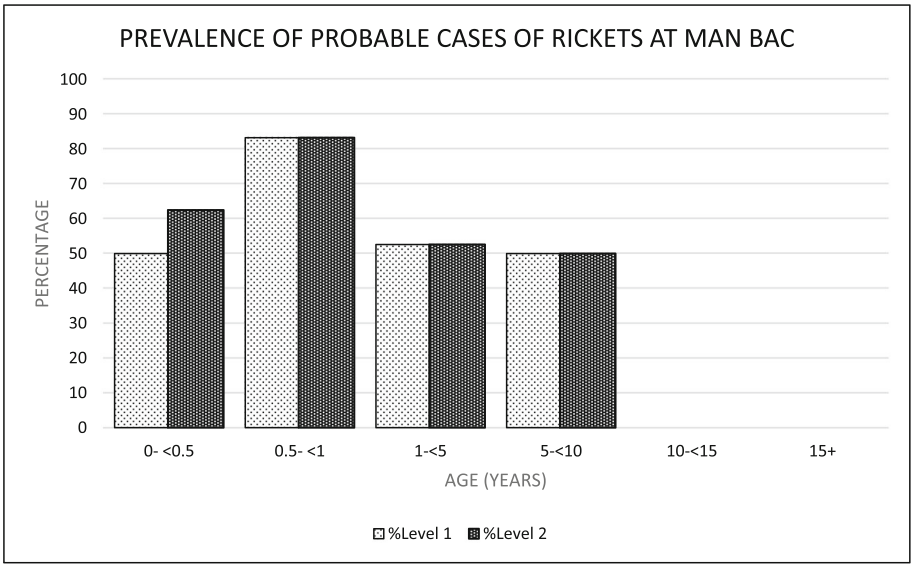

FIGURE 6 Hypomineralization disorder prevalence across different age-at-death cohorts.

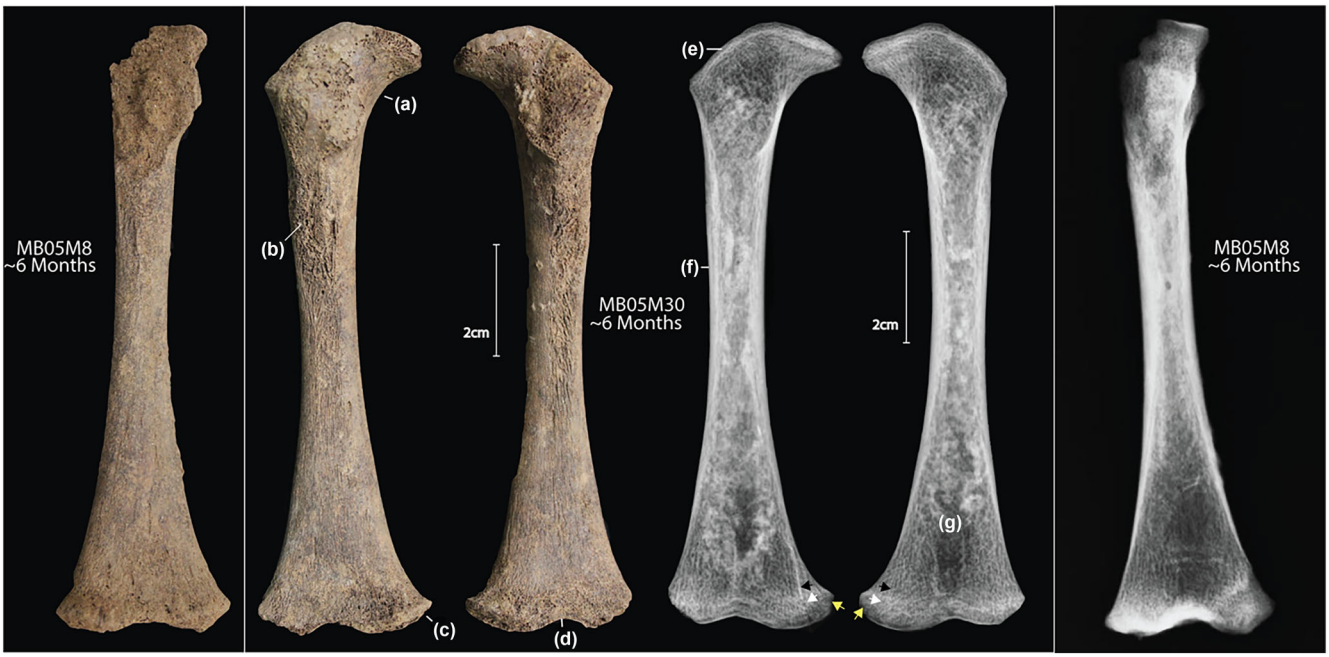

FIGURE 7 Macroscopic and radiographic features of hypomineralization disorder in the femur of a 6-month-old infant demonstrating multiple or sustained episodes of deficiency (MB05M30) compared with an individual of the same age not diagnosed (MB05M8). (a) *Coxa vara*, (b) layers of poorly mineralized new bone deposits (active), (c) thick metaphyseal plate (healed), (d) cupping appearing as invagination of the distal femur, (e) radiodense metaphyseal plate without underlying Trümmerfeld zone (healed), (f) multiple layers of cortical new bone deposit (hypertrophy), and (g) coarse trabeculae. MB05M8 has a comparatively thinner shaft diameter, lack of porosity, and poorly mineralized bone around the linea aspera; lacks *coxa vara*; and lacks the invagination of the distal femur. MB05M30 was also diagnosed with scurvy and healed Pelkan spurs (yellow arrows), Trümmerfeld zones, and white lines of Fraenkel are also present. MB05M30 also presented with multiple features highly consistent with hypomineralization disorder including kyphosis of the spine, thick and multi-layered deposits of poorly mineralized new bone on the cortical surfaces of multiple long bones, bending deformities of the humeri, and porosity of the metaphyseal plates of the proximal and distal tibiae (for a full description, photos, and radiographs of MB05M30, see Data S2, pp. 92–100). Note: There are radiodense soil concretions in the medullary canals of MB05M30 and of the distal and proximal ends of MB05M8. MB05M8 also presents with a distal metaphyseal fracture. [Colour figure can be viewed at wileyonlinelibrary.com]

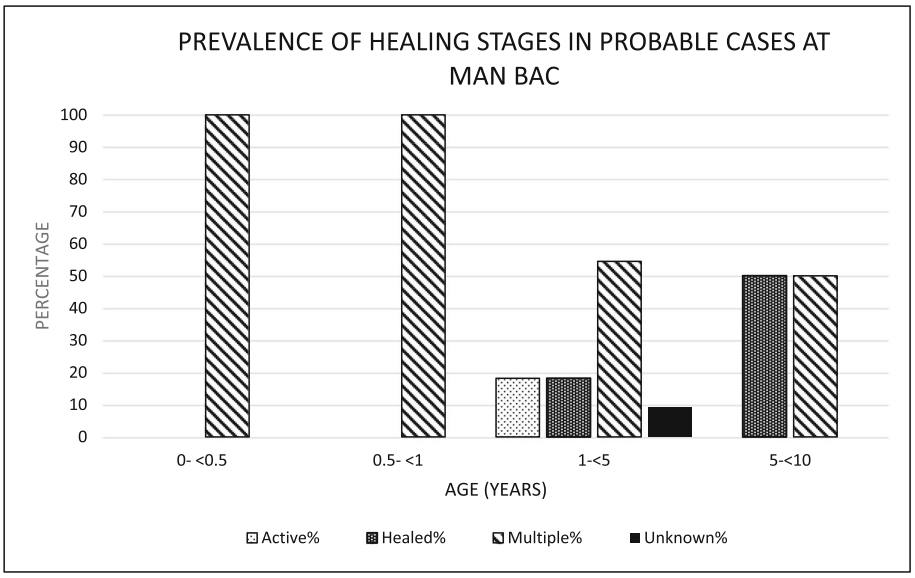

FIGURE 8 Prevalence of healing among probable hypomineralization disorder (Levels 1 and 2) cases.

FIGURE 9 Kaplan–Meier survival curves. [Colour figure can be viewed at wileyonlinelibrary.com]

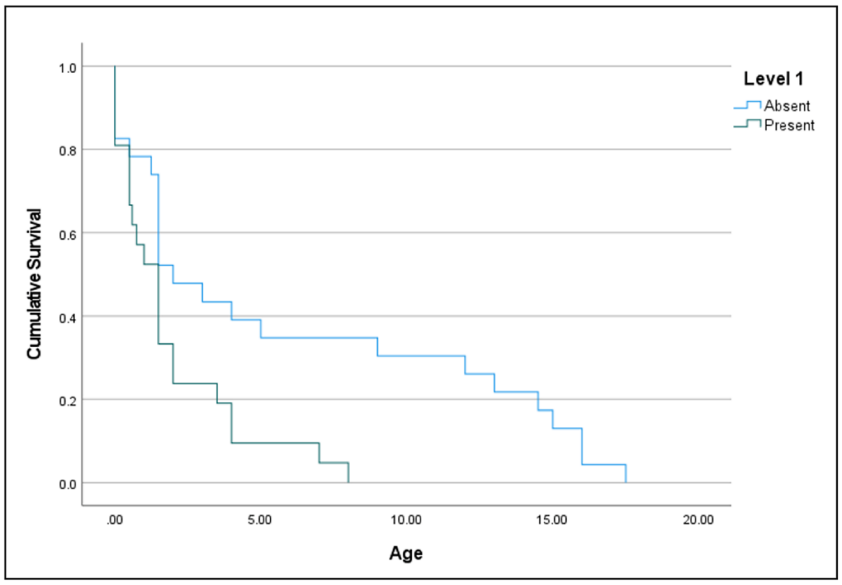

TABLE 5 Kaplan–Meier output for hypomineralization disorder.

Level 1 Diagnosis	Estimate	Std. Error	95% CI	Log-rank (Mantel–Cox)		
				Chi-square	*df*	*P*-value
Mean				7	1	**0.008**
Absent	5.92	1.34	**3.30–8.55**			
Present	1.92	0.49	**0.97–2.88**			
Overall	4.01	0.79	**2.46–5.56**			
Median						
Absent	2.00	0.60	0.83–3.17			
Present	1.50	0.32	0.87–2.14			
Overall	1.50	0.09	1.32–1.68			

Note: Outcomes involved in the interpretation of meaningful results are bolded.

4 | DISCUSSION AND CONCLUSIONS

Although there is a degree of overlap in the pathological features observed in hypomineralization disorder and the other conditions already reported at Man Bac (scurvy, thalassemia, and treponemal disease), the three-level system of diagnosis employed in this study presented evidence that hypomineralization disorder was likely present at high levels in the Man Bac non-adult assemblage. Only one probable case of hypomineralization disorder diagnosed as Level 2 did not present with multiple non-overlapping pathological features, and over 60% of the probable cases had lesions that were unambiguous lending strength to the diagnosis of hypomineralization disorder. If only these unambiguous cases were considered in the diagnosis, the prevalence is still over 30% ($n = 14/44$). It needs to be emphasized here that in isolation, the high crude prevalence observed at Man Bac does not necessarily reflect a very unhealthy population overall. The high fertility rate at Man Bac, leading to more than 60% of the entire assemblage being represented by non-adults under the age of 5 years at death, greatly skews the crude prevalence observed. The disease is clinically understood to be associated with a high relationship with mortality, even today (Uday & Högler, 2017), and this association is supported by our survivorship analyses.

Given that the age group with the greatest prevalence for hypomineralization disorder appears to be under 1 year of age-at-death (especially the 6-month to 1-year cohort), it is possible that factors influencing the age-of-onset of the condition are at play. Such factors include weaning time, stores of maternal calcium and vitamin D in utero and in breastmilk, and prematurity (in combination with primary hypophosphatemia). Infant swaddling may also reduce the access of UV rays for vitamin D synthesis and/or exacerbate the bending deformities (Backström et al., 1996; Gordon et al., 2008; Rowe et al., 1979; Veselka et al., 2015; Vlok, Snoddy, et al., 2023). Dietary requirements for calcium increase considerably after 6 months post-birth, and breastmilk is a poor source of vitamin D for breastfeeding infants (Almaghamsi et al., 2018; Beal, 1954). The high prevalence of multiple instances of hypomineralization disorder in perinates and young infants supports the development of nutritional hypomineralization disorder in utero, a condition known as "congenital rickets." Although rare, congenital rickets has been reported in the clinical and paleopathological literature (Bereket, 2003; Elidrissy, 2016; Giuffra

et al., 2015; Mohapatra et al., 2003; Morrone et al., 2021; Paterson & Ayoub, 2015; Schattmann et al., 2016; Veselka et al., 2021). The significant impact of hypomineralization disorder on mortality may underline why paleopathologists are more likely to observe cases in deceased perinates than clinicians who report hypomineralization disorder in live patients. In utero stores of vitamin D and calcium are frequently sufficient for normal fetal development even if the mother is deficient as the maternal body will prioritize the nutritional supplement of the fetus through physiological adaptation (Prentice, 2003; Weinert & Silveiro, 2015). It is possible that other calcium-regulating hormones such as oestradiol and prolactin take on more prominent roles during pregnancy as a physiological buffer to maintain calcium homeostasis (Kovacs, 2008). For example, calcium from an expectant mother's skeleton is leached to provide sufficient levels of calcium to the fetus in instances of deficiency (Olausson et al., 2012). Thus, for congenital rickets to occur, the expectant mother must also be experiencing calcium and/or vitamin D deficiency in extreme circumstances. As such, the perinates reported here are proxies for very poor maternal health at Man Bac. These findings are supported by Adams et al. (2021) who reported multiple episodes of in utero stress via nitrogen isotopes and deciduous linear enamel hypoplasia in the Man Bac infants. Adams et al. (2021) report a case of a 3-year-old at time of death who exhibited greater catabolism (higher $\delta^{15}N$ levels) due to stress in utero than after birth, a rare but important finding in the context of infant and maternal health during the Neolithic period of northern Vietnam.

As discussed by Vlok, Oxenham, et al. (2023), the high infectious disease burden at Man Bac, especially the evidence for the presence of malaria, would have contributed extensively to the physiological stress of mothers and their capacity to pass on micronutrients in utero. Pregnancy increases susceptibility to malarial infection, particularly in high transmission areas, and first-time mothers are especially vulnerable (Desai et al., 2007; Takem & D'Alessandro, 2013). Infection also appears to peak in the second trimester, although the dearth of data on infection in the first trimester is likely biasing this pattern (Desai et al., 2007; Takem & D'Alessandro, 2013). Kendall et al. (2020) demonstrated that higher $\delta^{15}N$ and lower $\delta^{13}C$ values were present in babies during the late fetal period, a similar finding to Adams et al. (2021). Kendall et al. (2020) interpreted this as due to higher inflammation during malarial infection inhibiting transfer of nutrients to the fetus. As such, the malarial burden in expecting mothers at Man Bac may have further contributed to insufficient levels of calcium, vitamin D, and vitamin C passing to the fetus.

Calcium and vitamin D deficiency significantly increases the risk of death of the expectant mother during labor, if these women also experienced pelvic skeletal changes related to deficiency in childhood or in adulthood, or the deficiency was associated with pre-eclampsia (Elidrissy, 2016; Högberg, 1985). Although not presented here, the adult assemblage was also assessed for evidence of osteomalacia and residual rickets (Vlok, 2020). No adult presented with signs of residual rickets or osteomalacia. Therefore, there is no clear evidence of increased mortality of expectant mothers at Man Bac related to vitamin D and/or calcium deficiency. However, clinical reports of congenital rickets have been associated with maternal cases of vitamin D and/or calcium deficiency not associated with clear skeletal deformity of the mother, instead of tetany (seizures) and bone pain even when the infant exhibited severe skeletal deformity (Paterson & Ayoub, 2015). The maternal mortality rate (MMR) for Man Bac is estimated at 152 (per 100,000), which is considered low (<323), even in the context of prehistoric Mainland Southeast Asia only (mean MMR = 298) (McFadden et al., 2020; Van Tiel & McFadden, 2021). This reflects the likelihood that the infants and children of Man Bac who died of hypomineralization disorder represent the cohort with the poorest state of health, were most vulnerable to the biosocial stressors of their time, and therefore likely do not represent the general state of health of the living population. Nevertheless, they are indicators that sub-clinical malnutrition was likely pervasive throughout the population.

Furthermore, these findings may also suggest that the high burden of increased fertility and disease fell on infants and children, but mothers appeared to be less affected (at least in the case of mortality) by these instances of disease around the time of pregnancy and the postpartum period. To what extent this affected female mortality later in life in terms of life history trade-offs is a point for future research. The Kaplan–Meier survivorship model clearly provides evidence for decreased survivorship of non-adults who suffered from hypomineralization disorder. These findings do not necessarily suggest that hypomineralization disorder was responsible for decreased survivorship, but rather that in conjunction with the suite of co-morbid factors, the presence of skeletal evidence of hypomineralization disorder was associated with a higher risk of death in childhood. The cumulative survival curve suggests that over 90% of non-adults who suffered from hypomineralization disorder in the Man Bac assemblage died by the age of 5. This finding further supports the argument that hypomineralization disorder was present in extreme cases of childhood disease at Man Bac, leading to early death.

4.1 | Scurvy and hypomineralization disorder at Man Bac

There appears to be a relationship between scurvy and hypomineralization disorder co-morbidity at Man Bac. Only one individual presented with hypomineralization disorder only, whereas all the other cases of hypomineralization disorder shared co-morbidity with scurvy. Cases of scurvy without hypomineralization disorder were more common. It is possible that co-morbidity of scurvy and hypomineralization disorder represents an extreme severity of nutritional disease. That is, although scurvy was a more common occurrence, those more severely affected by nutritional disease appear to present with signs of hypomineralization disorder as well. Two plausible scenarios for co-morbidity fit these outcomes. These children were either the worst cases of scurvy (e.g., suffered from pseudoparalysis from the exceptional pain caused by subperiosteal and muscular hemorrhaging) and therefore were bound indoors away from the sunlight, the scurvy and hypomineralization disorder share the same cause

(i.e., micronutrient deficiency of vitamin C and calcium), or a combination of both factors occurred. An adult male from Man Bac with intermittent quadriplegia for at least 10 years and likely paraplegia for most of his life exhibited no signs of osteomalacia or residual rickets, which would suggest that ill people in the community likely did receive sufficient sunlight even when immobile (Oxenham et al., 2009; Tilley & Oxenham, 2011). However, the case of this individual is unlikely to be representative of the behavioral norms across the entire population. Notably, this person survived their childhood, whereas the infants and children with hypomineralization disorder at Man Bac did not.

Based on epidemiological and clinical literature, a scenario where a spectrum of both vitamin D and/or calcium deficiency is present across the cohort with variable reasons for the development of hypomineralization disorder is the most plausible. This interpretation is supported by findings of calcium-predominant rickets in clinical cases in the tropics where UV rays are sufficient. Factors of undernutrition or a selective diet and cultural attitudes to sunlight impact vitamin D levels as well as contribute to hypomineralization disorder in these regions (see Vlok, Snoddy, et al., 2023, for discussion on vitamin D inadequacy in sunlit countries). The wearing of clothes that cover the skin, avoidance of the sun, chronic liver disease that can be secondary to infection such as from malaria, and poor supplementary dietary sources of vitamin D are primary factors in the presence of vitamin D deficiency in the tropics that may have also contributed to the development of hypomineralization disorder in prehistoric Vietnam (Joshi & Bhatia, 2014; Lee et al., 2019; Moy, 2011).

As is the case for the development of scurvy at Man Bac (Vlok, Oxenham, et al., 2023), the supplementation of domesticated rice may have contributed considerably to the development of hypomineralization disorder in Man Bac non-adults. Rice (*Oryza sativa japonica*) has approximately 32 mg/100 g of calcium with levels less than 300 mg/day causing calcium deficiency and increasing a child's risk of developing hypomineralization disorder independent of their vitamin D levels (Munns et al., 2016; Pettifor et al., 1981; US Department of Agriculture, 2019). Rice is also high in phytates, which further restricts calcium absorption in the gut (Pettifor, 2004). Calcium and vitamin D intake from faunal sources at the site were also low (McDonell & Oxenham, 2014), but the degree of wild plant intake remains unknown.

4.2 | Hypomineralization disorder and thalassemia at Man Bac

The significantly lower levels of hypomineralization disorder cases with thalassemia compared with those without thalassemia suggests that in predominant cases at Man Bac, the development of hypomineralization disorder was independent of thalassemia as an underlying cause. However, as 60% of non-adults with a diagnosis of thalassemia also presented with hypomineralization disorder, it is possible that in these cases, the secondary localized osteomalacia and vitamin D deficiency caused by the genetic condition contributed to the development of hypomineralization disorder in the thalassemic children.

4.3 | Consequences of hypomineralization disorder for the interpretation of disease burden of prehistoric Southeast Asia

The overall disease burden at Man Bac stands in contrast to a general trend in prehistoric Southeast Asia where low infectious and nutritional disease burdens are frequently documented. However, it is noted here that no sites outside of northern Vietnam have received significant attention regarding the identification of specific disease, and interpretation of health is instead reliant on the documentation of non-specific markers of stress. Thus, determining the extent to which Man Bac is an outlier for the agricultural transition, and Southeast Asia in general, is difficult. Con Co Ngua, a pre-Neolithic forager site dated approximately 2.5–3.5 thousand years before Man Bac, has also been heavily investigated for the above specific infectious and nutritional diseases. However, although the non-adult preservation was relatively poor compared with Man Bac, no evidence of hypomineralization disorder in the Con Co Ngua non-adults or adults was identified, as was also the case with scurvy (Vlok, 2020; Vlok, Oxenham, et al. 2023). As such, we can conclude that the contexts of the agricultural revolution in northern Vietnam generated a unique set of circumstances where infectious and nutritional diseases proliferated in the population and had a significant impact on both morbidity and mortality. Future research is necessary to explore spatio-temporal trends of specific infectious and nutritional diseases across Southeast Asia's prehistory, but especially during the early agricultural transition, to compare the trends observed at Man Bac to other prehistoric sites in the region.

4.4 | Limitations of the study and conclusions

Although multiple approaches were considered for diagnosis of hypomineralization disorders at Man Bac, the issue of complex co-morbidities at Man Bac especially with diseases that all contribute to the porosity of the skeleton obscures the true prevalence of these diseases in the assemblage. In addition, the issue of describing patterns of normal physiological growth remains a confounding factor. It is expected that the prevalence of the diseases identified at Man Bac will change as new research combating complex co-morbidities surfaces in the paleopathological literature. What is clear, however, is that the pattern of lesions interpreted here as relating to hypomineralization was highly associated with decreased survival, and the combination of multiple disease stressors had a significant impact on the survival of Man Bac individuals' past childhood.

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DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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