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A paleoepidemiological approach to the osteological paradox: Investigating stress, frailty and resilience through cribra orbitalia

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Abstract

Objectives: The Osteological Paradox posits that skeletal lesions may differentially be interpreted as representing resilience or frailty. However, specific consideration of the etiologies and demographic distributions of individual skeletal indicators can inform the criteria on which to differentiate stress, frailty, and resilience. Adopting a life history approach and adaptive plasticity model, this study proposes a framework for the analysis and interpretation of a commonly reported skeletal lesion, cribra orbitalia, which considers the underlying mechanisms of the condition, the clinical and epidemiological literature relating to anemia and malnutrition, and the bio-archeological evidence.

Materials and methods: Data were extracted from the European ($n = 33$ populations) and American ($n = 19$ populations) modules of the Global History of Health Project. Kaplan–Meier and Cox regression analyses were applied, where time was the age-at-death, and the factor or covariate was presence or absence of cribra orbitalia.

Results: Of 37 samples that produced significant results, 21 demonstrated a change in relationship when the subadults were excluded from analysis. When subadults were included, individuals with cribra orbitalia present had statistically significant lower survival time. With subadults excluded, the relationship either became nonsignificant or was reversed.

Discussion: We demonstrate that in many cases the inclusion of subadults in analysis impacts upon the apparent mortality associated with cribra orbitalia. Examining cribra orbitalia in children and adults has two separate goals: in children, to determine the prevalence and risk of death associated with active lesions and stress; and in adults, to determine whether childhood health assaults that cause cribra orbitalia are associated with frailty or resilience.

KEYWORDS

cribra orbitalia, resilience, frailty, stress, anemia, osteological paradox

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1 | INTRODUCTION

A substantial contribution of bioarcheology is the study of indicators of stress, frailty, and resilience in individuals and populations in the past. As modern humans, our adaptability and resistance to intrinsic and extrinsic pressures have been of significant interest from biological and evolutionary perspectives, and in terms of understanding our capacity for future survival and reproduction. Bioarchaeologically, stress is traditionally seen in terms of some form of homeostatic disruption (Larsen, 2015), the severity and nature of which is contingent upon the interaction among a range of environmental and socio-cultural variables and innate (host) resistance factors (e.g., Goodman, 1984; Goodman & Armelagos, 1989; Goodman, Brooke Thomas, Swedlund, & Armelagos, 1988). Host resistance and/or response has usually been couched in terms of negative outcomes, often discussed by way of differential frailty, with frailty potentially resulting in increased morbidity and mortality associated with stress, either as the result of inherent frailty, or frailty acquired through prior stress events. More positive responses and outcomes to stress, in contrast, can be characterized in terms of resilience, a term which reflects resistance to stress, and/or improved odds of surviving health assaults.

We believe that when exploring life history parameters, it is appropriate to frame the theoretical and analytical approach in terms of a modified version of the Developmental Origins of Health and Disease (DOHaD) model, or the view that experiences (environment, diet, health, and disease) in the early developmental stages of life potentially speak to later life health outcomes. Commonly, the DOHaD model spans the first 1,000 days from conception (with the traditional Barker hypothesis focusing on the fetal period and the consequences of maternal health and exposures) (Hoffman, Reynolds, & Hardy, 2017). However, in this study we modify the period of interest to include up to the approximate age of sexual maturity in order to capture further phases of biological development. This modification deviates from the traditional DOHaD model but is nonetheless grounded in the concept of developmental stress potentially having morbidity and mortality consequences in adulthood. Furthermore, we do this by way of coupling a life history approach with an epidemiologically focused methodology. We have adopted Temple's (2019) recent translation of traditional bioarcheological explorations of stress in the context of the burgeoning life history literature.

Within the context of a life history approach, the core concept is that of adaptive plasticity which refers to the variable ability of an organism to respond to stressors in a way that optimizes its ability to cope with the immediate biological requirements for survival. Such responses will invariably involve the redistribution of resources to critical areas during early growth and development. Immediate benefits of adaptive plasticity are generally clear (life as opposed to death), while the costs, or physiological constraints self-imposed on an organism, may not be as obvious, but may include negative health outcomes in later life (including increased frailty and reduced life expectancy).

What are normally seen as bioarcheological signatures of stress (e.g., periosteal lesions, enamel hypoplasia, cribra orbitalia etc.) are a

record of the life history of an organism. Evidence for surviving early life stress is attributable to adaptive plasticity, the reallocation of critical resources in the face of potential threats to survival. Operationally, physiological constraint and acquired frailty are somewhat synonymous, with both speaking to adult mortality and morbidity risks with respect to the survival of stress in earlier life.

The integration of pathological and demographic evidence permits us to investigate both inter- and intra-population differences in the impacts of, and responses to, stress and the stimuli that cause it. Notably, our understanding of health is more limited, being based on the absence of evidence of stress, and falling well short of a more holistic and comprehensive concept of health incorporating socio-cultural factors and individual perception of wellbeing (Temple & Goodman, 2014; Tilley & Oxenham, 2011).

The pursuit of skeletal and dental signatures of the interplay between stress and adaptive plasticity or negative physiological constraints ultimately leading to differential frailty (or resilience), has revealed a host of challenges. Macroscopically at least, bone has a limited range of responses to stimuli through deposition, resorption, or some combination of these processes. Consequently, similarities in skeletal expressions of pathological conditions are abundant and unique signatures of specific conditions and diseases are rare. In many cases, a number of diagnostic criteria are implemented to try and overcome this issue. As an alternate solution, bioarcheology has cautiously accepted many skeletal lesions to be nonspecific indicators of stress. While this limits interpretations to overall or general health assaults, it may still afford opportunities to investigate stress, frailty, and resilience broadly.

Associating lesions within a paleodemographic framework, including sex, age, and status, can highlight demographic biases in the distribution and effects of stress and disease. In turn, this may be used to assess the outcomes (both positive and negative) of adaptive plasticity of specific parts of the population. Notwithstanding, the Osteological Paradox (Wood, Milner, Harpending, & Weiss, 1992) highlighted that the same skeletal lesions may differentially be interpreted as representing frailty or resilience (the closest to the concept of resilience in their paper is the term "less frail"). Wood et al. (1992) posited that on one hand skeletal lesions may indicate a population with several and severe assaults on their health (an unhealthy population), whilst on the other may indicate a population which has survived ill-health long enough for it to leave an impression on the skeleton. Further, skeletal lesions may indeed be inactive at the time of and unrelated to the cause of death. Thus, individuals with lesions may be interpreted as being frail as a result of the diseases they have suffered, or less frail (resilient) for the fact they have survived (Wood et al., 1992). Goodman (1993) objected to the paradox as an oversimplification and a "stale characterization of palaeoepidemiology" (p.282). He argued the paradox could be overcome through the use of multiple sources of evidence, including both pathological and demographic information, and a robust framework for the evaluation of morbidity and frailty (rather than cause-specific mortality). Defending bioarchaeologists who pursue such research, Goodman (1993) observed that many have expanded their expertise to include modern epidemiology, nutrition,

and physiology. A further consideration is the potential impacts of the age-at-death distribution on paleoepidemiological analyses. As observed by Wood et al. (1992), Wright and Yoder (2003) and DeWitte and Stojanowski (2015), the distribution of lesions amongst subadults in comparison to adults may have differential and significant interpretive implications.

While the paradox is frequently discussed (with over 1,400 citations on Google Scholar) and progress reviewed (DeWitte & Stojanowski, 2015; Sołtysiak, 2015; Wright & Yoder, 2003), the discipline has yet to accept any broad solution to the paradox overall. Evaluating Wood et al.'s (1992) proposition in light of the original discipline of paradox—philosophy—may hold some clues to resolving it. Sorites paradoxes, or those of vagueness, result from the failure or inability to delineate between categories. A common representation of this is the removal of single grains of sand from a heap (sorites in Greek), with the question arising, at what point does it cease to be a heap? Several resolutions have been proposed, including defining the term (e.g., a heap is that which is equal to or greater than 100 grains of sand), but others contend that such definitions are arbitrary and frequently unknowable (Sorensen, 2003). There are some parallels between the sorites and osteological paradoxes. First, we must determine on what basis we evaluate stress and the differentiating features of frailty and resilience. Similarly, the answer is not simple, nor will a one-size-fits-all approach be suitable (i.e., any single definition would be arbitrary and inaccurate) but framing the question in this way may improve our ability to overcome the inherent challenges. The etiologies and demographic distributions (earliest and latest ages of onset, sex-biases, etc.) of individual skeletal indicators must be considered to determine the criteria on which to differentiate stress, frailty, and resilience. Ultimately, the matter comes down to defining these general terms in the context of specific lesions and conditions: where sufficient clinical and epidemiological evidence are available, as noted skeletal indicators can be interpreted in the context of adaptive plasticity in the face of environmental and/or cultural stressors, where physiological constraints speak to a continuum of frailty or resilience responses. It is through an empirically informed paleoepidemiological model that such stressors and responses are best understood. This paper seeks to explore these issues in the context of the commonly reported skeletal lesion *cribra orbitalia*.

Cribra orbitalia is perhaps one of the most cited conditions in the bioarchaeological literature. There is also a much less prolific, but growing, literature on *cribra orbitalia*, for the most part addressing the underlying etiology of the condition (e.g., Oxenham & Cavill, 2010; Rivera & Lahr, 2017) and/or defining the lesions characteristic of *cribra orbitalia* in distinction to sometimes confounding or conflated lesions. The latter include, for instance, the scorbutic lesions characteristic of scurvy (Brickley, 2018), which are blastic rather than lytic in manifestation, through to pseudo-lesions caused by a range of post-mortem taphonomic processes (e.g., Wapler, Crubezy, & Schultz, 2004). Indeed, if we are to exclude blastic and postmortem lesions from the definition of *cribra orbitalia* we have a reduced scope of etiologies to consider for the remaining lytic lesions. Reportedly, acute orbital hemorrhage (see Ortner, Kimmerle, & Diez, 1999; Roberts &

Manchester, 1997) and some types of tumor (Ortner, 2003) can cause these lesions, but neither occur in prevalences anywhere near those that would be consistent with the ubiquity and frequency of *cribra orbitalia* in bioarchaeological and modern skeletal samples. Consequently, anemia (in its various forms, including iron deficiency, megaloblastic, and hemolytic anemias) is the most likely cause of *cribra orbitalia* both based on the biological mechanics of lesion development and epidemiological understanding of population prevalence and distribution. It is also noteworthy that active *cribra orbitalia* lesions have only ever been observed in subadults, further reinforcing this etiology on the basis of differential red marrow distribution (Brickley, 2018).

In this paper, we propose a framework for the evaluation of *cribra orbitalia*, which considers the underlying mechanisms of *cribra orbitalia*, the clinical and epidemiological literature relating to anemia and malnutrition, and the bioarchaeological evidence. To demonstrate the impacts of the proposed framework, we re-analyze existing data on *cribra orbitalia* from the Global History of Health Project using a clinically and epidemiologically informed approach. It was hypothesized that the high prevalence of *cribra orbitalia* in subadults was the result of this being the only age group in which the lesions can develop and, in many cases, an indicator of active anemia which increases the risk of both comorbidities and mortality. It was further hypothesized that the increased risk of death for subadults with active anemia, combined with the higher prevalence for clinical reasons, would in many cases give the false impression of *cribra orbitalia* resulting in adult frailty, due to the subadults effectively decreasing the average age-at-death of those with lesions. As *cribra orbitalia* has a different nature and implications in subadults compared to adults, we analyzed samples as a whole, and then with subadults removed, to examine the effects. Reflecting upon the outcomes of this re-evaluation, we make recommendations for future studies of *cribra orbitalia* and advocate a similar approach to other skeletal lesions. In doing so, our understanding of stress, frailty, and resilience can be greatly improved.

2 | MATERIALS AND METHODS

Data were extracted from the European and American modules of the Global History of Health Project (GHHP) (Steckel, Larsen, Roberts, & Baten, 2018; Steckel & Rose, 2002). Individuals were analyzed as a cohort by site identifier (hereafter referred to as samples), with the variables of interest being age-at-death and the presence or absence of *cribra orbitalia*. Only samples with more than 100 individuals total, at least three subadults, and at least two cases of *cribra orbitalia* represented were analyzed, and only individuals with one or both orbits present and observed were included in each sample analysis. The GHHP uses a four-grade recording protocol for *cribra orbitalia*. For the European project, these are: 0—no orbits present; 1—absence of *cribra orbitalia* with at least one observable orbit; 2—a cluster of mostly fine foramina covering <1 cm²; and 3—>1 cm² covered by small or large clustered foramina (Steckel et al., 2018). For the

Western Hemisphere project, the grades of present cribra orbitalia are: 2—presence of a lesion; 3—gross [lytic] lesions with excessive expansion and large area of exposed diploe (Steckel & Rose, 2002). Importantly, the descriptors for present cribra orbitalia (grades 2 and 3) indicate that only lytic lesions have been included (they do not include bone deposition typical of infection, scurvy, etc.) and therefore these data are suitable for examining anemia. Notwithstanding, the European codebook has a separate recording protocol for scorbutic lesions (osteoperiostitis), making confusion with traditionally defined cribra orbitalia difficult. The WH codebook does not have separate recording protocols for scorbutic orbital lesions but does allow for identification of periosteal reactions. In summary, we are confident that the identification and recording of cribra orbitalia in both datasets refers to lytic lesions of the orbital roof and that accidental misidentification of scorbutic lesions as manifestations of cribra orbitalia would be very limited.

Grading of cribra orbitalia were condensed into presence (grades 2 and 3 collapsed into a score of 1) and absence (grade 1 was given a score of 0); those with no observable orbits (grade 0) were excluded from analysis. The GHHP recording protocols for cribra orbitalia do not differentiate between active and inactive lesions so unfortunately the impacts of this could not be assessed. Further information regarding the categorization of cribra orbitalia for the GHHP can be found in the module codebooks (Steckel et al., 2018; Steckel & Rose, 2002). Two separate analyses were run for each sample: the first was the sample as a whole and the second was the sample with all individuals aged under 15 years removed. Thirty-three samples were identified for inclusion for the European module and 19 samples for the American module. Kaplan–Meier and Cox regression analyses were applied in SPSS (2017), where time was the age-at-death, the factor or covariate was presence or absence of cribra orbitalia, and there were no censored individuals (i.e., status was consistent for all individuals).

Finally, Steckel (2005) had previously analyzed the relationship between cribra orbitalia (amongst other stress indicators) and survival in data from the American module of the GHHP, however, this study was restricted to individuals who died aged 15–30 years. Similarly, Roberts and Steckel et al. (2018) evaluated cribra orbitalia from the perspective of the DOHaD model, but also only examined adult individuals. Moreover, both studies utilized fundamentally different types of statistical analyses to those used in this study.

3 | RESULTS

Summaries of the statistical significance and outcomes of the analyses are provided in Tables 1–3 and Figures 1–3. Sample-by-sample results and Cox regression outputs are included in the supplementary information (Table S1). For the 33 European samples, five produced non-significant results both when the samples were analyzed as a whole and when they were analyzed with subadults removed. Of the remaining 28 samples, 16 demonstrated a change in relationship when the subadults were excluded. Specifically, when subadults were

included, individuals with cribra orbitalia present had lower mean and median survival time than individuals without the lesions; after their removal, the difference in survival was not significant. Twelve samples continued to show reduced survivorship amongst lesioned adults.

For the 19 American samples, nine had non-significant results in both analyses. Six of the remaining ten samples exhibited either no difference in survivorship, or favorable survivorship for those with cribra orbitalia, when subadults were excluded. Four samples showed consistent decreased survivorship for lesioned individuals with or without subadults.

In total, of 37 samples with significant results (including those that were significant and became nonsignificant and vice versa), 21 (57%) demonstrated a nil relationship between lesions and survivorship once subadults were excluded, or improved survivorship for those with lesions. Sixteen (43%) samples maintained poorer survivorship for individuals with lesions regardless of the inclusion or exclusion of subadults. Differences in the results may be explained by a

TABLE 1 European Global History of Health Project (GHHP) summary results

<i>European GHHP</i>	Total sample analysis	Subadults excluded analysis
Significant—lesions associated with lower mean survival	28	12
Significant—lesions associated with higher mean survival	0	0
Not significant (in one analysis only)	0	16

TABLE 2 American Global History of Health Project (GHHP) summary results

<i>American GHHP</i>	Total sample analysis	Subadults excluded analysis
Significant—lesions associated with lower mean survival	9	4
Significant—lesions associated with higher mean survival	0	2
Not significant (in one analysis only)	1	4

TABLE 3 Combined Global History of Health Project (GHHP) summary results

<i>Combined GHHP</i>	Total sample analysis	Subadults excluded analysis
Significant—lesions associated with lower mean survival	37	16
Significant—lesions associated with higher mean survival	0	2
Not significant (in one analysis only)	1	20

FIGURE 1 European Global History of Health Project (GHHP) summary results graph

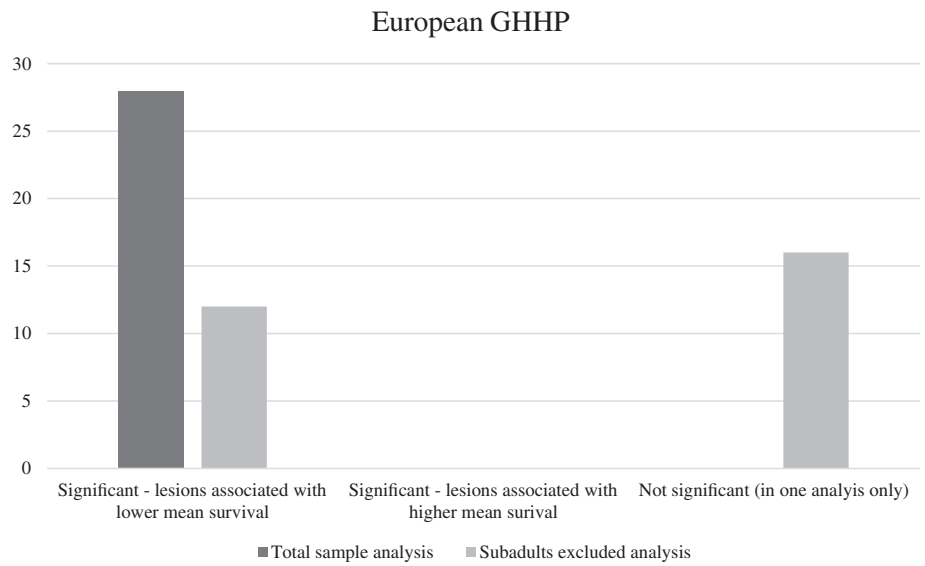


FIGURE 2 American Global History of Health Project (GHHP) summary results graph

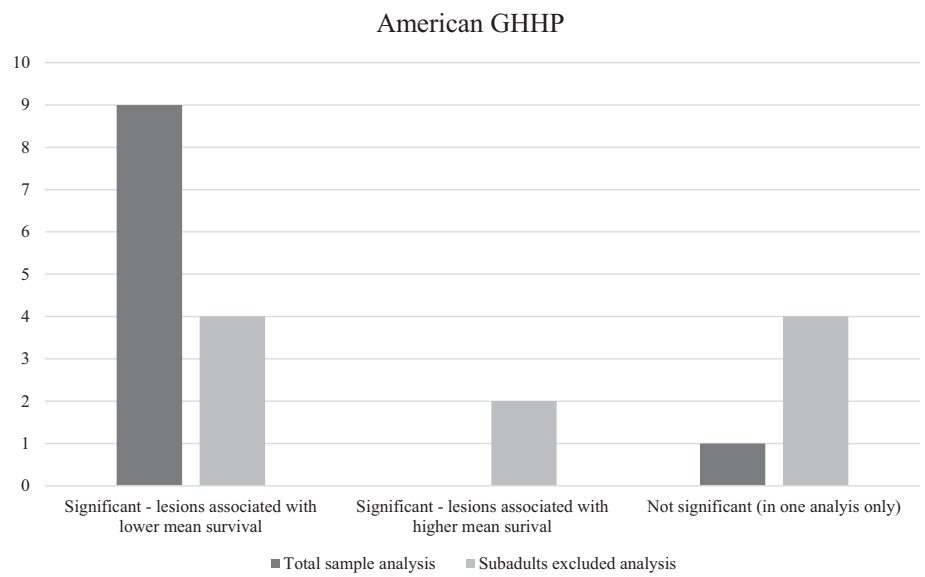
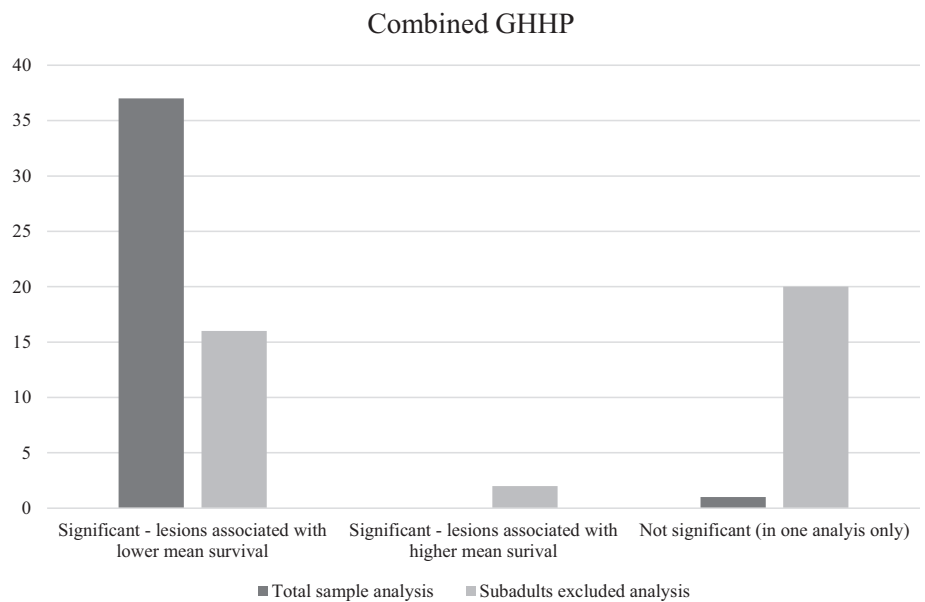


FIGURE 3 Combined Global History of Health Project (GHHP) summary results graph



variety of factors, including comorbidities and the type of anemia causing the cribra orbitalia.

4 | DISCUSSION

The results of this study suggest that morbidity and mortality associated with cribra orbitalia is higher in subadults. By extracting subadults from the sample, we can begin to understand whether cribra orbitalia is associated with frailty or resilience in the context of the adaptive plasticity model, noting that it may be associated with one or the other in different populations, depending on etiology and other environmental variables. Whether the higher prevalence in subadults is the result of the nature of lesion development, or whether it truly indicates higher mortality as a result of anemia stress, is discussed below. The implications for frailty and resilience in adults are also discussed, and a new model for evaluating cribra orbitalia (and potentially other skeletal lesions) is proposed.

4.1 | Cribra orbitalia: manifestation and etiology

For our purposes a critical question is whether certain genetic and acquired anemias can cause lytic lesions in the orbital roof of the kind often referred to as cribra orbitalia. To answer this question, we must look at the underlying pathophysiology of the relevant anemias, as well as potential mechanisms that may be associated with cribrotic lesions.

Ineffective erythropoiesis (IE) is characteristic of the hemolytic anemias (HAs) (e.g., Thalassemia and Sickle Cell anemia) (Harteveld & Higgs, 2010) and is known to occur in the megaloblastic anemias (e.g., folate and B12 deficiency) (Hoffbrand, 2018). Early research demonstrated a link between IE and iron deficiency anemia (IDA) (e.g., Robinson, 1969; Robinson & Koepfel, 1971). The relatively recent appreciation of the crucial role of Heme-regulated eIF2a kinase (HRI) in erythropoiesis (e.g., Han et al., 2001) has led to a proliferation of studies exploring the molecular mechanisms of IE in (artificially) HRI-deficient animal models (e.g., see Chen, 2014; Zhang et al., 2018). Finally, the differential diagnosis of high concentrations of RDW (red blood cell width distribution- a measure of the concentration of immature red blood cells) includes, among other factors, IE due to IDA, B12 and folate deficiency (Inuzuka & Abe, 2015). IE aside, a common outcome of the HAs, megaloblastic anemias, and IDA is erythroid hyperplasia (Orazi, O'Malley, & Arber, 2006).

It is known that marrow expansion due to erythroid hyperplasia can lead to trabecular and cortical bone atrophy, including perforation of the cortical bone (Jaffe, 1972). The observation that the orbital roof is relatively very thin, generally only 1 mm or less in thickness (Whitnall, 1932:29; Palmieri & Ghali, 2012:650) with a very thin diploic space when present, makes the potential effects of erythroid hyperplasia all the more significant in this location. There is a robust literature describing the potential skeletal effects of the HAs (e.g., Hoffbrand & Moss, 2016). Neural tube defects and cleft palate are risk factors for infants born to mothers deficient in B12 and/or

folate (megaloblastic anemias) (Hoffbrand, 2018), while a number of early papers described the skeletal effects of IDA. An important large-scale clinical study demonstrating cortical bone atrophy (thinning) in association with IDA was carried out by Agarwal, Dhar, Shah, and Bhardwaj (1970). They assessed 164 children for IDA of which 70% were under 3 years of age. A total of 147 of these individuals met their requirements for IDA, with roentgenologic results indicating 100 of these displayed osteological changes. Of these 100 cases, all showed evidence of mild to moderate osteoporosis, while 95 displayed cranial outer table atrophy (95/147, 64.62%), with only two (2/147, 1.36%) displaying diploic expansion, although they state that only one individual (1/147, 0.68%) had changes consistent with HA. Agarwal et al. (1970) suggest that these changes (cortical thinning and diploic widening) are due to marrow hyperplasia. The most plausible explanation for the common finding of cranial cortical bone thinning with IDA (without associated diploic expansion) is that it is a response to increasing pressure caused by hyperplastic bone marrow.

Children are highly susceptible to osteological changes associated with conditions leading to erythroid hyperplasia and subsequent marrow expansion. First, all bone marrow is hemopoietic in infants and is progressively replaced with fatty marrow with age, so that by 10–11 years, very little hemopoietic marrow remains in the cranial bones (Brickley, 2018; Hoffbrand & Moss, 2016). This means any skeletal effects of erythroid hyperplasia are very unlikely to occur in the cranium of older children and adults. Secondly, significant differences in the histology of children's cranial bones relative to adults makes children's more susceptible to the effects of marrow expansion. For instance, children display a smaller mean mineralized area, greater vascularization, and smaller diploe than older teen and adult cranial bones (Gil et al., 2016). If it is accepted that children, and not adults, are at risk of developing osteological changes (e.g., cribra orbitalia) in response to erythroid hyperplasia, why are these changes still seen in some adults?

The presence of any skeletal lesion will, among other things, be a product of time since occurrence, severity, and remodeling activity history of the individual. There are four main forms of bone remodeling encompassing targeted and non-targeted forms (Eriksen, 2010; Robling, Castillo, & Turner, 2006): biochemical (calcium and phosphate homeostasis), Haversian (age-related secondary tissue formation), biomechanical (maintenance of mechanical strength), and pathological (response to injury/infection). Bone remodeling is energetically expensive, with most of this expenditure focused on the first three forms of remodeling, while tissue reconstruction associated with disease or trauma will be an added energy expense in times of need.

The normal cortical bone turnover rate, for the purposes of maintaining biomechanical strength, is only 2 to 3% per year (Clarke, 2008: S134), with the cranium (occipital at least) having the slowest remodeling rate in the human skeleton (Fahy, Deter, Pitfield, Miszkiewicz, & Mahoney, 2017). Moreover, Mendelson and Wong (2012:754) note that the orbital rims are more stable with respect to other facial bones in terms of age-related (remodeling) changes. The relatively low bone remodeling rates in the cranium,

coupled with the energy requirements of remodeling and the putative lack of a functional need to repair cortical porosity may explain the retention of cribra orbitalia, acquired by children, into adulthood.

4.2 | Anemic stress

If cribra orbitalia (a skeletal signature of anemia) can only form in childhood, by definition this is the only period during which this lesion can be related to active disease. Therefore, active anemic stress as indicated by the lesion can only be examined in this age group. Several epidemiological studies report that young children aged 1–3 years have the highest prevalence of anemia (e.g., Alvarez-Uria, Naik, Midde, Yalla, & Pakam, 2014; Arlappa, Balakrishna, Laxmaiah, & Brahman, 2010). The prevalence in adults will be highly dependent on the mortality in children associated with the condition/s that produce the lesions. Low morbidity in adults may be the result of high morbidity and mortality in children, while high morbidity in adults may indicate low mortality in children. This, in and of itself, is one of several possible causes for the differing results reported in this study (others are discussed in detail below). It is therefore essential to evaluate the potential impacts of anemic stress in subadults, not solely to understand its impact on children, but to better understand its distribution in adults too.

Brabin, Premji, and Verhoeff (2001) reported that a 10 g/L decrease in hemoglobin at six months of age was associated with a 1.72 times increase in mortality. Malarial anemia is reportedly associated with higher mortality than IDA (Brabin et al., 2001), however, a limiting factor in our understanding of this is that there are few studies in non-malarial regions (Scott, Chen-Edinboro, Caulfield, & Murray-Kolb, 2014). Childhood malnutrition increases susceptibility to infectious diseases including respiratory, gastrointestinal and systemic bacterial infections through compromised immune function, and thus indirectly increases mortality (Ibrahim, Zambruni, Melby, & Melby, 2017; Martins et al., 2011). Certainly, the risk of death once infection is acquired is substantially heightened (Ibrahim et al., 2017; Martins et al., 2011; Pelletier, Frongillo Jr, & Habicht, 1993; Rytter, Kolte, Briend, Friis, & Christensen, 2014), with infectious disease being the leading cause of death in malnourished children (Rytter et al., 2014), though Habicht (2008) argues the elevated mortality is directly caused by malnutrition. Compounding the issue, the relationship is bilateral, with malnourished subadults being at greater risk of infection, and repeated infections contributing to malnutrition (Ibrahim et al., 2017; Walson & Berkley, 2018). Regardless of the relationship direction or precise cause, it is clear that childhood malnourishment increases the risk of death during the active period of deficiency, either directly or indirectly. As an indicator of malnourishment, active cribra orbitalia may be associated with increased comorbidities, particularly infectious disease, and mortality. In subadults, differentiation of active and inactive lesions allows us to examine childhood frailty and the impacts on innate and acquired immunity.

4.3 | Responses to physiological constraint

Turning to adults, for whom we cannot presently evaluate active anemic stress due to a lack of skeletal indicators, we may instead investigate questions relating to physiological constraint or frailty in the context of childhood disease. Bioarchaeologically, adaptive plasticity operates within the framework of physiological and socio-cultural factors: resistance to stress and disease forms a substantial component of physiological resistance or susceptibility. Individuals with robust innate or acquired immunity possess a greater resilience to stress and disease, and/or may have increased capacity for surviving such assaults. Innate immunity comprises defense mechanisms including physical barriers such as skin, chemicals, and immune cells, all of which protect from or attack foreign cells in the body (Alberts et al., 2002). There is variation in the capacity for individuals to enact their innate response and much of this is genetically determined. Those with an over or underactive immune system may experience different costs and benefits, for example, an underactive system may result in higher susceptibility to infection, while an overactive system can cause the body to attack healthy tissues (Brower, 2004). Adaptive immunity is an antigen-specific response, whereby the immune system must process, recognize and create a response which is then memorized for future attacks (Alberts et al., 2002). Both types of immunity are influenced by genetics and environmental influences, however, it is only adaptive immunity that produces a retained response to a specific exposure (Alberts et al., 2002). It is well known that exposure to infectious diseases, and in more recent years vaccination, may result in acquired immunity and subsequently resilience to specific pathogens.

Exposure to bacteria, viruses, parasites and toxins may produce an adaptive response while nutritional deficiency may reduce the effectiveness of both innate and acquired immune responses (Chandra & Chandra, 1986; Maggini, Pierre, & Calder, 2018). Anemia, broadly, is a morbidity and mortality risk as anemic individuals suffer immunological incompetence to varying degrees: the function of both the innate and adaptive immune systems can be compromised, and individuals are at an increased risk of both developing or contracting disease and dying from it. Thus, individuals with robust pre-existing immunity (innate and/or adaptive systems that are resilient to compromise) at the time of or following exposure to anemia may have improved outcomes over those with a comparatively frail immune system.

Frailty is concerned with prior health assaults, existing conditions, and genetic factors that may leave an individual more susceptible to morbidity or mortality. Genetic factors will often be invisible in the bioarchaeological record, but prior health assaults and existing conditions may be indicated by skeletal lesions. In the case of nutritional and infectious anemias, there is no significant epidemiological evidence of long-term frailty resulting from the conditions in childhood. Phiri et al. (2008) found young children with severe anemia (defined as <5 g/L hemoglobin) were at an increased risk of death from all causes for several months only following discharge from hospital. Follow-

ups ceased at 18 months, but it appears that the risk largely plateaued between 8 and 18 months following discharge, with the highest risk between 0 and 6 months (Phiri et al., 2008). While immunological competence may be temporarily compromised by anemia, there is no evidence to suggest the impacts of this last far beyond the cessation of active disease. If children are less than 8 months past the age at which lesions can develop, they may still be susceptible to mortality as a direct or indirect result of the stress incurred. This should be differentiated from frailty, however, as it is not indicative of recovery from stress and subsequent morbidity or mortality.

Notwithstanding, there are recognized adult health compromises associated with other and combined childhood vitamin deficiencies. In a large scale, multi-national study, Victora et al. (2008) found undernutrition at 2 years of age was associated with reduced adult height, educational and economic outcomes, lung function, and increased risk of some cancers, mental illness, high glucose concentrations, high blood pressure and harmful lipid profiles. Childhood malnourishment appears to have morbidity consequences in adulthood, however, the effect on mortality is less clear. Elo and Preston (1992) reviewed epidemiological evidence for an increased risk of mortality in adulthood via various specific morbidities, based on a range of childhood conditions. Due to the multitude of confounding factors and complexities, only very general statements about risk of premature death in adults could be made, specifically that we may expect childhood health conditions to impact adult mortality (Elo & Preston, 1992).

Examining frailty in subadults, male infants are more susceptible to both nutritional deficiencies and mortality resulting from such deficiencies. The impacts of this must be considered in the bioarchaeological context, as observed by Roberts and Steckel (2018). Subadults, for whom sex is rarely estimated or reported, may have a sex-bias in both morbidity and mortality associated with anemia and cribra orbitalia. Balsara, Faerber, Spinner, and Feudtner (2013) examined mortality data for all deaths in individuals aged under 20 years from the United States (years 1999–2008) and found males experienced higher mortality at all ages from birth, with a relative risk ratio of 1.44 when compared to females. Excluding injuries, they found a range of medical conditions were responsible for increased deaths, indicative of greater robustness in females or greater susceptibility in males. The bias extends to gestational age, where male infants experienced higher mortality across nearly all weeks. Male subadults were at higher risk of morbidity and mortality associated with infectious and parasitic (RR 1.14), digestive (RR 1.29), and nutritional and metabolic (RR 1.17) diseases (Balsara et al., 2013). Wieringa et al. (2007) specifically investigated sex differences in anemia, analyzing pooled data from Southeast Asia. They found at five months of age, male infants had lower hemoglobin concentrations than females, with the situation worsening by 11 months of age. Male infants were at 1.6 times risk of having anemia and 3.3 times risk of having IDA, though mortality was not evaluated (Wieringa et al., 2007). This suggests that male subadults, particularly infants, are more frail, especially with regards to the impacts of anemia and may be at greater risk of morbidity and mortality as a result. Notably, childhood sex-bias in anemia-

related morbidity and mortality may impact the distribution of lesions in the adult population and the way they are interpreted. The susceptibility of male infants to malnourishment and death may leave a more robust cohort entering late childhood/adulthood. In contrast, females are more likely to survive malnourishment, and this may explain the often-observed higher prevalence of adult females with cribra orbitalia. Notwithstanding, strong sociocultural influences may counteract this, with Alemayehu, Meskele, Alemayehu, and Yakob (2019) finding female infants at greater risk of anemia in rural Southern Ethiopia, likely due to gender bias in feeding and care.

A further consideration is the more general implications of childhood stress for adulthood health. Initially the DOHaD hypothesis posulated that fetal stress may be a predictor of health outcomes later in life (Barker, Eriksson, Forsén, & Osmond, 2002), however, the period during which predictive stress may be incurred has been expanded to include early infancy (Gluckman & Hanson, 2006; Hoffman et al., 2017; Mandy & Nyirenda, 2018). Health, stress and disease in fetuses and infants, which are proving pivotal to adult health, may be impacted by both social and gender inequality and extends the potential negative effects of disadvantage early in life across the entire lifespan. Increasingly, bioarchaeological studies of children are attempting to include the DOHaD model in interpretations of health (Gowland, 2015; Mays, Gowland, Halcrow, & Murphy, 2017; Roberts & Steckel, 2018) and indeed, from a theoretical perspective, the DOHaD hypothesis contributes to our concept of frailty as posited under the Osteological Paradox (Wood et al., 1992). However, cribra orbitalia is rarely observed in infants that fall within the Barker hypothesis (Barker et al., 2002) age group and thus its contribution to the traditional model is limited. Cribra orbitalia reportedly appears from six months of age onwards (Mittler & Van Gerven, 1994) and as such has greater potential to contribute to the extended DOHaD model (the commonly referenced “first 1000 days of life from conception,” see Hoffman et al., 2017, or the extended model utilized in this study), however, this contribution is still limited as it is not currently possible to determine the age at which cribra orbitalia lesions were acquired. Linear enamel hypoplasia provides more promise in this area, having the capacity to develop in utero (Armélagos, Goodman, Harper, & Blakey, 2009). Explorations of LEH within the context of the DOHaD model have been carried out (e.g., Lorentz et al., 2019; Temple, 2014) with recent work by Cares Henriquez and Oxenham (2020) on enhancing the accuracy with which age-of-onset, duration and periods of stress and recovery can be mapped providing further opportunities in this regard.

As Wood et al. (1992) noted, we only have the deceased individuals to evaluate. But we may observe that under this model the frail and disease-exposed typically die at younger ages and the robust survive into older age. Frailty and exposure therefore may be expected to result in premature death with or without lesions, whilst resilience and exposure may be expected to result in survival with lesions. Those without lesions who survive to later ages will represent a mix of the frail and unexposed, the resilient and unexposed, and potentially the highly resilient and exposed (resilient to the extent that lesions do not form). As such, the differences in resilience between the lesioned and

un-lesioned cohorts may be subtle in some cases and not necessarily visible in the age-at-death distribution. Nonetheless, combining the presence and absence of lesions with mortality data may be able to tell us about frail and resilient cohorts, though is limited in what it tells us of individual susceptibility or resistance.

The interaction of hemolytic anemias with the immune system may be expected to differ from nutritional and malarial anemias. Relatively common hemolytic anemias such as thalassemia and sickle cell offer immunological benefits and compromises. Alpha-thalassemia and the sickle cell anemias provide protection against malaria (Roberts, 2019), which may reduce the risk of mortality. There is evidence to suggest that individuals with sickle cell anemia may have an improved adaptive immune response to malaria (Roberts, 2019). Individuals with alpha-thalassemia may be more susceptible to nonlethal and less severe malarial infections which protect against more severe infections (Roberts, 2019), and there does not appear to be any greater risk of non-malarial disease associated with this condition (PLoS Med, 2006). In contrast, beta-thalassemia provides little to no protection against malarial infection, significantly compromises the immune system and is associated with increased morbidity and mortality (Farmakis, Giakoumis, Aessopos, & Polymeropoulos, 2003; O'Donnell et al., 2009). As such, consideration of the likely category of anemia and contextualization based on geography, epidemiology and archaeology is essential to our interpretation of cribra orbitalia and its relationship with morbidity and mortality.

4.4 | Towards an improved understanding of cribra orbitalia: Applying a considered paleoepidemiological model to skeletal lesions

On the basis of the above discussion, children should be analyzed separately from adults for conditions such as cribra orbitalia which develop their skeletal signatures in childhood only. In such cases, the nature and implications of the lesions are significantly different between the two broad groups. In subadults, we may seek to examine active anemic stress both in terms of morbidity and mortality, and underlying childhood frailty by evaluating active compared to inactive lesions. For the latter, it is particularly pertinent to consider the epidemiological literature relating to male frailty in infancy (see above). In adults we are limited to investigations of frailty and resilience, as active anemic stress is not observable. If those who are resilient are more likely to survive the childhood health assaults that cause cribra orbitalia and do not incur significant immunological compromise, then we would expect to see improved survivorship in adult individuals with lesions over those without. In contrast, frail individuals may be expected to suffer increased morbidity and mortality during and following the period of active anemia. While both subadults and adults contribute important information regarding stress and adaptive plasticity (with differential frailty though to resilience being outcomes), it is proposed that they should be statistically analyzed as separate groups. The nature of their disease and condition is substantially

different, but the results should be contrasted and evaluated in parallel to gain the greatest insights. By taking this approach, with an improved, empirically informed basis for analyzing cribra orbitalia, we may overcome the issues of the Osteological Paradox as they relate to resilience and frailty.

Notably, without consideration of comorbidity, a potentially poor approximation of frailty and resilience is obtained. A key example of this is the children from the Man Bac site in Vietnam (Oxenham, Matsumura, & Dung, 2011), where perinates with scorbutic lesions fall into the “cribra orbitalia absent” category, whilst clearly experiencing a significant health assault. This in effect reduces the mortality associated with cribra orbitalia and thus the subadults with the lesions appear more resilient than those without. Comorbidities or evidence of disease in individuals without the lesions of interest (in this case cribra orbitalia) undoubtedly complicate analyses of mortality. As discussed earlier, a common sense, considered and holistic approach is essential to our understanding of palaeoepidemiology. In this context it needs to be stressed that the approach proposed in this paper is suggested for the evaluation of single lesion types, independently. Whilst Cox regression can accommodate multiple covariates, they must be of the same nature (i.e., either develop in subadults only or develop at all ages). Risk ratios, when appropriately targeted, may provide an alternative means of evaluating comorbidities with different age distributions.

The proposed interpretive model for cribra orbitalia may be transferable to other conditions that develop only in childhood, such as linear enamel hypoplasia (LEH). Though it is inherently more difficult to develop a sensible and informative measure that encapsulates frequency, severity, age of occurrence and distribution, the interpretive framework within which such a theoretical measure could be evaluated can arguably be derived from the cribra orbitalia model proposed here. That is, that LEH may be an indicator of active stress in children only and in all other cases indicates frailty or resilience in association with mortality data. However, this model is not suitable for all skeletal lesions. Those that can develop at any age will require a different interpretive framework, but by taking a similar approach to incorporating clinical and epidemiological literature, undoubtedly improved interpretations can be made and, in many cases, the concerns of the Osteological Paradox can be addressed. A decision tree for informing analyses and interpretations of lesions as they relate to stress, frailty and resilience is provided (Figure 4).

5 | CONCLUSIONS

The nature of cribra orbitalia formation, being that it only develops in children, should mean its association with low life expectancy when the population is analyzed as a whole is hardly surprising. The condition manifests in children and is an indicator of some kind of health compromise, thus in many cases it appears more frequently in deceased children than in deceased adults. But examining cribra orbitalia in children and adults has two separate goals: in children, to determine the prevalence and risk of death associated with

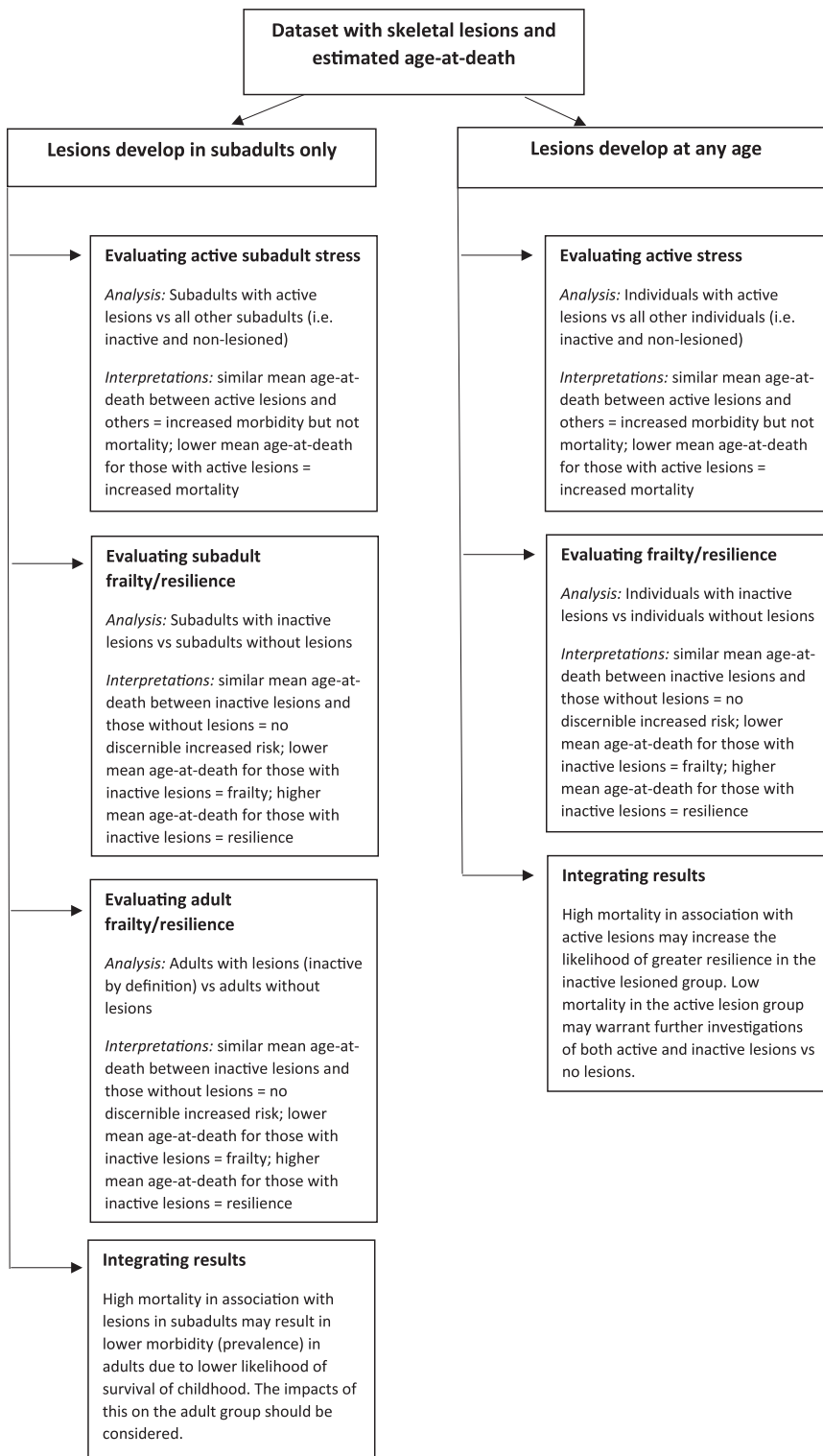


FIGURE 4 Decision tree for analysis and interpretation of lesions

active lesions and thus active disease; and in adults, to determine whether childhood health assaults that cause cribra orbitalia are associated with frailty or resilience in the context of adaptive plasticity.

A new approach to the evaluation of skeletal lesions has been proposed and applied to cribra orbitalia. Specifically, this approach

involves defining the etiology and expected morbidity and mortality trajectories of a disease and using this to inform the most appropriate approach to analysis. Analyzing data from the GHHP, it has been demonstrated that in many cases (57%) different results are produced when mortality associated with cribra orbitalia is examined in the sample as a whole, compared to the sample with subadults

removed. Contextualization is essential: geographic and bioarchaeological information may inform the likelihood of a particular type of anemia (e.g., malarial or hemolytic) and subsequently clinical and epidemiological literature should be used to interpret cribra orbitalia results for subadults, adults and the population as a whole. In doing so, we may overcome many of the concerns of the Osteological Paradox, and gain a more accurate, insightful understanding of palaeoepidemiology.

AUTHOR CONTRIBUTIONS

Clare McFadden: Conceptualization; data curation; formal analysis; investigation; methodology; validation; visualization; writing-original draft; writing-review and editing. **Marc Oxenham:** Conceptualization; data curation; formal analysis; investigation; methodology; validation; visualization; writing-original draft; writing-review and editing.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the Global History of Health Project (GHHP) at <https://economics.osu.edu/global-history-health-project>. These data were derived from the following resources available in the public domain: the European and American modules of the GHHP (Steckel and Rose, 2002; Steckel et al., Larsen, Roberts and Baten, 2018).

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SUPPORTING INFORMATION

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

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