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# Paleoepidemiology of cribra orbitalia: Insights from early seventh millennium BP Con Co Ngua, Vietnam

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## Abstract

**Objectives:** We test the hypothesis that the condition(s) leading to the development of cribra orbitalia at Con Co Ngua, an early seventh millennium sedentary foraging community in Vietnam, effectively reduced the resilience of the population to subsequent health/disease impacts. An assessment of both the implications and potential etiology of cribra orbitalia in this specific population is carried out.

**Methods:** The effective sample included 141 adults aged ≥15 years (53 females, 71 males, and 17 unknown sex) and 15 pre-adults aged ≤14 years. Cribra orbitalia was identified by way of cortical bone porosity of the orbital roof initiated within the diplöic space, rather than initiated subperiosteally. The approach is also robust to the misidentification of various pseudo-lesions. Resultant data was analyzed using Kaplan–Meier survival analysis.

**Results:** Median survival is higher in adults aged ≥15 years without cribra orbitalia than those with this lesion. For the pre-adult cohort, the opposite pattern is seen where median survival is higher in those with cribra orbitalia than those without.

**Conclusion:** Adults displayed increased frailty and pre-adults increased resilience with respect to cribra orbitalia. The differential diagnosis for a survival analysis of adults and pre-adults with and without cribra orbitalia included iron deficiency anemia and B12/folate deficiency, parasitism (including hydatid disease and malaria) in addition to thalassemia. The most parsimonious explanation for observed results is for both thalassemia and malaria being the chief etiological agents, while appreciating these conditions interact with, and can cause, other forms such as hematinic deficiency anemias.

KEYWORDS
anemia, hunter-gatherers, malaria, paleoepidemiology, Southeast Asia, thalassemia

## 1 | INTRODUCTION

This article uses a paleoepidemiological approach to observed cribra orbitalia in an early seventh millennium BP forager sample located in what is now geo-politically northern Vietnam. The value of such a perspective, which incorporates a range of paleodemographic data, such as sex, age, and fertility, in terms of understanding potential effects of exposures to stressors and disease in past populations, has been recently detailed by McFadden and Oxenham (2020). Such work builds upon a growing body of literature that examines paleopathology at a population, rather than individual, level using modern epidemiologically informed approaches that evaluate the demographic distribution of any particular lesion (e.g., Blondiaux et al., 2015; DeWitte, 2014; Snoddy et al., 2016; Vlok & Buckley, 2021). McFadden and Oxenham (2020) have operationalized a way in which to explore outcomes of physiological disruption, or stress, in the context of the opposing outcomes of negative physiological constraints and adaptive plasticity, which in turn can be identified as various manifestations of frailty or resilience. They have argued that the adoption of such a paleoepidemiological framework provides a mechanism through which many of the concerns raised by the osteological paradox can be effectively dealt with.

Here we are specifically interested in the skeletal response to one or more forms of anemia, cribra orbitalia. Cribra orbitalia is here defined as the presence of porosity of the cortical bone forming the orbital roof that has been initiated within the diplöic space rather than subperiosteally. This is an important distinction as evidence for porosity of the frontal bone portion of the orbit initiated subperiosteally can be related to, among other processes, postmortem taphonomic changes (see Wapler et al., 2004), and various forms of eye infection and metabolic diseases such as scurvy (Klaus, 2017; Snoddy et al., 2018). There is a considerable history of work exploring the role of cribra orbitalia in past populations, and a more limited corpus of research that has explored the etiology of this lesion in any detail (see McFadden & Oxenham, 2020; Oxenham & Cavill, 2010; Rivera & Mirazón Lahr, 2017). There are good reasons to suppose cribra orbitalia is for the most part caused by one of the anemias, in particular iron deficiency anemia, megaloblastic anemia (e.g., a function of B12 or folate deficiency), anemia of inflammation, or one of the inherited hemolytic anemias (e.g., thalassemia) (for discussions of this see Walker et al., 2009; Oxenham & Cavill, 2010; Brickley et al., 2020; Rivera & Mirazón Lahr, 2017; McFadden & Oxenham, 2020), although other conditions need to be considered on a sample-by-sample basis (e.g., see Wapler et al., 2004).

As cribra orbitalia is a signature for a number of conditions leading to anemia, investigating the etiology of these lesions within the context of a given assemblage is essential in order to properly understand the impact on health and wellbeing in the past. Different conditions causing cribra orbitalia have variable influences on morbidity and mortality outcomes. Therefore, across different populations that share a similar prevalence of cribra orbitalia the influence on overall health of the underlying causes of this lesion may vary considerably. Assessing the impact of conditions that cause cribra orbitalia on mortality, alongside other demographic factors, is necessary in order to wholly describe the effect on health via this particular lesion.

The population of interest is a pre-neolithic forager community that lived in northern Vietnam almost 7000 years ago. The site and skeletal assemblage is named Con Co Ngua and represents the more southerly distribution of a widely dispersed concentration of foraging communities that inhabited a region extending from southern China (known as the Dingsishan culture) down into northern Vietnam (known as Da But culture sites) from perhaps as early as 10 millennia ago until around 5000 years ago (Oxenham et al., 2018). Collectively, the hundreds of sites making up these sedentary, complex foraging communities can be referred to as the Da But-Dingsishan complex. A picture of the lifeways, diet, subsistence strategies, technology as well as the health and diseases characterizing the Con Co Ngua community is summarized below.

The chief aim of this article is to analyze evidence for cribra orbitalia at Con Co Ngua within a paleoepidemiological framework. We examine evidence for both frailty and/or resilience in separate adult and pre-adult samples and explore both the implications and potential etiology of cribra orbitalia in this large sedentary complex foraging community. Frailty and resilience have at times been loosely defined and differently interpreted in the bioarchaeological record, an issue that is further complicated by the often indirect or indeterminate association between skeletal lesions and the conditions that cause them, and those conditions and mortality.

McFadden and Oxenham (2020, figure 4, p. 10), define frailty as comparatively reduced resilience to stressors as measured by relatively reduced mean-age-at death for lesioned individuals in comparison to the non-lesioned component of any given sample. Resilience, on the other hand, is the converse situation where an increased mean-age at-death is observed for the lesioned cohort. Within this framework, our working hypothesis is that the condition(s) leading to the development of cribra orbitalia at Con Co Ngua effectively reduced the resilience of the population to subsequent health/disease impacts. In effect, we would expect the cohort of Con Co Ngua individuals (pre-adults and/or adults) with cribra orbitalia to have a lower mean-age-at-death relative to the non-lesioned cohort, thus indicating reduced resilience, or elevated frailty.

## 2 | MATERIALS AND METHODS

### 2.1 | Biocultural context

The site of Con Co Ngua lies in Thanh Hoa Province, located within the karst limestone region of the Bac Bo plain, northern Vietnam (Jones et al., 2019). The site was first excavated by the Vietnam Institute of Archaeology, Hanoi, during 1979–1980 and re-excavated collaboratively by researchers from The Australian National University and the Vietnam Institute of Archaeology in 2013. Results of radiocarbon dating on tooth enamel from both human and faunal remains as well as charred *Canarium* suggest occupation from at least the early seventh millennium cal BP (Oxenham et al., 2018).

Con Co Ngua is ascribed to the Da But Culture which was part of a much larger concentration of sedentary, complex hunter-gatherer communities that inhabited what is now southern China (the Dingsishan culture) and northern Vietnam. In general, these communities, dating from the early Holocene, were "characterized by large open-air cemetery and living sites, a broad range of polished stone, bone and shell implements (including knives, arrow heads and fish hooks), and the extensive use of pottery" (Oxenham et al., 2018, p. 941). Moreover, and at Con Co Ngua specifically, the Da But culture is known for funerary behaviors that include postmortem corpse mutilation and subsequent interment predominantly in squatting (within circular earthen pits) and also to a lesser degree side flexed positions (Oxenham et al., 2018; Oxenham et al., 2022). From a population history perspective, the inhabitants of this site were indigenous hunter-gatherers who occupied the region prior to the intrusion of Neolithic communities from what is today geo-politically southern China. While the climate is currently classed as sub-tropical, including hot monsoonal summers, in the past temperatures and rainfall were higher than today. To date, the only identified recovered floral remains include *Canarium*, various species of which are still cultivated and consumed in the region today. A wealth of faunal remains were recovered and identified in the 2013 excavation, including mammals (the assemblage was dominated by large bodied bovids), reptiles, sharks/rays, and birds. The range of identified taxa indicate exploitation of an extremely diverse range of habitats including ocean, riverine, estuarine, wetlands, swamps, grasslands, woodlands and forests.

In terms of health, the 1979/80 sample was found to have relatively low levels of dental caries (1.5% by tooth count (Oxenham, 2006)), while the degree of serious healed trauma was somewhat elevated in comparison to other assemblages in Southeast Asia (Oxenham et al., 2001). A subsequent study of the 2013 sample indicated the frequency and type of trauma was consistent with the management of wild herds of large bodied bovids (Scott et al., 2019). Elevated levels of hydatid disease, indeed the only evidence for this disease in the region to date (Vlok et al., 2022), in the community is also consistent with a close association with wild cattle. Recently, it was demonstrated macroscopically and microscopically (and independently of evidence for cribra orbitalia) that the Con Co Ngua community suffered from thalassemia, a hemoglobinopathy associated with an evolutionary adaptation to high endemic malarial loads (Vlok et al., 2021). No evidence for nutritional diseases such as scurvy and rickets were identified in the 2013 assemblage (Vlok, 2020).

## 2.2 | The sample

Two skeletal assemblages are examined in this study: one is the series recovered during the 1979/80 excavation (see Oxenham, 2016) and the other is that from the 2013 excavation (see Oxenham et al., 2018; Scott et al., 2019). A total of 275 individuals were identified and recovered during these two excavations (1979/80: 87 adults ≥15 years, 7 pre-adults ≤14 years; 2013: 116 adults ≥15 years, and 65 pre-adults ≤14 years). The unusually small proportion of pre-adults in the 1979/80 sample is believed to be attributable to excavation and recovery techniques employed at the time. For the purposes of this study the 1979/80 and 2013 samples are combined. The total assessable sample (see below for cribra orbitalia scoring criteria) in this study, defined as any individual with at least one observable orbital roof, totaled 141 adults aged ≥15 years (53 females, 71 males, and 17 unknown sex) and 15 pre-adults aged ≤14 years.

## 2.3 | Methods

### 2.3.1 | Sex, age-at-death, and the identification of cribra orbitalia

Adult sex was established using sample-specific post-cranial functions (Oxenham, 2016), while non-metric estimation used a range of cranial and pelvic standards (Buikstra & Ubelaker, 1994; Phenice, 1969; Walrath et al., 2004). Dental eruption and development standards were used to determine pre-adult age-at-death (Moorrees et al., 1963), while epiphyseal fusion timing was used for adolescent and young adult estimation (Scheuer & Black, 2000).

A paleoepidemiological analysis requires individual point estimates of age, or an approximation of this. Our approach to this is based on the empirically demonstrated correlation between the proportion of pre-adults in a population to the actual age-at-death distribution of the same sample (McFadden et al., 2019). For instance, if one had a sample of 120 individuals, of which 50 were pre-adults (≤ 14 years) and 70 were adults (≥ 15 years), the D0-14/D proportion would be 0.42 with the predicted age-at-death distribution apportioning 11% ($n = 13$) of the adults to the 15–34 year cohort, 3% ($n = 3$) to the 35–39 year cohort, and so forth until all 70 adults were distributed. To identify which specific individuals fall within each adult age cohort, the sample in question needs to be seriated from youngest to oldest in some way. Typically, and as was the case for the Con Co Ngua sample, the seriation is performed using molar wear scores, with the seriation checked (where possible) by comparing the relative positions of individuals in the seriation that had age-at-death estimates independent (e.g., cases for which an age-at-death was estimated using epiphyseal fusion, pubic symphyseal morphology, etc.) of the dental wear scores. The adult age-at-death point estimates, for the purposes of survival analysis, were then generated by taking the average of each adult age-at-death cohort (e.g., the age cohort 45–49 years receives an age point estimate of 47 years, etc.).

Using this approach, the 2013 season's sample (116 adults, 65 pre-adults) was used to model the original age-at-death distribution. The proportion of pre-adults (D0-14/D ratio) for 2013 was used to estimate the proportion of pre-adults for the biased 1979/80 sample (original: 87 adults, and 7 pre-adults). Subsequently, the actual number of adults in the combined sample ($n = 203$) and estimated total number of pre-adults ($n = 114$) was used to model the age-at-death distribution for the entire adult sample (see Table 1). It should be noted that while the effective (able to be assessed for cribra orbitalia) adult sample was 69.5% (141/203) of the total aged sample, only

**TABLE 1** Age distribution of combined Con Co Ngua samples

| Total sample | | Effective sample |
|---|---|---|
| Age (years) | *N* | *N* |
| 0–14 | 72 | 15 |
| 15–34 | 37 | 24 |
| 35–39 | 9 | 7 |
| 40–44 | 17 | 11 |
| 45–49 | 11 | 8 |
| 50–54 | 13 | 10 |
| 55–59 | 12 | 8 |
| 60–64 | 27 | 22 |
| 65–69 | 17 | 10 |
| 70–74 | 27 | 23 |
| 75+ | 33 | 18 |

20.8% (15/72) of the pre-adult aged sample could be assessed for cribra orbitalia.

As noted, cortical bone porosity of the frontal bone portion of the orbit initiated within the diplöic space (not initiated subperiosteally) is the minimum criterion for the identification of cribra orbitalia in this study. The underlying cause of such porosity is the expansion of red marrow within the diplöic space due to erythroid hyperplasia, a situation which can only occur in the context of one or more of the anemias. Individuals exhibiting evidence for vascular grooves in the orbital roof (e.g., see Oxenham, 2016, figure 5.6), without associated lysis of the cortical bone, were not identified as being positive for cribra orbitalia. Further, porous subperiosteal new bone formation on the orbital roof, often associated with other metabolic conditions such as scurvy (Klaus, 2017; Snoddy et al., 2018), was not scored as positive for cribra orbitalia. Tumors, albeit rare, may account for orbital porosity in a very small percentage of the assemblage (Ortner, 2003, p. 89). We follow Klaus (2017, p. 99) where "rigorous macroscopic observation of orbital lesions" can differentiate between anemia and scurvy, and indeed other potential causes. This includes the sorts of potential pseudo-lesions or taphonomic damage (e.g., see Wapler et al., 2004) that can be recognized by way of discoloration and/or post-mortem damage to the orbits and/or edges of the lesions.

Operationally, cribra orbitalia was scored in both samples by the same author (MFO) and followed the same protocol, whereby only lytic or porotic lesions (e.g., see Rivera and Mirazón Lahr's (2017) classes 1–4; Oxenham (2016) figures 5.4 and 5.5) were scored as positive. Figure 1 provides an example of cribra orbitalia from the Con Co Ngua series. The minimum threshold for recording anemia-associated cribra orbitalia was the preservation of at least one orbital roof.

### 2.3.2 | Statistical approach

Kaplan–Meier survival analysis is a statistical tool for examining time to event data. It is a non-parametric test which can be used to evaluate differences in time until events such as death, remission, or some other response type, between two groups (Kaplan & Meier, 1958). While this provides a comparison at each time point, the log rank test is commonly used as an additional analysis to compare the total survival experience of the groups across all time points collectively (Bland & Altman, 2004). It is used to address the null hypothesis that there is no difference in the probability of an event between the two groups and provides a measure of statistical significance (Bland & Altman, 2004). Kaplan–Meier survival analysis and the log rank test were used to compare the age-at-death profiles for those with (group = 1) and without (group = 0) evidence for cribra orbitalia (CO) (Bland & Altman, 2004; Johnson & Shih, 2012). For these analyses, each sample is characterized by three variables: (1) serial time (in this case, estimated age-at-death); (2) status at the end of the serial time (with 1 indicating the occurrence of an event, and 0 censored; in bioarchaeological analyses all individuals are scored 1); and (3) the study or exposure group they are in (in this case, 1 indicates the presence of CO, and 0 indicates an absence of evidence for CO) (Johnson & Shih, 2012). As Kaplan–Meier analysis requires point estimates of age, the midpoint of the five-year age ranges to which individuals were assigned (see above) was used in lieu of a genuine point estimate. Notably, this creates a stepped effect to the distribution, as various individuals that in reality had specific and different age points within a five-year interval are instead represented as having the same mean age. The dataset is provided in the Supplementary Information table.

**FIGURE 1** Cribra orbitalia in the orbit of an approximately 13-year-old individual from the 2013 excavation season, Con Co Ngua

## 3 | RESULTS

Figure 2 illustrates the different survival times between the groups when considering the overall lifetime association between cribra orbitalia and death, where median survival is higher in adults ≥15 years

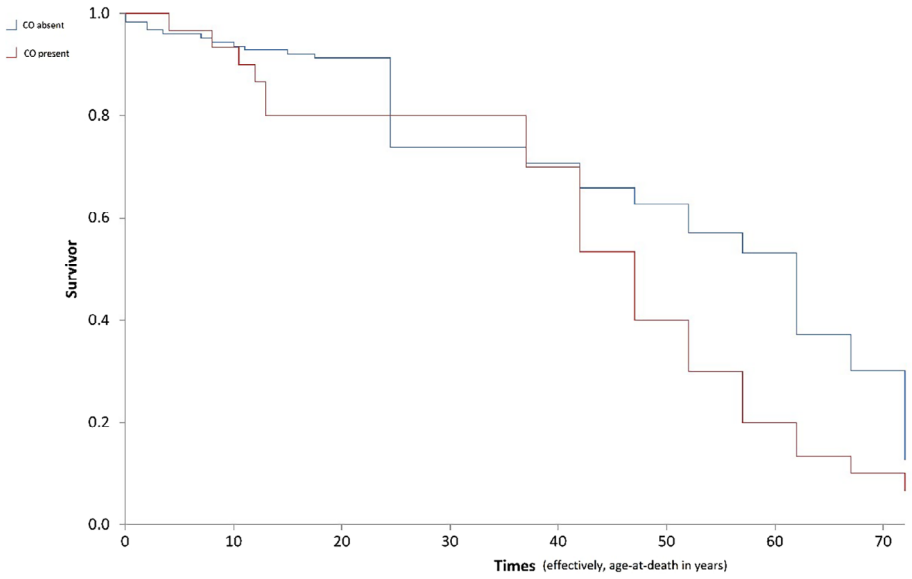


**FIGURE 2** Kaplan–Meier survival analysis results for CO lesion status: red line represents people with CO, and blue line those without

**TABLE 2** Results of the log rank tests for each analysis

| Kaplan–Meier analysis | N= | Relative risk rate for presence of cribra orbitalia | Chi-square for equivalence of death rates | p-value |
|---|---|---|---|---|
| All individuals | 156 | 1.48 | 7.14 | 0.01 |
| Adults up to 70 years of age | 85 | 1.41 | 4.36 | 0.04 |
| Preadults | 15 | 0.61 | 5.81 | 0.02 |

**TABLE 3** Median survival times and confidence intervals.

| Kaplan–Meier analysis | Cribra status | N= | Median survival time (years) | 95% confidence interval (years) |
|---|---|---|---|---|
| All individuals | Present | 30 | 47 | 41–53 |
| | Absent | 126 | 62 | 58–66 |
| Adults up to 70 years of age | Present | 21 | 47 | 41–53 |
| | Absent | 64 | 57 | 53–61 |
| Preadults | Present | 6 | 10.5 | 6–15 |
| | Absent | 9 | 3.5 | 0–8 |

without cribra orbitalia (blue line, 62 years) than those with the lesion (red line, 47 years). It is notable that the survival curves cross over at 25 years of age and again in the early 40s. This is typically seen in clinical studies where one group exhibits greater variance in survival time than the other (Bouliotis & Billingham, 2011). Alternatively, this may represent differential age impacts of the condition. In this study, the survival cross-overs are likely the result of variance in the representation of individuals in each age category between the two samples ($n = 30$ with cribra orbitalia and $n = 126$ without) and should not be considered a true product of the impacts of cribra orbitalia on survival. The relative risk of death for individuals with cribra orbitalia lesions was 1.48 ($p < 0.05$) compared to their non-lesioned counterparts, based on the log rank test (Table 2). There was no overlap in the 95% confidence interval for median survival times (41–53 years for those with cribra orbitalia and 57–66 years for those without cribra orbitalia) (Table 3). This might stem from the overlap of survival curves for individuals with an age-at-death greater than or equal to 70 years in both groups ($n = 42$), which accounts for more than 1/4 of the total population. The overlap is potentially caused by either the nature of the data, that is, with 75+ being the oldest age cohort and all samples dead, the two survival curves are "forced" to converge at their ends to reach 0 cumulative survival; or the intrinsic high frailty associated with the elderly, whose survivorship is expected to flatten.

Excluding the 70+ cohort (see Figure 3) makes little difference with median survival still somewhat higher in people without cribra orbitalia (blue line, 57 years) than those with (red line, 47 years). There is no overlap in the 95% confidence intervals for these means, and the log rank test found an increased risk of death of 1.41 ($p < 0.05$) for those with cribra orbitalia lesions.

When only examining pre-adults, Figure 4 illustrates the different survival times between the groups, where median survival is higher in pre-adults with cribra orbitalia (red line, 10.5 years) than those without (blue line, 3.5 years). The 95% confidence intervals for median survival overlap, (0–8 years for those without cribra orbitalia lesions and 6–15 years for those with cribra orbitalia lesions, Table 3) and are notably wide due to the very small sample sizes. The increased risk of death is 1.76 ($p < 0.05$) for pre-adults without cribra orbitalia based on the log rank test. However, log rank tests on small sample sizes are known to be subject to distortion effects which may produce an inaccurate significant result (Wang et al., 2010). As such, this result must be treated with caution and is tentative at most.

## 4 | DISCUSSION

The risk of death for adults with cribra orbitalia is greater than for those without while the reverse pattern is seen with pre-adults where those without lesions experience a greater risk of death. Given cribra

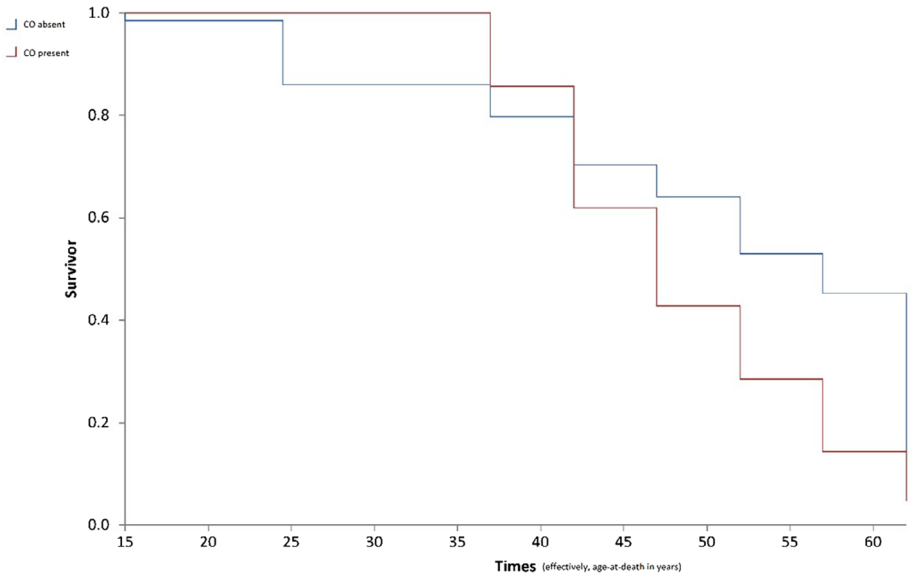


**FIGURE 3** Kaplan–Meier survival analysis results for CO lesion status, with 70+ cohorts excluded. Red line represents people with CO, and blue line those without

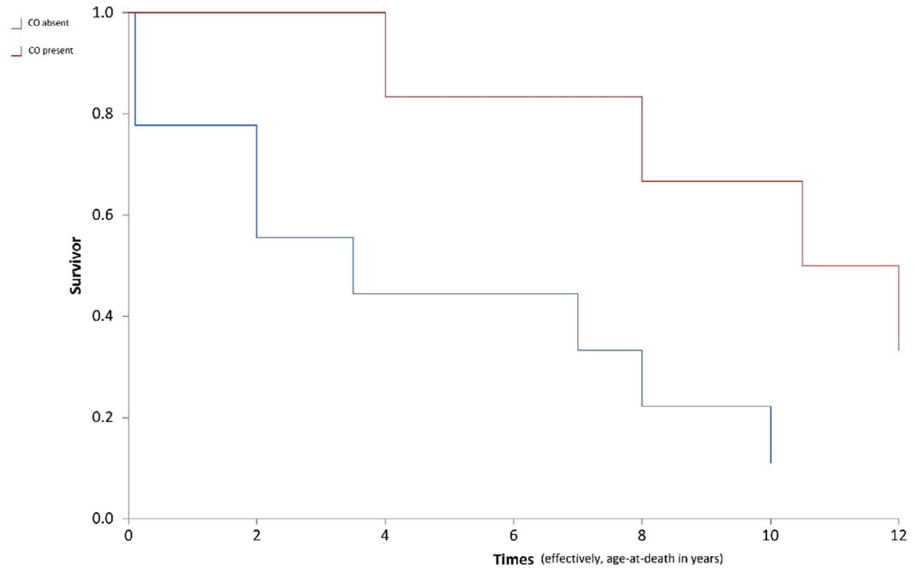


**FIGURE 4** Kaplan–Meier analysis on pre-adults only. Red line represents people with CO, and blue line those without

orbitalia only develops in children (McFadden & Oxenham, 2020), the apparent benefit to adults of experiencing the condition that causes cribra orbitalia (as children) would seem to reduce with increasing age. Another way to look at this relationship is that children display a degree of resilience to the underlying cause(s) of cribra orbitalia, while with increasing age the relationship changes with adults having experienced ill health leading to cribra orbitalia as children being frailer later in life.

Currently, the most widely accepted underlying cause of cribra orbitalia as defined in this study is one or more of the anemias (Brickley, 2018; McFadden & Oxenham, 2020; Oxenham, 2018; Oxenham & Cavill, 2010). It seems to be a condition that can only develop in early childhood (Brickley, 2018; McFadden & Oxenham, 2020) with its presence in older children and adults a function of original severity, remodeling rates, and time since occurrence (McFadden & Oxenham, 2020, p. 6). The question then arises, which of the various forms, or combinations, of anemia might be responsible for the pattern and degree of cribra orbitalia seen in this early seventh millennium hunter-gatherer assemblage from northern Vietnam? Previously we have stressed that an understanding of the geographic and bioarchaeological context of the population of interest is critical in inferring the type of anemia that may be responsible for the majority, at least, of cribra orbitalia observed in a series (McFadden & Oxenham, 2020, p. 11). The most likely candidates include iron deficiency anemia, megaloblastic anemia (e.g., folate and/or B12 deficiency), one of the hemolytic anemias (e.g., a form of thalassemia) or anemia acquired through malarial infection. The remaining discussion explores the question of the most likely etiological agent(s) in the cause of cribra orbitalia at Con Co Ngua and how this may inform an interpretation of pre-adult and adult survival with and without these lesions.

### 4.1 | Iron deficiency anemia and folate/B12 deficiency

It is well known that hematinic deficiency (particularly iron, folate and B12) can lead to anemia. In modern developing countries, anemia, particularly iron deficiency anemia associated with malnutrition, is a significant burden for children aged between 1 and 3 years (Alvarez-Uria et al., 2014; Arlappa et al., 2010). Iron deficiency induced by parasites, including hookworm and roundworm, also contribute to high iron deficiency anemia morbidity in Southeast Asian children (Loukas et al., 2016). It should be noted that hydatid disease, caused by a parasitic tapeworm, was a significant burden at Con Co Ngua (Vlok et al., 2022); however, while anemia is commonly observed in infected individuals, it tends to be anemia of chronic disease/infection (Krige & Beckingham, 2001) which is not associated with the mechanisms that can lead to cribra orbitalia (Oxenham & Cavill, 2010).

While iron deficiency anemia and B12 or folate deficiency mediated (megaloblastic) anemia involve quite different mechanisms, one of the key common responses to both conditions, when severe enough, is erythroid hyperplasia which can lead to marrow expansion and subsequent cortical and trabecular bone atrophy and, depending again on severity and duration, cribrotic lesions of the orbit (see discussion in McFadden & Oxenham, 2020, p. 6). There seems little doubt that iron deficiency anemia needs to be included in any discussion of the potential etiology of cribra orbitalia (McFadden & Oxenham, 2020; Oxenham & Cavill, 2010). However, despite B12 and folate deficiencies being seen as an important underlying cause of anemia and/or cribra orbitalia in the bioarchaeological literature (e.g., Walker et al., 2009; Brickley et al., 2020, p. 205), the role of such deficiencies in significant anemia burdens needs some scrutiny.

While B12 deficiency has a rather low prevalence in developed countries (although it increases in prevalence with increasing age), high levels have been reported in developing countries: as much as 70% in a study of Kenyan school children and 80% of Indian preschool children (Allen, 2009, p. 694S). Notwithstanding, a comprehensive global survey of the overall effects of B12 and/or folate deficiency found that such deficiencies played a minor role in the world anemia burden (Metz, 2008). While both folate and B12 deficiency is common in developing countries in general, and among certain dietarily restricted groups, there are few data linking such deficiencies directly to the development of anemia (Metz, 2008). In the case of folate deficiency anemia (noting B12 deficiency can be a cause of folate deficiency), while it is seen in modern developing countries this is often in areas where there are high loads of iron deficiency anemia, malaria and or hemoglobinopathies (Metz, 2008: S79). The role of B12 and folate deficiencies, as is perhaps also the case for iron deficiency, are more relevant in the context of the synergistic relationship between nutritional deficiencies in general, and increased risk of disease (see below).

### 4.2 | Malaria

Malarial anemia is a complex suite of pathophysiological conditions including but not limited to malaria-induced anemia by dyserythropoiesis (defective erythrocyte development) and erythrocyte hemolysis (destruction), hypersplenism, immune hemolysis, and secondary iron and folate deficiency (Ghosh & Ghosh, 2007; Menendez et al., 2000). Severe malarial anemia is more likely to present in populations with holoendemic or hyperendemic malaria (White, 2018). As noted above, malaria has been endemic to Southeast Asia for at least 7000 years and likely much longer, and high endemicity is suggested by the emergence of thalassemia as an evolutionary adaptation at this time (Vlok et al., 2021). The two main causes of morbidity and mortality in the region being *Plasmodium falciparum* and *Plasmodium vivax*. Notwithstanding, other variants in the region are known that can be transmitted by mosquito vectors between primates and humans (Antinori et al., 2021) and presumably this also occurred in deep antiquity.

While *P. vivax* is generally known to have a significantly lower mortality rate than *P. falciparum*, both are associated with high levels of morbidity (Anstey et al., 2009; Mendis et al., 2001; Naing et al., 2014). Further, almost equivalent levels of mortality for both forms have been observed in Papuans, albeit in the context of very low (and potentially anomalous) case fatality rates for *P. falciparum* (Tjitra et al., 2008). Indeed, despite the complications of various potential co-morbidities, including evolutionary responses to malaria infection (see thalassemia below), other parasitic infections (e.g., hookworm), and nutritional deficiencies (including potential synergistic relationships between malnutrition and malaria status) (Poespoprodjo et al., 2009; Williams et al., 1997), anemia is a significant risk factor for *P. vivax* infections particularly among children (Anstey et al., 2009, p. 222; Naing et al., 2014).

With respect to ancestry, there are some data suggesting a greater susceptibility of Papuan populations to severe anemia induced *P. vivax* infection, possibly related to complement receptor-1 (CR1) having a lower erythrocyte expression in such populations (Anstey et al., 2009, p. 224). Whether Con Co Ngua individuals, believed to be ancestral to modern Australo-Papuan populations (Matsumura & Oxenham, 2014), also experienced low CR1 erythrocyte expression is unknown. A further potentially relevant factor is that *P. vivax* infection appears to peak in children below 5 years of age, in contrast to *P. falciparum* where infection rates peak between 15 and 25 years and indeed is not commonly seen in Melanesian and Papuan adults (Poespoprodjo et al., 2009, p. 1708). Notwithstanding, elevated adult mortality associated with *P. vivax* appears to be often associated with pre-existing comorbidities such as severe respiratory distress syndrome and pulmonary edema, rupture of the spleen, and multi-organ dysfunction (Lacerda et al., 2012). It is perhaps best to consider both *P. falciparum* and *P. vivax* as possible if not likely candidates for the malarial load experienced by the Con Co Ngua population.

### 4.3 | Thalassemia

In the context of our discussion of malaria, the most relevant hemolytic anemias in Southeast Asia are the thalassemias, hereditary disorders of globin synthesis (Oxenham, 2018). These hereditary disorders emerged in the region as a protective mutation against malaria

(Wiwanitkit, 2008) and can clearly lead to a range of skeletal changes in children, including cribra orbitalia (Oxenham & Cavill, 2010). The archeological context of thalassemia in mainland Southeast Asia has recently been discussed by Techataweewan et al. (2021), and therefore only summarized here. The profound skeletal signatures of beta thalassemia major, and also alpha thalassemia major to an extent, are well documented, with some of these changes also apparent in less severe forms of thalassemia (see Lewis, 2012; Vlok et al., 2021). Recently, evidence for alpha and beta thalassemia, with the possibility of their co-occurrence has been demonstrated for Neolithic northern Vietnam, while thalassemia without attribution to the beta or alpha forms has been identified in the Con Co Ngua assemblage (Vlok et al., 2021). Moreover, there is compelling evidence to suggest that thalassemia was a significant health cost to other ancient Southeast Asian populations (Tayles, 1996; Vlok et al., 2021).

## 4.4 | Iron deficiency and malaria interactions

While the potential etiological role of various deficiency anemias, inherited anemias and malarial-induced anemia in the development of cribra orbitalia have been discussed above, it has also been noted that these conditions can manifest as co-morbid conditions, thus obscuring the primary etiological agent. Moreover, in the case of iron deficiency and iron deficiency anemia, specifically, there is a reported survival advantage against malaria (Adam, 2016; Spottiswoode et al., 2014). Iron is an essential component of multiple metabolic pathways of the parasite (Mabeza et al., 1999). Inflammation increases the production of hepcidin subsequently reducing available iron within the body and may be an underlying adaptive response to a number of infections including malaria (Camaschella, 2015). Iron withholding as a protective mechanism against malaria and other infectious disease (e.g., tuberculosis) is a long-held hypothesis, one explored in detail with respect to the Pacific (Buckley, 2016), and has been recently supported by empirical studies on populations of different cohorts. Gwamaka et al. (2012), in studying a cohort of Tanzanian children aged from 0 to 3 years old, found that iron deficiency in this group is strongly associated with lower future risk of severe malaria; Jonker et al. (2012) noted that iron deficient Malawian children (6 months–5 years) showed a lower incidence of malaria in the following year; Kabyemela et al. (2008) found that in north-eastern Tanzania, pregnant women with iron deficiency were less susceptible to *P. falciparum* malaria. Likewise, an array of studies has found that iron supplementation may elevate the susceptibility of vulnerable populations to malaria (Murray et al., 1978; Oppenheimer, 2001; Sazawal et al., 2006). Thus, supplementing iron to populations in malaria endemic regions has long been viewed as problematic (Oppenheimer, 2001; Spottiswoode et al., 2014). However, other studies have argued that iron deficiency does not protect against infections (Keusch, 1999, p. 328), including malaria, or have suggested a lack of association between iron supplementation and malaria severity (Desai et al., 2003; Ouédraogo et al., 2008). Additionally, the *Plasmodium* parasite is responsible for destroying red blood cells, slowing down production of new red blood cells, decreasing iron absorption, and increasing folate requirements, all contributing to anemia morbidity (Menendez et al., 2000). Questions remain regarding the adaptive measures of survival of the parasite versus the host's physiological response to reduce iron availability in the body. Notwithstanding these contrary studies, the correlation between iron availability and malaria appears robust, considering the large amount of supporting evidence (Nairz et al., 2014). Though the specific mechanism has yet to be fully understood, the phenomenon of iron deficiency/iron deficiency anemia associated with reduced malaria severity might be linked with (1) iron mediated anti-malaria immune defense system; (2) decreased iron availability for pathogen replication; or (3) decreased availability of young RBCs, which *P. falciparum*, and possibly *P. vivax*, prefers (Clark et al., 2014; Douglas et al., 2012; Nairz et al., 2014).

## 4.5 | Etiology of Cribra Orbitalia at con Co Ngua

Given the preceding discussion, is it possible to isolate one or more likely causes for the contrasting epidemiological pattern seen with respect to anemia in children and adults at Con Co Ngua? In an important review study, Brabin et al. (2001) state that over 50% of children in developing countries have been reported to have anemia, for the most part due to iron deficiency or malarial parasitemia. Notwithstanding, and despite severe anemia associated with malaria being a higher mortality risk factor than that caused by iron deficiency alone, they stress that there is currently a poor causative link between iron deficiency anemia and mortality in children (Brabin et al., 2001, p. 644S; see also Stoltzfus, 2003; Stoltzfus et al., 2004). Part of the issue is a lack of studies of any association between iron deficiency anemia and mortality risk in non-malarious populations. Nonetheless, there is a clear association between iron deficiency anemia and malnutrition, and malnutrition significantly increases the risk of developing infectious disease and, subsequently, risk of mortality (Ibrahim et al., 2017; Martins et al., 2011; Pelletier et al., 1993; Rytter et al., 2014). In this context it is worth noting that a survey of undernutrition in modern day South and Southeast Asia reported high rates of anemia in children under 5 years of age ranging from 20% in China, 34.1%% in Vietnam through to 63.4% in Cambodia and 78% in Nepal (Pasricha & Biggs, 2010, p. 498; see also Stoltzfus, 2003; WHO, 2006). It is clear that vitamin deficiencies associated with undernutrition in childhood are associated with increased risks of a wealth of morbidities in later adult life (Elo & Preston, 1992; Victora et al., 2008). Moreover, despite a lack of research specifically examining iron deficiency anemia being a direct cause of childhood mortality, the condition is associated with adverse health outcomes that are more directly attributable to elevated childhood mortality.

Iron deficiency anemia in isolation, or even as a factor associated with malnutrition, parasitism or subsequent infectious disease, would seem to be an unlikely primary candidate for cribra orbitalia in children that demonstrate greater mean survival relative to their presumably unaffected, non-deficient, counterparts. If iron deficiency anemia, and folate/B12 deficiencies, are themselves unlikely primary candidates for the quite different childhood and adult risks of mortality seen at Con Co Ngua, then what are?

The identification of various forms of thalassemia as being a significant health burden from the early seventh millennium BP through to the Neolithic several thousands of years later in northern Vietnam suggests that both thalassemia and malarial parasitemia, likely involved in complex relationships with iron deficiency and/or iron deficiency anemia (if not other hematinics), are the most likely candidates. We believe thalassemia to be a significant etiological agent in the underlying cause of cribra orbitalia at Con Co Ngua and can most parsimoniously explain the differing pre-adult and adult survivorship patterns seen in this study. The premise being that children with one or more forms of thalassemia, which led to or contributed to the development of cribra orbitalia, were more resilient to the effects of malarial parasitemia than children without this blood pathology. However, this benefit in childhood became a liability in later adulthood.

Taher and Cappellini (2018), in a study examining health outcomes in transfusion dependent (treated) and non-transfusion dependent (a cohort not necessarily treated) thalassemia individuals, noted that anemia associated with non-transfusion dependent beta thalassemia progresses with age, as does morbidity. Ineffective erythropoiesis leads to primary iron overload (cumulative with increasing age as the body cannot remove iron), which in turn increases the risk of a range of morbidities. The complications of iron overload can include localized osteomalacia, osteoporosis, hypertension, thrombosis, heart and liver failure, diabetes mellitus, hypothyroidism, and extramedullary hematopoietic tumors (Koohi et al., 2019; Skordis, 2009; Taher & Saliba, 2017). Heart failure is the greatest risk of death caused by iron overload and results in 71% of deaths of individuals with beta thalassemia major as a direct result of iron accumulation (Koohi et al., 2019). The pattern seen at Con Co Ngua is consistent with a significant thalassemia load in children, which confers a degree of protection from malarial parasitemia in this (subsequently lesioned) cohort, but then goes on to develop into an ever-increasing risk factor for a range of fatal secondary morbidities with increasing adult age.

A significant role for thalassemia, both with respect to anemia burdens at Con Co Ngua and subsequent adult risk of morbidity/mortality, should also be seen within the context of malaria itself. With respect to the discussion of malaria above, it should be noted that the burden of severe malarial induced anemia experienced in early childhood may also have some relevance with respect to the pattern of pre-adult cribra orbitalia observed in the Con Co Ngua assemblage. Minimally, the lower risk of death of Con Co Ngua children with cribra orbitalia (ostensibly caused by severe anemic response(s) to the parasite) suggests a degree of resilience by this cohort to the effects of malaria during childhood. It is worth noting that some 30% of African childhood mortality rates in the 1990s were attributed to malaria (Snow et al., 2001). However, surviving malaria infers a degree of subsequent immunity to the disease, which is only maintained through frequent reinfection (Langhorne et al., 2008). Both thalassemic children and non-thalassemic children that survived malaria should in theory have a degree of immunity to the disease into adulthood. The increased mortality risks of adults with thalassemia have been discussed above. However, it is unclear why malaria-resistant non-thalassemic adults (that developed cribra orbitalia as children) might be frail, with a lower median age at death, than non-lesioned adults. In this context it is worth noting that while repeated malarial reinfection in children is associated with an elevated risk of mortality, relative to adults (Dini et al., 2020), little data are available with respect to adult mortality and morbidity risks in the face of frequent malarial reinfection. However, a large-scale prospective study of South and Southeast Asian children and adults, where protective immunity from malaria is low due to "low and unstable transmission" rates, with severe anemia found an increased risk of mortality with increasing age (Dondorp et al., 2008, p. 155). It was suggested that renal impairment (which also increased with increasing age) contributed to increased risk of adult morality in this cohort (Dondorp et al., 2008, p. 155). Another large-scale study in South Asia has also demonstrated elevated malarial mortality risks in both children and among adults, which increases with increasing age, while the underlying specific causes of adult mortality are unclear (Dhingra et al., 2010). For the Con Co Ngua community, it may be that a physiological trade-off regarding lower mortality in the face of malaria as a child was later adult frailty in the face of either further malarial infections and/or a range of conditions that acted synergistically with malaria to increase the risk of death in later adulthood.

## 5 | CONCLUSIONS

The hypothesis that the underlying cause(s) of cribra orbitalia in the Con Co Ngua sample effectively decreased resilience to the impacts of subsequent conditions or diseases is supported for the adult cohort. Conversely, pre-adults with cribra orbitalia had better survival, or resilience, than pre-adults without this lesion.

The pattern whereby children with cribra orbitalia are relatively more resilient while adults with cribra orbitalia are frailer than their comparative cohort is arguably most parsimoniously explained in the context of malaria and one or more of the thalassemias. The evidence for malaria is inferred from previous work which identified the presence of thalassemia (independent of evidence for cribra orbitalia), essentially an evolutionary adaptation to high malarial loads, at Con Co Ngua.

While thalassemia and malaria are the most probable chief etiological agents for anemia at Con Co Ngua, it is also clear that both conditions interact with, and can indeed cause, other forms of anemia. For instance, iron deficiency anemia would clearly have played a significant morbidity and mortality role within the Con Co Ngua community, however, it is simply not possible to tease out its specific or independent importance as a risk factor for morbidity or mortality. Apart from an inferred high level of parasitemia due to malaria, the only parasite definitively identified at Con Co Ngua, and which was a major health burden, is hydatid disease which is associated with anemia of chronic disease, a condition that cannot lead to cribra orbitalia. Nonetheless, it is perhaps likely that other parasites contributed to a substantive degree of parasitemia in this community, much of which may have contributed to iron deficiency anemia.

Con Co Ngua was a complex sedentary foraging community chiefly characterized by wild cattle management, the use of pottery and complex mortuary rituals. It is but one of scores of such

communities, of which we still know very little, that inhabited what is now northern Vietnam and southern China: the Da But-Dingsishan foraging complex. These populations struggled with elevated levels of parasitemia, with evidence indicating evolutionary adaptations to malaria thousands of years prior to the emergence of farming in the region. Notwithstanding, the health trade-offs associated with adaptations, such as thalassemia, to high disease loads were clearly significant for such sedentary complex hunter-gatherer communities.

## AUTHOR CONTRIBUTIONS

**Tianyi Wang:** Conceptualization (equal); investigation (equal); methodology (equal); writing – original draft (equal). **Clare McFadden:** Data curation (equal); formal analysis (equal); writing – review and editing (equal). **Hallie R Buckley:** Investigation (equal); writing – original draft (equal); writing – review and editing (equal). **Kate Domett:** Investigation (equal); writing – review and editing (equal). **Anna Willis:** Investigation (equal); writing – review and editing (equal). **Hiep Hoang Trinh:** Investigation (equal); writing – review and editing (equal). **Hirofumi Matsumura:** Data curation (equal); writing – review and editing (equal). **Melandri Vlok:** Investigation (equal); writing – original draft (equal); writing – review and editing (equal). **Marc F Oxenham:** project administration (lead); conceptualization (lead); funding acquisition (lead); investigation (lead); methodology (equal); writing – original draft (equal), review and editing (equal); data curation (equal).

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## CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

## DATA AVAILABILITY STATEMENT

The data set used in this paper is provided in full in Supplementary Information.

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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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