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Cribra orbitalia in the ancient Nile Valley and its connection to malaria

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ABSTRACT

Cribra orbitalia is a common skeletal lesion found on ancient human remains excavated from the Nile Valley. Recent etiological research implicates hemolytic anemia as a main factor leading to the formation of cribra orbitalia. Further, an association between the hemolytic anemia caused by malaria and cribra orbitalia has been demonstrated. The presence of malaria in the ancient Nile Valley has been verified directly through genetic and immunologic studies of Egyptian mummies, but its prevalence and spread remain unknown. As some models have pointed to the Nile Valley as the pathway of malarial dispersion during the Egyptian Dynastic period, variability in cribra orbitalia rates should provide a way to track the disease spread. This study surveyed cribra orbitalia frequencies at 29 ancient Nile Valley sites, representing 4760 individuals ranging from prehistoric to Christian periods and situated between the 3rd Cataract and Nile Delta. Results showed high cribra orbitalia rates, with an overall mean of 42.8% of the total population affected. Over time and space, the data showed no significant correlation, suggesting high levels of anemia affected individuals in the Nile Valley equally from late pre-dynastic to Christian periods. These findings suggest widespread endemic malaria in the Nile Valley before Dynastic Egypt.

1. Introduction

Cribra orbitalia is one of the most common skeletal lesions noted in ancient human skeletal remains excavated from the Nile Valley (Hillson, 1980). Researchers have long explained this porous lesion of the eye orbits, along with the similar porous cranial vault lesions (porotic hyperostosis), as an expansion of the marrow space in the cranial vault caused by iron-deficiency anemia (Carlson et al., 1974; El-Najjar et al., 1976, 1975; Lallo et al., 1977; Mensforth et al., 1978; among others). This iron-deficiency anemia hypothesis has recently been called into question by a number of researchers, including Walker and coworkers (2009), who maintain the depression of red blood cell production in iron-deficiency anemia excludes the possibility of its participation in the stimulation of increased marrow space involved in porotic hyperostosis and cribra orbitalia formation.

While Walker and coworkers' (2009) etiological reappraisal is still being debated (Oxenham and Cavill, 2010; Rothschild, 2012; McIlvaine, 2013), other researchers have shown an association between cribra orbitalia and malarial infection (Rabino Massa et al., 2000; Nerlich et al., 2008; Gowland and Western, 2012). Malaria has been identified in the mummified tissue of ancient Egyptians of various time periods, dating to as early as 3200 BCE using ancient DNA (aDNA) sequencing and antigen evidence (Miller et al., 1994; Bianucci et al., 2008; Nerlich et al., 2008; Hawass et al., 2010). This direct genetic and immunological evidence verifies the presence of malaria in antiquity, but leaves the prevalence and spread of the disease unknown.

Although there are many factors that could have potentially contributed to the overall anemia seen in the human skeletal remains of ancient Egypt, malarial infection has been shown to have a major synergistic effect with other factors to increase overall anemia levels; thus, would have arguably raised the overall frequencies of cribra orbitalia (Nájera and Hempel, 1996; Gilles, 1997; Lusingu et al., 2004; Shanks et al., 2008). The present study surveys the temporospatial variability in rates of cribra orbitalia reported at archaeological sites along the Nile Valley in order to estimate ancient prevalence and distribution of malaria in this region. Tracking changes in cribra orbitalia in the Nile Valley provides not only a more holistic picture of ancient Egyptian anemia, but also a potential way to test theoretical models of malaria's spread out of Africa.

1.1. Porotic hyperostosis, cribra orbitalia, and anemia

Genetic conditions conferring resistance from malaria (e.g. thalassemia and sickle cell disorder) have been argued to cause skeletal lesions such as porotic hyperostosis and cribra orbitalia in the ancient Mediterranean and Near East (Angel, 1964, 1966, 1967, 1972; Zaino, 1964). However, there is a discrepancy between the low rates of these genetic disorders in modern endemic populations

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and the high rates of these skeletal lesions within ancient populations (Hengen, 1971). Consequently, paleopathologists turned to iron-deficiency anemia, a main contributor to anemia in modern populations, as the main causative agent implicated for these lesions (Hengen, 1971; Carlson et al., 1974; El-Najjar et al., 1976; Lallo et al., 1977; Mensforth et al., 1978; Stuart-Macadam, 1987). This hypothesis has been linked with agriculture through studies showing higher rates of porotic hyperostosis and cribra orbitalia in maize agriculturalists as compared with populations whose diets included meat (El-Najjar et al., 1976).

The porous lesions of the vault (porotic hyperostosis) and those of the orbits (cribra orbitalia) tend to show a connection, but also variability, in etiology (Stuart-Macadam, 1989; Walker et al., 2009). Some consider cribra orbitalia as an early indicator of anemia, and porotic hyperostosis as an indicator of a more chronic, long term anemic state (Hrdlička, 1914; Caffey, 1937). Only children tend to display active lesions, leading to the widely held explanation that these lesions form during childhood and are only maintained due to lack of bone turnover in adults (Stuart-Macadam, 1985; Mittler and Van Gerven, 1994).

However, many anthropologists have pointed out flaws in the iron-deficiency anemia hypothesis. Many discredit the attribution of dietary lack of iron as the main causative factor of the cranial lesions, and have instead suggested a multi-factorial etiology including diet and other factors such as parasitic and diarrheal disease (Hengen, 1971; Lallo et al., 1977; Mensforth et al., 1978; Walker, 1986; Holland and O'Brien, 1997; Wapler et al., 2004). However, the role of parasites in the etiology of cribra orbitalia has also been disputed (DeGusta, 2009). Gleń-Haduch and coworkers (1997) found no significant correlations between the levels of iron in teeth and presence of cribra orbitalia, suggesting other etiological factors are more important than lack of iron in the development of this lesion. Further, McClure and coworkers (2011) found high rates of cribra orbitalia with concurrent high isotopic levels of dietary animal protein in a population in Spain, precluding the possibility of iron-deficiency.

The biggest criticism of the iron-deficiency anemia hypothesis came in an article by Walker and coworkers (2009). They reasoned that iron-deficiency anemia could not in fact induce the bone marrow hypertrophy responsible for producing these lesions because this type of anemia depresses red blood cell production. Instead, they pointed to megaloblastic and hemolytic anemia as the main factors triggering the formation of these skeletal lesions. The former type of anemia arises in individuals with a nutritional deficiency in B_{12}, and the latter arises in individuals with genetic disorders conferring protection from malaria, as well as in individuals with a malarial infection (Walker et al., 2009).

Walker's article is still a matter of debate currently, with some researchers suggesting that iron deficiency could still contribute to marrow space expansion because it causes ineffective erythropoiesis rather than a complete dyserythropoiesis (Oxenham and Cavill, 2010). However, others refute this ineffective erythropoiesis claim, and instead insist that iron deficiency anemia is a side effect, not the cause, of porotic hyperostosis (Rothschild, 2012). Further, McIlvaine (2013) suggests that if the iron-deficiency anemia hypothesis is refuted, the B_{12} deficiency explanation should also be refuted because the mechanisms behind both types of anemia are the same. At this point, the exact etiology of porotic hyperostosis and cribra orbitalia remains uncertain, but appears to a combination of many factors (McIlvaine, 2013).

1.2. Differential diagnosis of anemia in the Nile Valley

The high frequencies of cribra orbitalia in the Nile Valley have been attributed to many causes, including schistosomiasis, intestinal worms, dietary deficiencies, brucellosis, and malaria. Schistosomiasis (a blood fluke infection) in ancient Egypt has been evidenced directly from mummified tissues and indirectly from ancient texts (Brier, 2004). However, antigenic evidence of schistosoma infection was not shown to associate with skeletal lesions of anemia in non-adults at the Nubian site of Semna South (Alvrus, 2006: 167), indicating other etiological factors are more important than schistosomiasis in the formation of these lesions in the Nile Valley.

Hookworms, common in modern tropical areas, are a notorious cause of iron-deficiency anemia, and have been implicated in causing higher rates of cribra orbitalia in equatorial areas (Hengen, 1971). If Walker and coworkers' (2009) position that iron-deficiency anemia is unable to cause porotic hyperostosis and cribra orbitalia is correct, then this type of anemia would be unlikely to generate these lesions. Vitamin B_{12} deficiency caused by hookworm infestation could be a factor, as the malabsorption of nutrients due to chronic diarrhea is attributed to megaloblastic anemia, which has been implicated as a cause of marrow hypertrophy (Walker et al., 2009; but see McIlvaine, 2013 for critique). Nevertheless, Vitamin B_{12} deficiency-induced megaloblastic anemia is not a major contributor to total anemia worldwide, even in tropical, developing nations (Kassebaum et al., 2014). Therefore, neither hookworms nor other sources of Vitamin B_{12} deficiency were likely responsible for high skeletal anemia rates in the Nile Valley.

Brucellosis is a disease underestimated by paleopathologists in the past, consisting of a bacterial zoonotic infection passed from domestic cattle to humans usually through ingestion of raw milk (D'Anastasio et al., 2011). Brucellosis causes undulating fevers and hemolytic anemia similar to malaria, potentially inducing skeletal lesions of anemia like cribra orbitalia. However, brucellosis maintains a low prevalence in humans, even in high-risk occupational groups like dairy farmers (Lopes et al., 2010). Due to this low prevalence, and even lower chance of anemia severe enough to make a mark on the skeleton, it is not likely that high rates of skeletal anemia in the Nile Valley were caused by this disease.

Malaria is a disease caused by parasites of the genus *Plasmodium*, which is transmitted by the *Anopheles* mosquito vector. There are five species of the parasite known to infect humans: *Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae, Plasmodium ovale, and Plasmodium knowlesi*. Malaria is one of the causative agents implicated for the chronic anemia pattern in the ancient Nile Valley. In ancient Egyptian medical texts, the annual plague described in the Edwin Smith Surgical Papyrus has been attributed to seasonal epidemics of malaria during periods of annual Nile River flooding (Brier, 2004). This disease does not discriminate against age or class, although it does contribute to higher rates of anemia in women and children (World Health Organization, 2014). Malaria is known to cause hemolytic anemia, which is capable of producing marrow hyperplasia (Walker et al., 2009). In addition to the classic model of skeletal anemia by expansion of marrow space, recent clinical research has suggested that the hemolysis occurring during the schizogony phase of a malarial infection may contribute to porous skeletal lesion formation due to the release of acid phosphate, free heme, and the malarial pigment hemozoin into the bloodstream. This leads to an imbalance in bone remodeling by stimulating osteoclasts while simultaneously impairing osteoblasts (D'Souza et al., 2011; Moreau et al., 2012). Furthermore, severe malarial anemia may induce extramedullary erythropoiesis, which is known to cause cortical thinning and coarse trabeculation (Al-Aabassi and Murad, 2005). Malaria is also known to have a synergistic effect with other diseases, combining especially with respiratory and diarrheal diseases as the most important factor in all-cause mortality in historical and modern accounts of epidemics (Duffy, 1952; Boyd, 1999; Shanks et al., 2008). This synergistic tendency suggests malaria may have a strong impact on all-cause anemia in areas endemic for the disease by increasing the total anemia burden.

Caution must be taken when considering the rates of cribra orbitalia reported in the Nile Valley due to the possibility for misdiagnosis (Wapler et al., 2004). Eye infections seem to have been common in ancient Egypt, with descriptions and treatments for such ailments appearing in medical papyri (Andersen, 1997; Heagren, 2003; Scheidel, 2012). It is likely that some of the cribra orbitalia reported at sites in the Nile Valley was caused by such superficial lesions or inflammation rather than a systemic cause such as anemia. However, eye infections such a trachoma and glaucoma are common in other areas of the world as well; thus, are not likely to have had a major impact on the overall cribra orbitalia rates in the Nile Valley comparatively.

1.3. Models of malaria origin and spread

In his classic paper published in 1958, Livingstone was the first to consider malaria's evolution in social, environmental, and genetic contexts. He suggested that malaria caused by the *P. falciparum* species (referred to as falciparum malaria) existed in tropical West Africa, but did not reach epidemic status until the advent of slash-and-burn agriculture in the region (approximately 2000–4000 years ago), which created pools of water suitable for higher populations of *Anopheles* mosquitoes to breed. This connection between tropical forest deforestation and increased malaria risk has been widely demonstrated in modern populations (Yasuoka and Levins, 2007; Afrane et al., 2008; Hahn et al., 2014). According to Livingstone, it was during this period of agricultural innovation and larger population sizes, that falciparum malaria was able to get a foothold on human populations. In turn, humans with abnormal hemoglobin such as thalassemia and the sickle-cell trait had a greater chance of survival, leading to the increase in these genetic traits in human populations (Livingstone, 1958, 1971). This idea of balanced polymorphisms, the increased survival of heterozygous individuals for these deleterious genes due to their conference of malarial resistance, explained the presence of these genes in African, Asian, and Mediterranean populations today (Livingstone, 1958, 1971).

The origins of *P. falciparum* malaria are still the subject of debate today due to the pathogen's mosaic genome, which complicates its hypothesized evolutionary history (Zilversmit and Hartl, 2005). There is a general consensus that this malaria species originated in Africa, most likely in the tropical West African region (Sherman, 1998). Attempts at dating the genome of the falciparum species have resulted in many far-reaching estimations for the age of this parasite, projecting its evolution anywhere from as recently as 5000 years to as ancient as 3–4 million years (Hume et al., 2003; Datta and Chauhan, 2010). Some have suggested that both of these age estimations are correct, and represent two separate regional expansions of the genome, with the most recent corresponding to the advent of agriculture in West Africa (Zilversmit and Hartl, 2005).

As the most virulent of the malarial species, researchers have presumed that falciparum malaria evolved recently under the assumption that over time parasites will evolve a more symbiotic relationship with their hosts in order to propagate their offspring rather than killing off their hosts quickly (Livingstone, 1958; Capasso, 1998; Baum and Bar-Gal, 2003). However, this theoretical assumption has been modified recently to consider the evolutionary advantage of virulence in immobilizing hosts for more effective spread of vector-borne diseases (Ewald, 2003). Nevertheless, genetic polymorphisms that confer resistance or immunity to malaria appear to have arisen within the last 5000 years, giving support to theories of recent evolution of the more virulent falciparum malaria (Hedrick, 2012).

Since *Anopheles* mosquitoes generally need clean, fresh water in which to breed, they tend to be found in marshy environments today. It is hypothesized that the seasonal flooding of the Nile River and its utilization by ancient Egyptians through irrigation canals may have worsened an already prime niche for malaria to thrive (Scheidel, 2012). Evidence for the use of irrigation in the Nile Valley dates back to 3200 BCE, but it is likely that the practice arose in earlier predynastic times (Nicholson and Shaw, 2000). Considering this environmental advantage, coupled with the large cities of clustered potential hosts, researchers have generally hypothesized that malaria spread out of Africa and into Europe through the Nile Valley pathway (Bruce-Chwatt, 1965; Schlagenhauf, 2004). Some have theorized that the spread of malaria out of Africa occurred recently, as late as 2000 years ago (Bruce-Chwatt and de Zulueta, 1980; De Zulueta, 1987). Bruce-Chwatt and de Zulueta based their reasoning for this late malarial diaspora on the assumption that efficient mosquito vectors had not yet migrated into the Mediterranean areas between the last glacial period (c.a. 12,000 years ago) and the Roman era (Bruce-Chwatt and de Zulueta, 1980:11–13). However, this assumption is difficult to prove due to the scarcity of *Anopheles* mosquitoes in the fossil record (Capasso, 1998).

Table 1
Chronology of Ancient Egypt and Nubia (after Baines and Malek, 1983).

Date	Egyptian	Nubian
4400–2600 BCE	Late Pre-Dynastic/Early Dynastic	A-Group
2600–2134 BCE	Old Kingdom	–
2134–2040 BCE	1st Intermediate Period	C-Group
2040–1640 BCE	Middle Kingdom	(Egyptian occupation)
1640–1550 BCE	2nd Intermediate Period	(Egyptian occupation)
1550–1070 BCE	New Kingdom	(Egyptian occupation)
1070–332 BCE	3rd Intermediate/Late Period	–
332 BCE–1500 AD	Greco/Roman/Christian	Meroitic/X-Group/Christian

1.4. Paleopathology and malaria

Advances in aDNA extraction and immunological assays from skeletal and mummified tissues have revealed direct evidence for malaria's presence in the ancient Nile Valley through genetic markers of the *P. falciparum* malaria parasite in ancient mummified tissue (Miller et al., 1994; Bianucci et al., 2008; Nerlich et al., 2008; Hawass et al., 2010). However, these genetic and immunological studies are limited to providing evidence for presence, but not prevalence, of the disease in the past.

Malaria is often dismissed in differential diagnoses by paleopathologists, many of whom hold that the disease does not manifest itself upon the skeleton (Nunn and Tapp, 2000; Roberts, 2000). However, recent research has provided evidence to the contrary. Rabino Massa and coworkers (2000) provided a link between direct evidence for malaria and skeletal lesions of anemia. They tested ancient Egyptian mummies for malarial antigens, and of those testing positive for falciparum malaria, 92% had porotic hyperostosis and cribra orbitalia. This link was corroborated through a similar aDNA study by Nerlich and coworkers (2008). Similarly, Gowland and Western (2012) mapped and associated cribra orbitalia with the distribution of large populations of *Anopheles* mosquitoes, lower altitude and marshy environments, and higher incidence of historic "fever and ague" (an archaic term synonymous with malaria) across Great Britain. Their study found a correlation between vivax malarial infection and cribra orbitalia, which gives additional support to the hypothesis that malaria does indeed manifest itself in the skeleton.

The present study brings the literature on falciparum malaria's dispersion out of Africa into conversation with the literature on the skeletal manifestation of the disease. Due to malaria's tendency to co-infect with other anemia-causing health factors such as diarrheal diseases, it is argued here that malaria would have a strong

Table 2
Crude prevalence rates of cribra orbitalia by site and basic sex and age composition of the population.

Site	Time period	Region	Cribra orbitalia		Sex composition at site			Age composition at site		
			n[a]	%	*n*[b]	Females (%)	Males (%)	*n*[c]	Nonadults 0–17 years (%)	Adults 18+ (%)
Abusir (Mastaba of Ptahshepses)	Late Period	Lower Egypt	142	26.8	159	44.7	55.3	296	46.3	53.7
Abydos	Early Dynastic	N. Upper Egypt	106	49.1	–	–	–	–	–	–
Abydos	Old Kingdom	N. Upper Egypt	28	78.6	–	–	–	–	–	–
Abydos	Middle Kingdom	N. Upper Egypt	41	68.3	–	–	–	–	–	–
Abydos ('Tombs of the Courtiers')	Early Dynastic	N. Upper Egypt	30	40.0	–	–	–	–	–	–
Adaïma	Late Predynastic	S. Upper Egypt	272	26.5	–	–	–	272	100.0	0.0
Amarna (STC)	New Kingdom	Middle Egypt	103	42.7	–	–	–	–	–	–
Aswan	Old Kingdom	S. Upper Egypt	18	61.1	–	–	–	–	–	–
Aswan	Middle Kingdom	S. Upper Egypt	47	63.8	–	–	–	–	–	–
Dendara	1st Intermediate	N. Upper Egypt	76	53.9	–	–	–	–	–	–
Dishasha	Old Kingdom	Middle Egypt	21	42.9	–	–	–	–	–	–
El-Badari (Badarian graves)	Late Predynastic	N. Upper Egypt	30	63.3	–	–	–	–	–	–
Elephantine	1st Intermediate	S. Upper Egypt	32	75.0	41	68.3	31.7	60	26.7	73.3
el-Raqaqna	Old Kingdom	N. Upper Egypt	17	52.9	–	–	–	–	–	–
el-Tarif	Middle Kingdom	S. Upper Egypt	54	55.6	–	–	–	–	–	–
Gebelein	Old Kingdom	S. Upper Egypt	23	73.9	30	43.3	56.7	35	8.6	91.4
Gebelein	1st Intermediate	S. Upper Egypt	47	78.7	55	43.6	56.4	72	20.8	79.2
Gebelein	Late Period	S. Upper Egypt	17	52.9	–	–	–	–	–	–
Hierakonpolis (HK27C)	1st Intermediate, Middle Kingdom	S. Upper Egypt	21	28.6	52	65.4	34.6	74	29.7	70.3
Hierakonpolis (HK43)	Late Predynastic	S. Upper Egypt	145	13.1	262	59.5	40.5	415	20.9	79.1
Hierakonpolis (Prehistoric and 'Fort' cemeteries)	Late Predynastic	S. Upper Egypt	39	71.8	–	–	–	–	–	–
Kerma	2nd Intermediate	Upper Nubia	306	13.7	294	61.5	38.5	307	4.2	95.8
Kulubnarti (21-R-2)	Christian	Upper Nubia	164	39.0	–	–	–	–	–	–
Kulubnarti (21-S-46)	Christian	Upper Nubia	170	51.8	–	–	–	–	–	–
Memphis	New Kingdom	Lower Egypt	306	24.8	99	44.3	55.7	103	3.9	96.1
Missiminia	Meroitic – Christian	Upper Nubia	333	27.9	333	48.3	51.7	–	–	–
Naqada (Great, B, and T cemeteries)	Late Predynastic	N. Upper Egypt	97	40.2	126	35.7	64.3	132	0.0	100.0
Naqada B cemetery	Late Predynastic	N. Upper Egypt	20	60.0	–	–	–	–	–	–
Naqada T cemetery	Late Predynastic	N. Upper Egypt	23	43.5	–	–	–	–	–	–
Qaw el-Kebir	Old Kingdom	N. Upper Egypt	27	70.4	–	–	–	–	–	–
Qaw el-Kebir	1st Intermediate	N. Upper Egypt	69	63.8	–	–	–	–	–	–
Qubbet el Hawa	Old Kingdom	S. Upper Egypt	156	48.7	467	39.4	60.6	578	19.2	80.8
Qubbet el Hawa	1st Intermediate	S. Upper Egypt	32	34.4	54	27.8	72.2	66	18.2	81.8
Qubbet el Hawa	Middle Kingdom	S. Upper Egypt	18	50.0	30	46.7	53.3	42	28.6	71.4
Qubbet el Hawa	2nd Intermediate	S. Upper Egypt	60	63.3	60	45.0	55.0	87	31.0	69.0
Qubbet el Hawa	Late Period	S. Upper Egypt	146	36.3	302	45.4	54.6	364	17.0	83.0
Qurneh	New Kingdom	S. Upper Egypt	172	16.3	161	52.0	48.0	174	7.5	92.5
Shellal	New Kingdom	Lower Nubia	154	20.1	151	47.7	52.3	157	3.8	96.2
Sidmant	1st Intermediate	Middle Egypt	55	67.3	–	–	–	–	–	–
Sidmant	Middle Kingdom	Middle Egypt	15	53.3	–	–	–	–	–	–
SJE (C-Group)	Middle Kingdom	Lower Nubia	205	14.1	217	64.8	35.2	249	12.9	87.1
SJE (Pharaonic)	New Kingdom	Lower Nubia	73	23.3	78	55.1	44.9	92	15.2	84.8
Tarkhan	Late Predynastic–Early Dynastic	Middle Egypt	29	72.4	–	–	–	–	–	–
Tarkhan	Early Dynastic	Middle Egypt	26	34.6	–	–	–	–	–	–

Table 2 (*Continued*)

Site	Time period	Region	Cribra orbitalia		Sex composition at site			Age composition at site		
			n^a	%	n^b	Females (%)	Males (%)	n^c	Nonadults 0–17 years (%)	Adults 18+ (%)
Tell el-Dab'a	2nd Intermediate	Lower Egypt	41	26.8	120	40.8	59.2	257	48.1	51.9
Thebes-West	New Kingdom – Late Period	S. Upper Egypt	168	29.2	187	45.5	54.5	167	20.2	79.8
Thebes-West (Valley of the Queens)	Roman	S. Upper Egypt	212	18.4	288	48.0	52.0	1070	19.2	80.8
Tombos	New Kingdom	Upper Nubia	83	10.8	85	59.5	40.5	100	15.0	85.0
Wadi Halfa (24I3)	X-Group	Upper Nubia	45	26.7	30	50.0	50.0	54	29.6	70.4
Wadi Halfa (6B13)	Christian	Upper Nubia	28	14.3	–	–	–	37	32.4	67.6
Wadi Halfa (6B16)	Meroitic	Upper Nubia	62	11.3	48	58.3	41.7	129	17.1	82.9
Wadi Halfa (6G8)	Christian	Upper Nubia	29	13.8	–	–	–	33	39.4	60.6
Wadi Halfa (NAX)	X-Group	Upper Nubia	127	26.7	106	56.6	43.4	164	14.1	85.9

[a] Total individuals at the site with observable orbits.
[b] Total adult individuals at the site whose sex was determined.
[c] Total individuals at the site whose age was determined.

impact on cribra orbitalia formation in the Nile Valley. Using the variability in cribra orbitalia frequencies among ancient Egyptian and Nubian remains as a proxy for malarial infection, this study tests the theoretical Dynastic Egyptian time frame for the spread of malaria up the Nile Valley and out of Africa. If malaria did spread into Egypt during the Dynastic period, an increasing trend in cribra orbitalia frequency over time from South to North in the Nile Valley was predicted.

2. Materials and methods

Reports from 29 ancient Nile Valley sites were surveyed, representing 4760 individuals ranging from prehistoric to Christian periods (4400 BCE–1500 CE) and situated between upper Nubia and the Nile delta (see Table 1 and Fig. 1). Data collection was conservative, with several restrictions for unbiased comparison. If a report recorded fewer than 15 individuals containing observable orbits for scoring cribra orbitalia, then it was not included in the statistical analysis. If no number of observable individuals was mentioned in the report, the site was excluded. Similarly, sites reporting poor skeletal preservation were excluded.

Additional data on percentage of adult females (of the total number of adults assigned a sex) and nonadults under 17 years of age (out of total individuals assigned an age) in each sample population was collected when available. The specific demographic information for the individuals affected by cribra orbitalia or with observable orbits present was not obtainable from the reports

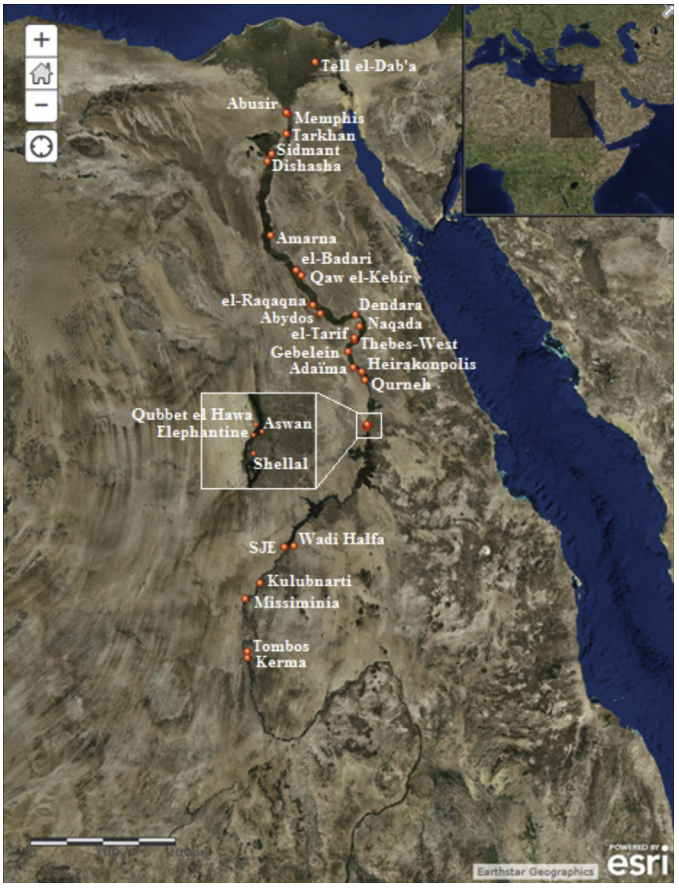

Fig. 1. Map of the location of the sites used for this study. Map created using ESRI ArcGIS 10.0. Satellite imagery © CNES/Airbus DS, Earthstar Graphics.

Source: Esri, DigitalGlobe, GeoEye, i-cubed, Earthstar Geographics, CNES/Airbus DS, USDA, USGS, AEX, Getmapping, Aerogrid, IGN, IGP, swisstopo, and the GIS User Community | Esri, HERE, DeLorme.

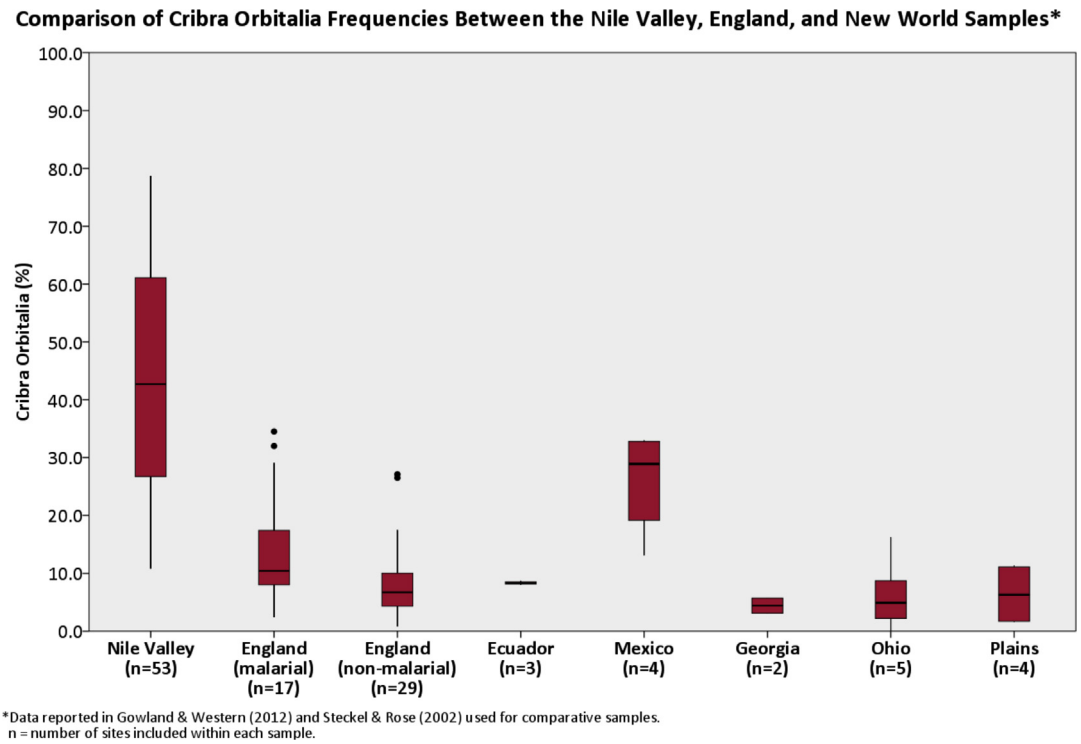

Fig. 2. Boxplot showing cribra orbitalia frequency distributions for each location, with the horizontal line representing the median, box representing 50% of the data, and vertical lines extending to 95% confidence interval limits. Dots represent outliers.

surveyed; thus, only the data on the basic demographic composition of each site was used in this study. The reason for collecting this demographical data was to ascertain any biases in the sample that would affect the total frequency of cribra orbitalia at the site. For example, since cribra orbitalia has been noted at higher rates in children, a skeletal sample containing mostly children may contain higher rates of cribra orbitalia (Stuart-Macadam, 1985). Similarly, since women and children are at higher risk for malarial

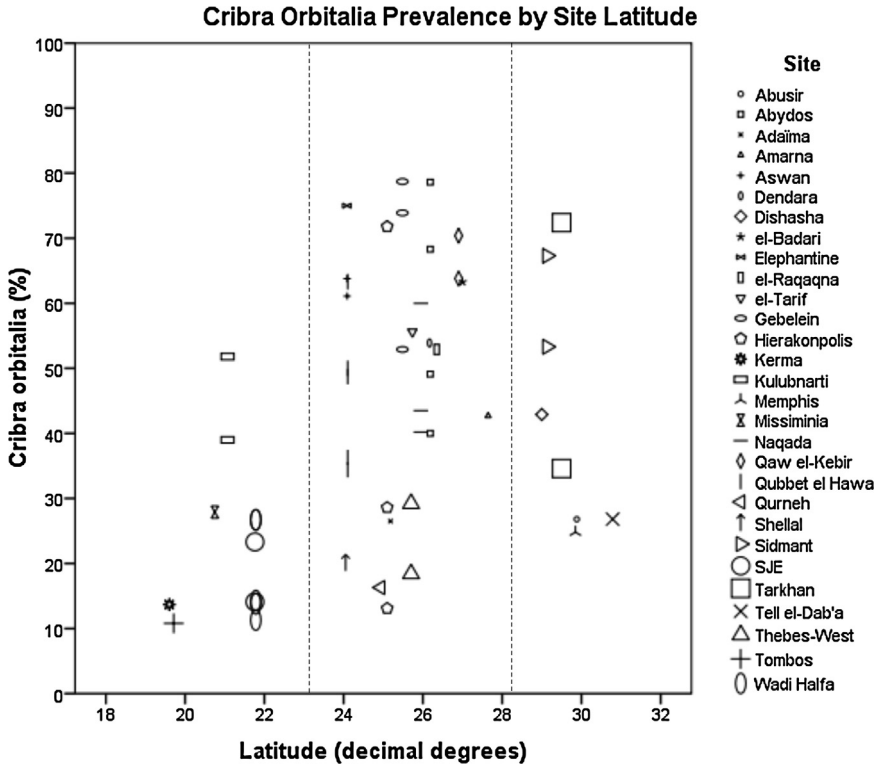

Fig. 3. Scatterplot showing no trend in cribra orbitalia rate over location in the Nile Valley. Dotted lines delineate the three geographical clusters (Nubia, left; upper/middle Egypt, center; lower Egypt, right).

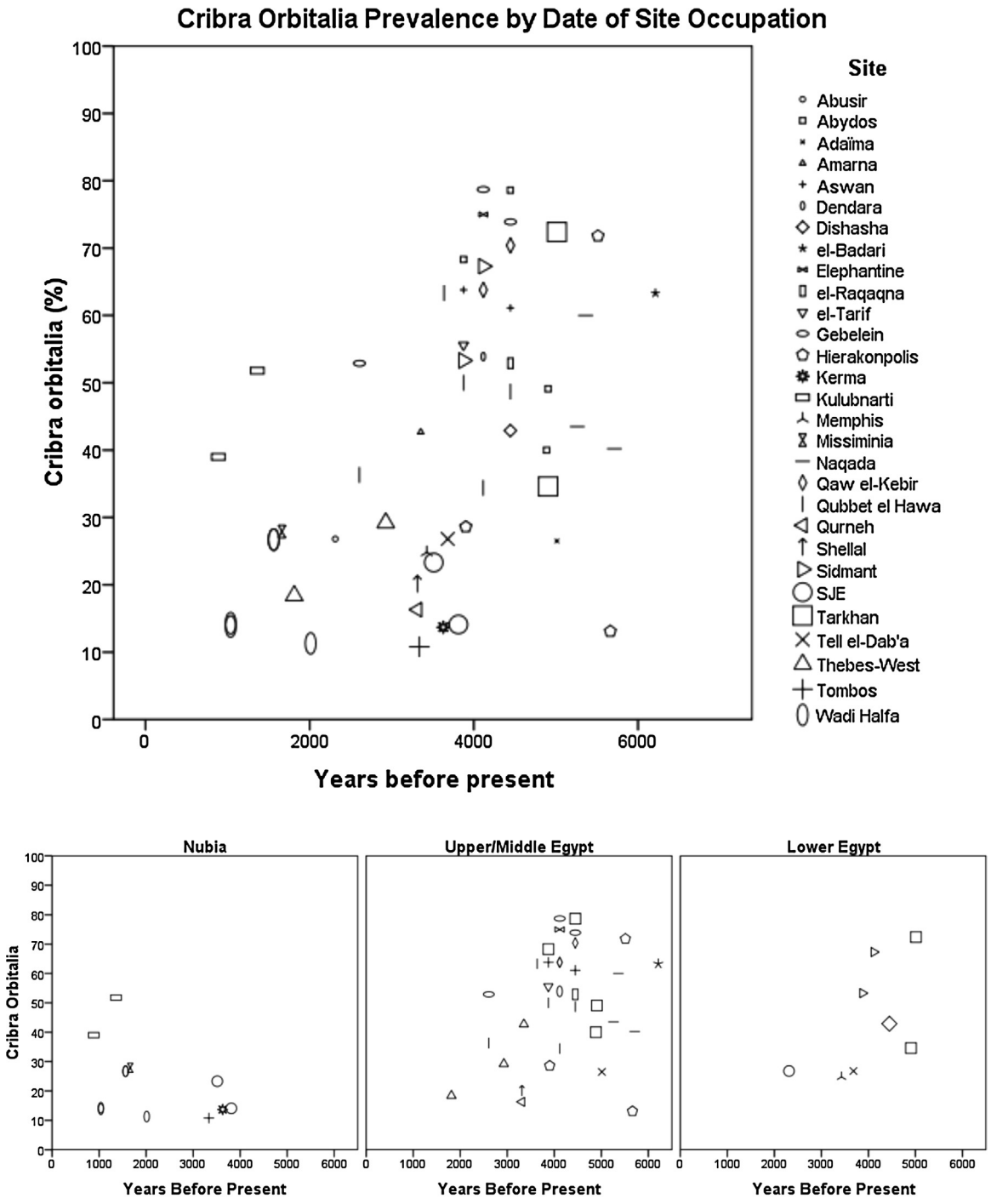

Fig. 4. Scatterplots showing no trend in cribra orbitalia rate over time in the Nile Valley. Total sample (top) and geographic clusters (bottom).

infections and bear a greater anemia burden than adult males in endemic areas, higher proportions of either of these groups at a site may influence the total cribra orbitalia rate of the sample population (Gilles et al., 1969; World Health Organization, 2007; Billig et al., 2012). Table 2 lists the crude prevalence rates of cribra orbitalia collected from the site reports and the basic demographic composition for each population.

Spatial comparisons between sites were analyzed by latitudinal coordinates of site location to visualize changes in anemia along the Nile River. Temporal comparison between sites was accomplished by taking the mean of the occupation dates for the site. Analysis of the data consisted of comparison of overall distribution of the data to other existing cribra orbitalia meta-analyses, comparison of means through Student's *t*-test, and determination of associations through Spearman's rank and Kendall's tau correlations. Statistical analyses were carried out using IBM SPSS 22.01. Statistical significance was set at $p \leq 0.05$.

Few meta-analyses have been published for comparison of cribra orbitalia rates across wide areas and time periods. The range of Nile Valley cribra orbitalia rates compiled in this study will be compared with other existing cribra orbitalia meta-analyses compiled from New World (Steckel and Rose, 2002) and English samples (Gowland and Western, 2012).

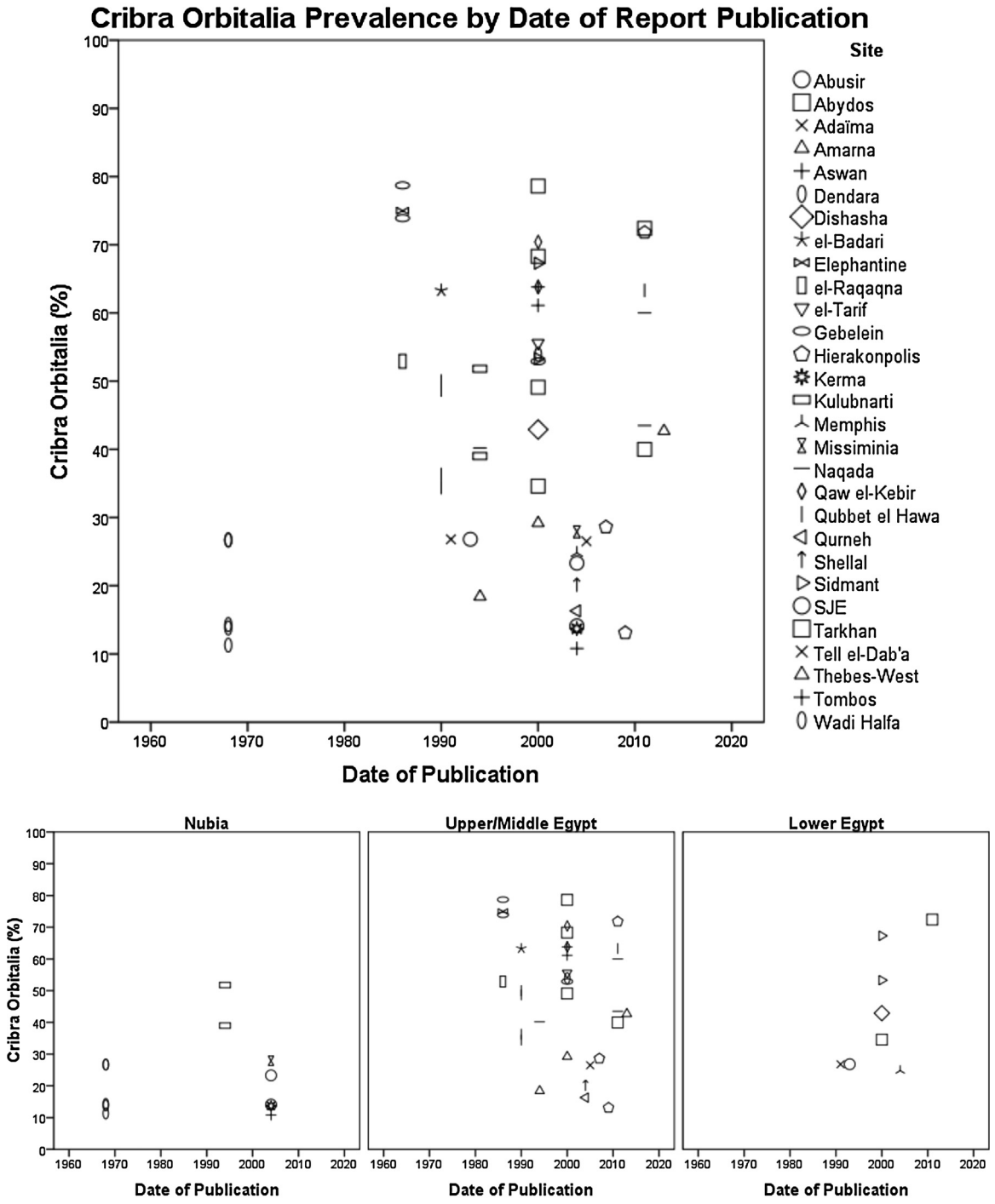

Fig. 5. Scatterplots showing no trend in cribra orbitalia rate over date of report publication. Total sample (top) and geographic clusters (bottom).

3. Results

Cribra orbitalia rates ranged between 10.8% and 78.7% in the surveyed sites, with an overall mean of 42.8%. Fig. 2 shows the greater overall rates of cribra orbitalia in the Nile Valley sample compared with other global cribra orbitalia meta-analyses. The comparisons with Steckel and Rose's (2002) meta-analyses, however, must be viewed with caution due to the small number of sites (between two and five) included by Steckel and Rose. Interestingly, the Nile Valley cribra orbitalia distribution only overlaps slightly results from the English sample that purportedly contained *P. vivax* malaria infections, with a significant difference in means of the two distributions ($t = 7.898$ (58), $p = 0.000$).

Scatterplots of the total cribra orbitalia frequency against latitude and date showed three geographical clusters: Nubian sites, Upper and Middle Egyptian sites, and Lower Egyptian sites (see Figs. 3 and 4). Thus, the data were analyzed separately within each of these groups and tested for correlations between cribra orbitalia and latitude, date of occupation, date of report publication, proportion of adults at the site classified as female, and proportion of

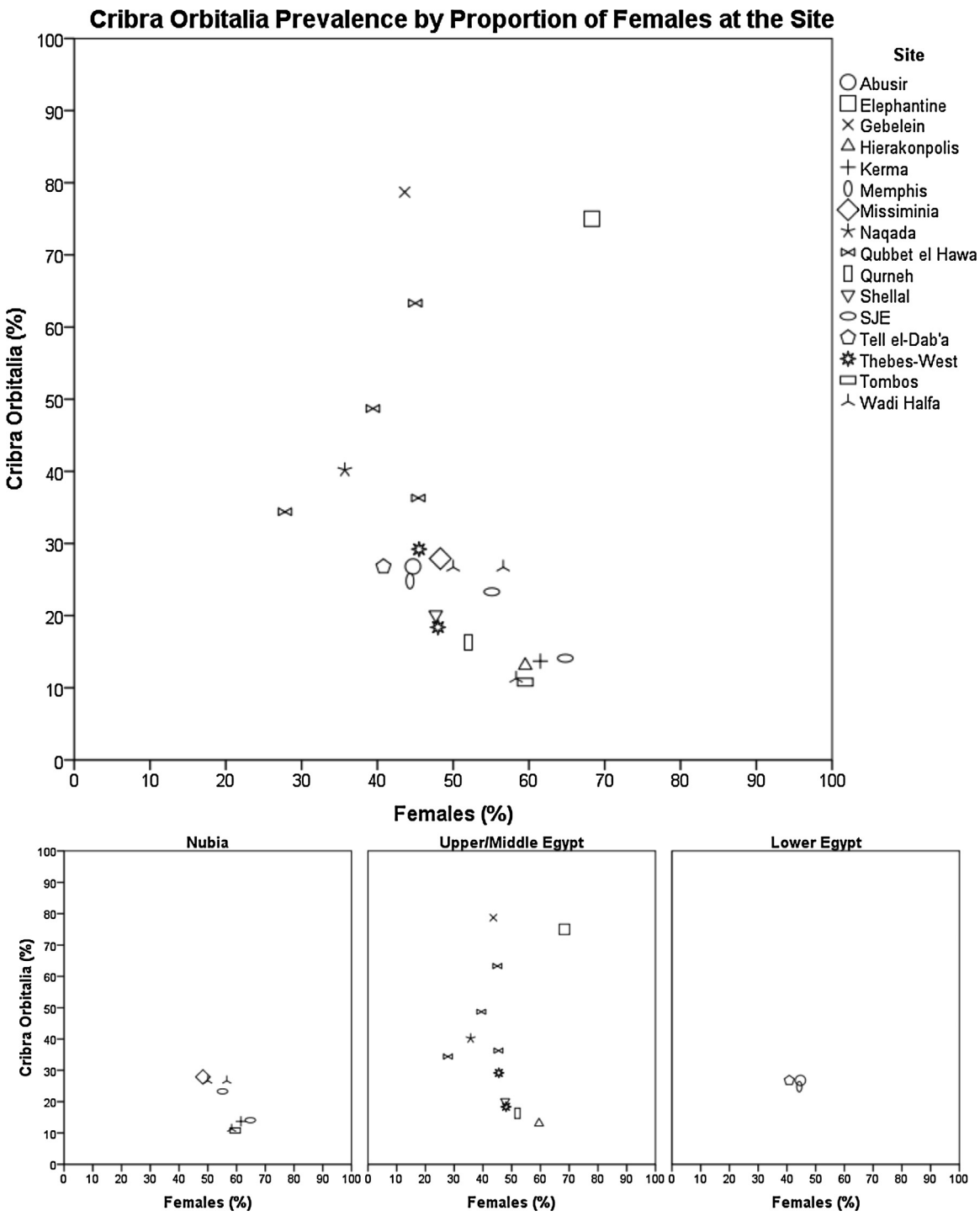

Fig. 6. Scatterplot showing no trend in cribra orbitalia rate over percentage of females at the site. Total sample (top) and geographic clusters (bottom).

individuals at the site classified as nonadults. There was no significant correlation for any of these variables (see graphs in Figs. 5–7; and Table 3 for statistical results).

Table 3
P-values showing no significant correlation between cribra orbitalia and other variables within three regions.

	Nubia	Upper/Middle Egypt	Lower Egypt
Latitude	0.886	0.327	0.164
Date of occupation	0.129	0.261	0.061
Date of publication	0.822	0.131	0.229
Females	0.061	0.075	–
Nonadults	0.543	0.582	0.221

4. Discussion

Although most theoretical models for falciparum malaria's spread out of Africa take place before or during Dynastic Egypt, the physical evidence goes against this model of disease spread. Genetic and immunological studies have provided direct evidence of malaria's presence in numerous Egyptian mummy studies dating

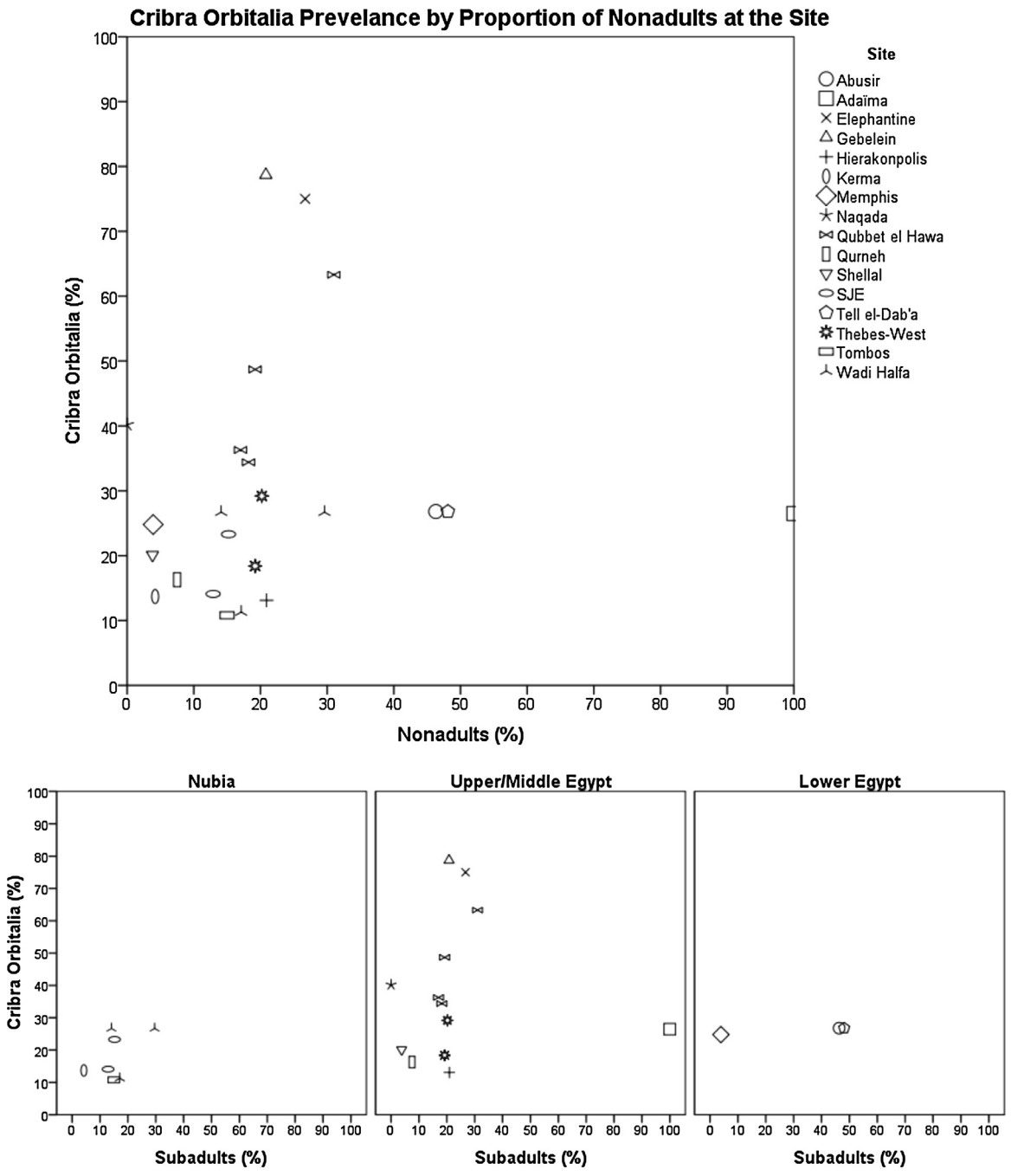

Fig. 7. Scatterplot showing no trend in cribra orbitalia rate over percentage of nonadults at the site. Total sample (top) and geographic clusters (bottom).

as far back as 3200 BCE (Miller et al., 1994; Bianucci et al., 2008; Nerlich et al., 2008; Hawass et al., 2010). This genetic evidence suggests high prevalence of malaria in the ancient Nile Valley, but does not provide information on prevalence rates.

Since cribra orbitalia has been linked to malaria infection in recent studies, an increasing frequency in these lesions in the Nile Valley was expected when compared by time and space in accordance with Bruce-Chwatt's (1965) theoretical model. Though cribra orbitalia is likely caused by multiple factors, malaria's synergistic role with other diseases and major impact on modern anemia rates in endemic areas indicate that the presence of this disease in the Nile Valley would have caused a general increase in overall cribra orbitalia rates (Nájera and Hempel, 1996; Gilles, 1997; Lusingu et al., 2004; Shanks et al., 2008). However, Nile Valley cribra orbitalia rates showed no trend throughout time and space, and they were generally high when compared with New World samples. There was no evidence to suggest malaria, or any other source of increased skeletal anemia, arrived suddenly in the Nile Valley during Late Predynastic through Christian periods. Moreover, there was no association of cribra orbitalia with location, estimated date, proportion of females versus males at the site, proportion of nonadults versus adults at the site, or date of report publication. The lack of any significant trend in cribra orbitalia over space or time highlights the importance of considering holistic trends rather than comparing only the skeletal assemblages of a few sites. The lack of association with publication dates suggests that researchers recognized the lesion during early excavations to the same extent as in present studies.

This study has three implications for interpreting the etiology of cribra orbitalia and health in the Nile Valley. First, the failure to correlate cribra orbitalia frequency with site-specific age proportions suggests that the main cause of the high cribra orbitalia rates is not age-specific. Cribra orbitalia is generally considered a lesion formed in childhood, due to the principal location of erythropoiesis in the cranium, thinner cranial bones, weaning stresses, and perhaps inadequate vitamin intake necessary for their growing bodies (Mittler and Van Gerven, 1994; Walker et al., 2009). The results of this study counter this assumption, as the amount of nonadults at the site did not affect cribra orbitalia rates. This lack of age-controlled prevalence suggests childhood factors such as diet, exposure to parasitic worms, or nutritional stress caused by weaning did not have a large effect on the formation of this lesion in the Nile Valley. Instead, the main contributing factor seems to be an infectious cause that affects all age groups indiscriminately.

Second, assuming that cribra orbitalia is indeed indicative of malarial infection (as suggested by Rabino Massa and coworkers (2000) and Gowland and Western (2012)), the ubiquity of high cribra orbitalia rates shown in this study suggest this disease had a general high prevalence in the Nile Valley long before Dynastic Egypt. This implication is supported by the aDNA evidence, and supports earlier theoretical timelines for malaria's spread out of Africa. From the differential diagnosis of the potential causes of anemia in the Nile Valley, it seems reasonable to assume that malaria would have had a great impact on the frequencies of cribra orbitalia in the region. Thus, if the high cribra orbitalia rates in the Nile Valley are tantamount to high malaria rates, malaria must have spread up the Nile Valley and out of Africa before the Badarian period (4400–4000 BCE), which is the earliest date used in this study. Alternatively, this higher anemia burden in the Nile Valley sites could simply reflect the multitude of factors combining to cause and aggregate anemia in this region.

Third, Gowland and Western (2012) showed an association of cribra orbitalia with *P. vivax* malaria infection in their meta-analysis of English sites, while the sites used in this study would have included individuals infected with the *P. falciparum* malaria species. The mean rates of the cribra orbitalia frequencies found in the English study and this Nile Valley study differed significantly, perhaps reflecting the higher levels of severe malarial anemia generally associated with *P. falciparum* infections (Billig et al., 2012; Botez and Doughty, 2014). This finding is important because it suggests that although *P. vivax* infections tend to involve a chronic, but less severe anemia than *P. falciparum* infections, the latter species is associated with higher rates of skeletal responses to infection.

One of the main limitations of this study involved the clustering of many dates and locations of sites, leading to a greater variability of cribra orbitalia frequencies in these clusters simply because of the greater number of sites. This limitation forced the statistical analysis to follow the clustering by separation into three groups by regional position. This study was also limited by the many sites that had to be excluded because they reported the presence of cribra orbitalia and porotic hyperostosis together, combined under the name porotic hyperostosis. Nevertheless, the great variation in cribra orbitalia rates of sites included in this study (i.e. some of the lowest and some of the highest rates found within very similar latitudes and time periods) is such that including more sites will not change the absence of a significant association between cribra orbitalia rates and date or latitude.

5. Conclusion

This study tested a method of identifying malaria in the Near East, and shed new light on the patterns of health in the ancient Nile Valley by providing a holistic view of anemia present throughout time and space. In compiling cribra orbitalia rates from sites along the Nile Valley from various time periods, no significant association was shown between cribra orbitalia rates and date or latitude. Furthermore, cribra orbitalia rates were not affected by the proportion of females or nonadults in the sample, or by the date of site report publication. These results support the notion of a major infectious causative factor for cribra orbitalia in the ancient Nile Valley, and add credence to previous studies associating cribra orbitalia with malaria. With Gowland and Western's (2012) English malarial sample, this study provided the first interspecific (*P. vivax* versus *P. falciparum*) malaria comparison through large-scale cribra orbitalia frequency comparisons across many sites.

The interpretations of this study rely on the assumption that the hemolytic anemia caused by malaria is responsible for high cribra orbitalia rates, but they do not account for additional skeletal lesions that may also be caused by malarial infection. To identify these potential additional skeletal lesions of malaria, future studies are planned involving a clinical comparison in a modern skeletal collection from an endemic malarial area, which will provide better diagnostic criteria for malaria.

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