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Research article

Cribriotic lesions in archaeological human skeletal remains. Prevalence, co-occurrence, and association in medieval and early modern Netherlands

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ABSTRACT

Objective: This paper studies the prevalence, co-occurrence, and association of cribra orbitalia, cribra humeri, and cribra femora to contribute to the complex debate on cribriotic lesions and their relationship with one another.
Materials: 179 adults and 53 non-adults from the medieval/early modern Netherlands (800–1600 CE) for whom all three lesions could be observed are included in this study.
Methods: Presence or absence of cribriotic lesions was studied macroscopically. Prevalence, co-occurrence, and association of lesions and their link to sex and age-at-death were assessed.
Results: A clear link between prevalence of the lesions and age-at-death is found. Co-occurrence and association of all three lesions is uncommon. There is a significant moderate correlation for cribra humeri-femora in non-adults.
Conclusions: Lesion prevalence is connected to age-at-death. However, while a similar age distribution and associations between pairs of lesions are noted, due to limited co-occurrence of the three lesions, the presence of a 'cribrous syndrome' cannot supported.
Significance: This is the first study investigating the prevalence, co-occurrence and association of cribra orbitalia, cribra humeri, and cribra femora in non-adults and adults contributing to discussions about the nature and the much-debated aetiology of these commonly encountered skeletal lesions.
Limitations: The number of non-adults in this study is limited, potentially obscuring meaningful patterns, as the cribrous lesions are significantly more common in younger individuals.
Suggestions for further research: More research into the prevalence of the post-cranial lesions and their co-occurrence as well as into bone growth and remodelling is warranted.

1. Introduction

Porotic, cribriotic, or cribrous lesions (used interchangeably here) are a common occurrence in archaeological skeletons and they have been encountered in human remains from all over the world and from different time periods (Brickley, 2018; Djurić et al., 2008; Walker et al., 2009). The cranial lesions known as cribra orbitalia (porosity of the orbital roof) and porotic hyperostosis (a term commonly used to indicate porosity on the cranial vault) are frequently studied and often used as indicators of non-specific stress such as chronic disease or malnutrition in past populations (e.g., Betsinger and DeWitte, 2017; Goodman and Armelagos, 1989; Gowland and Redfern, 2010; Lewis, 2018; O'Donnell, 2019; Scott and Hoppa, 2018; Walker et al., 2009). Generally, these cranial cribrous lesions are thought to be associated with childhood anaemia (Brickley, 2018; Lewis, 2018; Walker et al., 2009). Yet, while marrow hyperplasia associated with anaemia appears to be the favoured explanation for the lesions, it is important to consider that other conditions and pathological processes may result in porosity of bone as well (Brickley et al., 2020; Rothschild et al., 2020). In fact, Wapler and colleagues (2004) demonstrated that in more than half of the macroscopic cribra orbitalia cases in a Nubian population, there were no histological features suggestive of marrow expansion and thus anaemia (Wapler et al., 2004), indicating that other pathological or developmental processes were responsible for the observed orbital porosity. Moreover, even if anaemia can be considered as an explanation for the lesions in some cases, the underlying cause of this red blood cell disorder is also debated. Iron-deficiency, responsible for a microcytic anaemia, has been and still is considered as one of the main causes for the porotic lesions observed in archaeological skeletons (Godde and Hens, 2021; Hens et al., 2019; Oxenham and Cavill, 2010; Stuart-Macadam, 1992, 1985),

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but other scholars have argued that megaloblastic and/or haemolytic anaemias resulting from nutritional deficiencies or parasitic infections, including malaria, are more likely to be responsible for the lesions (Gowland and Redfern, 2010; Gowland and Western, 2012; Schats, 2015; Walker et al., 2009; Wapler et al., 2004). Cribra orbitalia in particular has been linked to past and present malaria infections due to its high prevalence in malaria endemic regions as compared to non-endemic areas (Gowland and Western, 2012; Schats, 2015; Smith-Guzmán, 2015a, 2015b). This already complex and debated aetiology is further complicated by the fact that many of these nutritional deficiencies and parasitic infections are often inter-related, making it very difficult to tease them apart (Brickley and Ives, 2008; Gowland and Redfern, 2010). In short, while these porous cranial lesions are amongst the ones that are encountered the most in skeletal collections, there are still many unresolved issues regarding their formation and aetiology (cf. Grauer, 2019).

While porous lesions also occur in the post-cranial skeleton, mainly on the humeral neck (cribra humeri), and femoral neck (cribra femora), far less research has been devoted to these porosities. In some skeletal studies, cribra femora is scored as a non-metric trait known as Allen's fossa and is therefore considered to be a normal variant of the femoral neck, even though this trait should present with a clear sclerotic margin (Finnegan, 1978; Radi et al., 2013). Cribra humeri is very rarely scored, although there are a few exceptions (Djurić et al., 2008, 2010; Erkelens, 2017; Garcia et al., 2002; Smith-Guzmán, 2015b). As for the cranial lesions, the aetiology of the post-cranial porosities is far from clear cut. Anaemia is considered to be a viable causative factor as well (Miquel-Feucht et al., 1999; Smith-Guzmán, 2015b); it is hypothesised that the marrow hypertrophy resulting in porosity of the orbits and cranial vault, can also be responsible for the porous, spiculated appearance of the proximal humerus and femur (Miquel-Feucht et al., 1999). Yet, this is solely based on the similar morphological appearance and not necessarily on the basis of the pathophysiology of the lesions (Mays, 2018). As discussed, there are several, pathological mechanisms that can result in a porous appearance of bone, and it is important to not conflate description of lesions with diagnosis (Grauer, 2019). Moreover, normal growth and development may also result in porosity of the lesion areas (Brickley et al., 2020).

Thus, even though cribrous bone lesions are a regular find in archaeological skeletons, it is clear that the formation and aetiology of both the cranial and the post-cranial lesions are not well understood. Furthermore, while a shared cause for the lesions on the basis of morphological similarity is suggested, the association between the different cranial and post-cranial cribrous lesions remains unclear. A better understanding of the relationship between the lesions can be a first step towards gaining more insights in this complex suite of porosities. In previous research, cribra orbitalia and porotic hyperostosis have been assumed to result from the same condition (Grauer, 2019; Stuart-Macadam, 1987a, 1987b), but more recent studies do not confirm this shared aetiology, nor does cribra orbitalia appear to be an early expression of the same condition (Cole and Waldron, 2019; Djurić et al., 2008; Rivera and Lahr, 2017; Rothschild et al., 2004). The link between the orbital and post-cranial cribrous lesions, cribra humeri and femora, appears to be more convincing, yet still not clear-cut. Miquel-Feucht et al. (1999) argue that these porous post-cranial lesions are macroscopically, microscopically, and radiographically very similar to cribra orbitalia and that therefore all three together constitute "*a similar lesion or anatomical-pathological entity*" (Miquel-Feucht et al., 1999: 12, translation by author). The authors note cortical thinning and expanding trabeculae in both the humeral and femoral lesions, as are also observed for the orbital lesions (Brickley, 2018; Miquel-Feucht et al., 1999; Wapler et al., 2004). In a study on Spanish skeletal remains the researchers demonstrated that the three lesions were correlated, albeit only in non-adults (Miquel-Feucht et al., 1999). Because of this association between the three lesions, the authors coined the term '*cribrous syndrome*'. While several later studies have found the three lesions to co-occur (Djurić et al., 2008; Garcia et al., 2002), others have failed to find a correlation (Erkelens, 2017; Smith-Guzmán, 2015b). Moreover, most of the studies have solely studied and reported on the co-occurrence, mainly in non-adults, and have not investigated the correlation between the lesions Smith-Guzmán (2015b) being a notable exception). Therefore, to contribute to the complex debate on cribrous lesions, their relationship with one another, and their potential (shared) aetiology, this paper studies the prevalence, co-occurrence, and association of cribra orbitalia, cribra humeri, and cribra femora in a large skeletal sample, including adults and non-adults, from the medieval/-early modern Netherlands (800–1600 CE) to evaluate the so-called cribrous syndrome. In linking prevalence and association data to sex and age-at-death, this study will gain a better understanding of these porotic lesions, particularly of the possible factors associated with their occurrence and co-occurrence. As the association between porotic hyperostosis and the other lesions has been demonstrated to be poor in several recent studies (Djurić et al., 2008; Erkelens, 2017; Rivera and Lahr, 2017; Smith-Guzmán, 2015b), this cranial vault lesion is not included in the current research, but focusses solely the three lesions hypothesised to be part of the cribrous syndrome as defined by Miquel-Feucht et al. (1999).

2. Materials

For this study, ten archaeological skeletal collections from the Netherlands were investigated (Fig. 1). All assemblages date to the medieval/early modern period (800–1600 CE) and are from both rural and urban environments. The individuals were analysed by the author within a larger project, which focuses on the presence and impact of malaria during the medieval period. Only individuals for which at least one orbit, one proximal humerus, and one proximal femur (either left or right) could be observed were included in the study. In total, there were 232 individuals in the sample meeting these selection criteria (53 non-adults and 179 adults). See Table 1 for an overview.

3. Methods

3.1. Estimation of sex and age-at-death

Adult sex (> 20 years) was estimated using the morphology of the cranium, mandible, and pelvis (Buikstra and Ubelaker, 1994; Ferembach et al., 1980; Phenice, 1969). Adult age-at-death was estimated using the morphology of the pubic symphysis (Brooks and Suchey, 1990), the iliac auricular surface (Buckberry and Chamberlain, 2002; Lovejoy et al., 1985), and the sternal rib ends (Işcan et al., 1984, 1985), as well as ectocranial suture closure (Meindl and Lovejoy, 1985). The adult individuals are placed in one of two age groups: younger adults (20–35 years) and older adults (> 35 years). While these are not the traditional demographic groups typically used by bioarchaeologists (i.e., young adult, middle adult, old adult), these two age groups were created to increase sample size in each category and to limit the number of adults who had to be placed in an undefined adult age group. Non-adult age-at-death was estimated using permanent dental development (Moorrees et al., 1963), dental eruption (AlQahtani et al., 2010; Ubelaker, 1979), epiphyseal fusion (Schaefer et al., 2009), and long bone length (Fazekas and Kósa, 1978; Maresh, 1970). The non-adult individuals are placed into one of the following age groups: infant (0–3 years), child (4–12 years), adolescent (13–19 years).

3.2. Scoring cribriotic lesions

The presence or absence of the porous lesions was established macroscopically, occasionally with the aid of a magnifying glass (10x). As this study only focuses on the prevalence, co-occurrence, and association of the lesions and the connection with sex and age-at-death, only the presence or absence of the lesions was included. No scores of severity

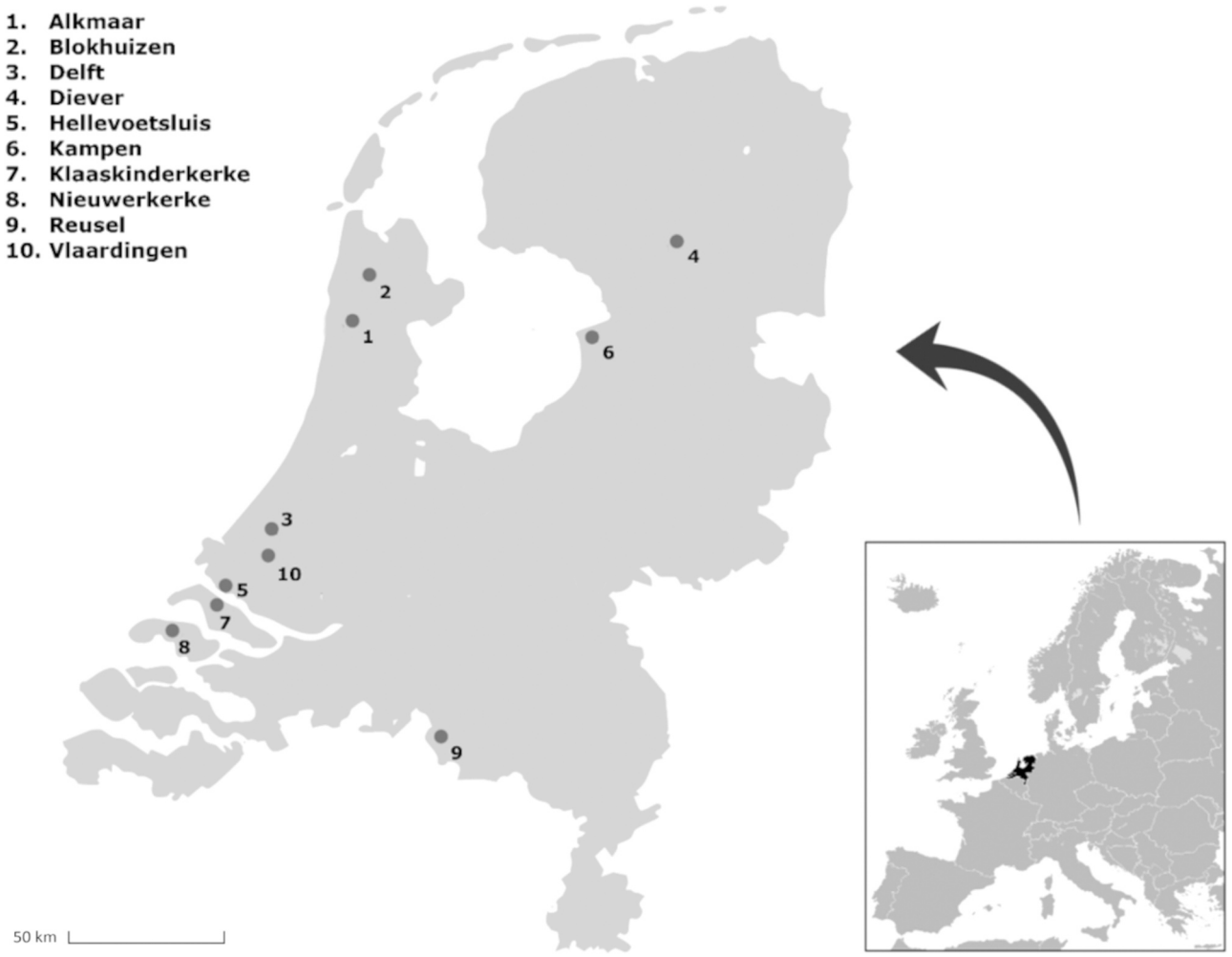

Fig. 1. The current Netherlands in Europe and a separate map of the Netherlands with studied sites indicated.

Table 1
Overview of skeletal collections and numbers of individuals included in the study.

Site	Dating	Total	Adults	Non-adults	Males	Females	Indet. sex
Alkmaar	1448–1572	46	36	10	16	20	0
Blokhuizen	~800–1196	6	5	1	4	1	0
Delft	1450–1572	38	32	6	22	9	1
Diever	500–1550[a]	4	4	0	2	2	0
Hellevoetsluis	1275–1314	28	21	7	13	7	1
Kampen	1300–1611	22	16	6	11	4	1
Klaaskinderkerke	1286–1570	21	18	3	12	6	0
Nieuwerkerke	1200–1570	45	33	12	21	12	0
Reusel	950–1450	8	7	1	3	4	0
Vlaardingen	1000–1050	14	7	7	5	2	0
Total	–	**232**	**179**	**53**	**109**	**67**	**3**

[a] More refined dating unavailable. References for sites: Alkmaar, Blokhuizen, Klaaskinderkerke: Schats (2016), Delft: Westen et al. (2013), Diever: Taayke, pers. comm., Hellevoetsluis: Carmiggelt (2017), Kampen: Schats and Klomp (2019), Nieuwerkerke: Huizinga (1951), Reusel: Nater et al. (2016), Vlaardingen: de Ridder (2019).

or state of healing were used, also because it is unclear how stages of severity and remodelling correlate to clinical measures (see also Grauer, 2019). Cribra orbitalia was considered present when porosity in one or both orbital roofs was observed following the descriptions outlined by Brothwell (1981), Rivera and Lahr (2017), and Stuart-Macadam (1985). Cribra humeri and cribra femora were scored as present when porosity was noted on the left, right, or both anterior-medial aspect(s) of the neck (s) of the humerus and femur according to the descriptions by Miquel-Feucht et al. (1999) and Smith-Guzmán (2015b). See Fig. 2 for examples.

3.3. Data analysis

Data were analysed by sex and age-at-death variables. The prevalence and association of the porotic lesions and the influence of age-at-death and sex were analysed for statistical significance using a chi-square test for independence as well as binary logistic regression. The strength and direction of association of the lesions was investigated by

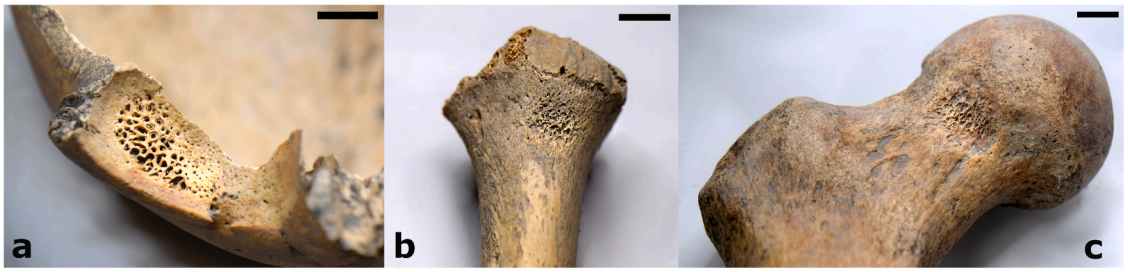

Fig. 2. Examples of scored cribrous lesions: a) Cribra orbitalia, b) Cribra humeri, c) Cribra femora. Bar = 1 cm.

using a Phi coefficient (φ). All statistical tests were executed using IBM SPSS Statistics Software 24. Statistical significance was set at $p \leq 0.05$. When multiple tests were performed on the same sample, the significance level was adjusted using a Bonferonni correction procedure to control for familywise error (cf. Brickley et al., 2018). All raw data produced from this publication are available online (Schats, 2021).

4. Results

4.1. Prevalence of cribriotic lesions

Table 2 shows the prevalence of the three cribriotic lesions by sex and age-at-death. Of the three lesions, cribra femora is most frequently observed in the studied skeletal collections. Males and females are equally affected by cribra orbitalia and cribra femora, but cribra humeri is statistically significantly more common in females. Age-at-death is an important factor in the occurrence of the lesions (Fig. 3). All studied cribriotic lesions are statistically significantly more commonly found in non-adults compared to adults. Within the three different non-adult age groups, there are no statistically significant differences. Infants appear to be the least affected, but this result may have been influenced by the small sample size of this age group. For adult age-at-death, the younger adults are statistically significantly more affected by cribra humeri and cribra femora compared to the older adults, yet no difference in prevalence is noted for orbitalia between the two adult age groups. These results are supported by binary logistic regression analysis (Table 3). With increasing adult age, there is a significant reduction in the likelihood of developing cribra humeri and femora, while this is not the case for cribra orbitalia. Sex is not a good predictor for cribra orbitalia and femora, yet, females have a 3.79 higher chance of being affected by cribra humeri.

4.2. Co-occurrence and association of cribriotic lesions

The co-occurrence of the lesions is shown in Table 4. It is rare for all three lesions to co-occur in the same individual, although this is slightly more common in the non-adult individuals. For adults, all lesions are more likely to be found independently than in association with other cribriotic lesions. Pairs of lesions are more common. Non-adults show that cribra femora is frequently found in association with cribra orbitalia and with cribra humeri. Few differences are found between males and females, although cribra orbitalia and femora are more likely to co-occur in females. It is clear that while it is more common for lesions to co-occur in the younger adults, differences are small. The statistical analyses (Table 5) demonstrate that for the non-adults there is a significant moderate association between cribra humeri and cribra femora. No significant associations between pairs of lesions are found for adults.

5. Discussion

5.1. Prevalence of cribriotic lesions

The aim of this paper was to study the prevalence, co-occurrence, and association of three cribriotic lesions and their relationship with sex and age-at-death. Cribra femora is the most prevalent lesion for both sexes and almost all age groups, a result also found by Djurić et al. (2008) in Serbia, where 83.3% of non-adults were affected by cribra femora. Cribra humeri was least prevalent of the three cribrous lesions examined here. From the prevalence data, it is clear that all three cribriotic lesions are related to the age-at-death of the individuals under study. While the lesions do occur in all age groups, cribra orbitalia, humeri, and femora are all significantly more commonly found in non-adult individuals. In addition, the three lesions demonstrate a very similar age distribution, with a peak in the child age category (4–12 years) and a decreasing prevalence after 12 years. Age distribution of skeletal lesions is a complex interplay between age of formation, bone remodelling, and the mortality associated with the causative factor (Brickley, 2018; Mays, 2018). The pattern observed here may tentatively suggest that the studied porous skeletal lesions are formed during childhood and may persist into adulthood, in some cases. Not persisting into adulthood could be due to death during childhood or remodelling of lesion areas. For cribra orbitalia, the greater prevalence in non-adults is an accepted and commonly observed pattern as this porotic lesion has often been considered to be an indicator of severe childhood anaemia

Table 2
Prevalence and statistical comparison of the three cribrous lesions in different age and sex groups.

Group	N	Cribra orbitalia					Cribra humeri					Cribra femora				
		n	%	χ^2	df	p	n	%	χ^2	df	p	n	%	χ^2	df	p
All	232	62	26.7	–	–	–	34	14.7	–	–	–	90	38.8	–	–	–
Males	109	19	17.4	2.225	1	0.136	5	4.6	8.441	1	**0.004**	26	23.9	1.189	1	0.275
Females	67	18	26.9				12	17.9				21	31.3			
Non-adult	53	25	47.2	14.664	1	**< 0.001**	17	32.1	16.667	1	**< 0.001**	43	81.1	51.860	1	**< 0.001**
Adult	179	37	20.7				17	9.5				47	26.3			
Infant	6	1	16.7	2.553	2	0.279	1	16.7	1.024	2	0.599	3	50.0	4.999	2	0.082
Child	21	11	52.4				8	38.1				19	90.5			
Adolescent	26	13	50.0				8	30.8				21	80.8			
Younger adult	78	16	20.5	0.038	1	0.845	12	15.4	6.031	1	**0.014**	30	38.5	14.661	1	**< 0.001**
Older adult	92	20	21.7				4	4.3				12	13.0			

N = studied individuals, n = affected individuals, df = degrees of freedom, statistically significant results in bold.

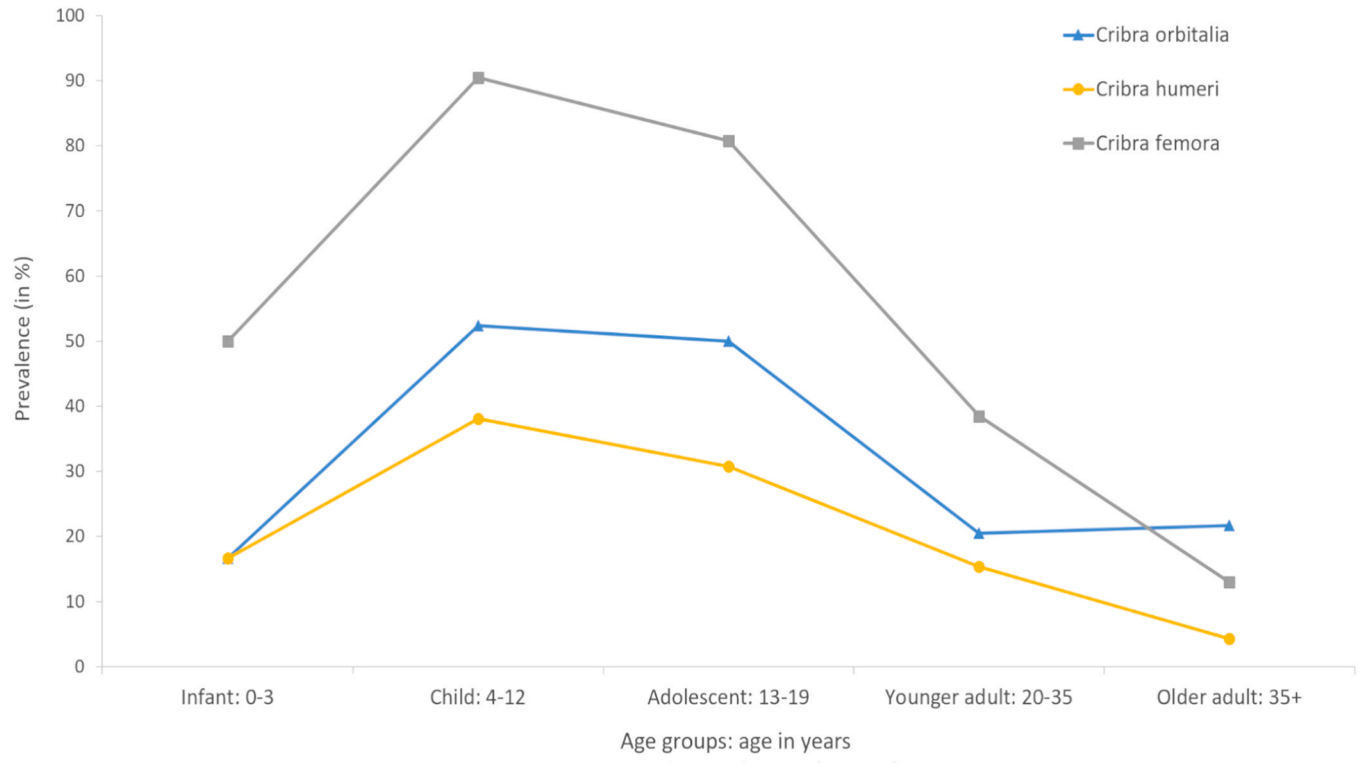

Fig. 3. Distribution of three types of cribrous lesions over the five age groups used in this study.

Table 3
Results binary logistic regression.

Adults (N = 168)								
	Independent variable	B	SE	Wald	p	Odds ratio	95% confidence interval	
							Lower	Upper
CO	Age-at-death	0.126	0.386	0.107	0.774	1.134	0.533	2.415
	Sex	0.568	0.386	2.162	0.141	1.764	0.828	3.758
	Constant	-2.292	0.899	6.495	0.011	0.101	–	–
CH	Age-at-death	-1.265	0.611	4.286	**0.038**	0.282	0.085	0.935
	Sex	1.331	0.576	5.351	**0.021**	3.786	1.225	11.669
	Constant	-2.486	1.303	3.639	0.056	0.083	–	–
CF	Age-at-death	-1.451	0.392	13.722	**< 0.001**	0.234	0.109	0.505
	Sex	0.137	0.384	0.128	0.720	1.147	0.541	2.434
	Constant	0.824	0.828	0.991	0.319	2.280	–	–

Only individuals for whom sex and age-at-death could be estimated are included. CO = cribra orbitalia, CH = cribra humeri, CF = cribra femora, statistical significant results in bold. Coding sex: Male = 1, Female = 2. Coding age-at-death: Younger adults = 1, Older Adults = 2.

Table 4
Co-occurrence of cribrous lesions.

Lesions	All		Non-adults		Adults		Males		Females		Younger adults		Older adults	
	n	%	n	%	n	%	n	%	N	%	n	%	n	%
None	104	44.8	5	9.4	99	55.3	66	60.6	30	44.8	35	44.9	60	65.2
only CO	27	11.6	5	9.4	22	12.3	14	12.8	8	11.9	6	7.7	16	17.4
only CH	10	4.3	0	0.0	10	5.6	3	2.8	7	10.4	6	7.7	8	4.3
only CF	42	18.1	13	24.5	29	16.2	20	18.3	9	13.4	18	23.1	29	8.7
CO + CH	1	0.4	0	0.0	1	0.6	0	0.0	1	1.5	1	1.3	0	0.0
CO + CF	25	10.8	13	24.5	12	6.7	4	3.7	8	11.9	7	9.0	4	4.3
CH + CF	14	6.0	10	18.9	4	2.2	1	0.9	3	4.5	3	3.8	0	0.0
CO + CH + CF	9	3.9	7	13.2	2	1.1	1	0.9	1	1.5	2	2.6	0	0.0
Total	**232**	**100.0**	**53**	**100.0**	**179**	**100.0**	**109**	**100.0**	**67**	**100.0**	**78**	**100.0**	**92**	**100.0**

n = affected individuals, CO = cribra orbitalia, CH = cribra humeri, CF = cribra femora

(Blom et al., 2005; DeWitte and Slavin, 2013; Djurić et al., 2008; Liebe-Harkort, 2012; McFadden and Oxenham, 2020; O'Donnell, 2019; Steyn et al., 2016). This abundant occurrence of cribra orbitalia in non-adults is thought to be directly related to the physiology of bone marrow. As the orbital lesions are generally assumed to be caused by marrow hyperplasia to increase erythrocyte production, the distribution

Table 5
Association of cribrous lesions.

Association		χ^2	df	*p*	*φ*	n
Non- adult	CO-CH	0.361	1	0.548	-0.083	53
	CO-CF	0.04	1	0.842	-0.027	53
	CH-CF	5.820	1	**0.016**	0.331	53
Adult	CO-CH	0.105	1	0.746	-0.024	179
	CO-CF	3.231	1	0.072	0.134	179
	CH-CF	0.792	1	0.373	0.067	179
Males	CO-CH	0.024	1	0.877	0.015	109
	CO-CF	0.077	1	0.782	0.027	109
	CH-CF	0.752	1	0.386	0.083	109
Females	CO-CH	0.774	1	0.379	-0.107	67
	CO-CF	3.981	1	0.046	0.244	67
	CH-CF	0.027	1	0.870	0.020	67
Younger adults	CO-CH	0.175	1	0.676	0.047	78
	CO-CF	2.691	1	0.101	0.186	78
	CH-CF	0.062	1	0.804	0.028	78
Older adults	CO-CH	1.162	1	0.281	-0.112	92
	CO-CF	1.090	1	0.296	0.109	92
	CH-CF	0.627	1	0.428	-0.083	92

CO = cribra orbitalia, CH = cribra humeri, CF = cribra femora, df = degrees of freedom, φ = strength of association (Phi coefficient), Bonferroni correction significance level set at p = 0.017, statistically significant results in bold.

of the red blood cell forming red (haematopoietic) marrow is therefore crucial in lesion formation and expression. In infants, the entire skeleton is filled with this reactive red marrow, but as an individual ages this will convert into yellow marrow, a process that takes up to the age of 25 years to be completed, although some mixed marrow may remain (Brickley, 2018; Małkiewicz and Dziedzic, 2012; O'Donnell, 2019). Therefore, if indeed caused by anaemia, cribra orbitalia visible in adult individuals is likely to be a remnant of non-adult stress and is unlikely to indicate active illness, although this assessment is complicated by the fact that it is difficult to evaluate if lesions are healed or active. While the anaemia is the favoured explanation for the orbital lesions in non-adults, it is important to keep in mind that other conditions can cause bone porosity as well. Brickley et al. (2020) indicate that there are three main mechanisms that can produce porous lesions in addition to the marrow expansion associated with anaemia, which include a vascular inflammatory response, subperiosteal bone deposition, and impaired mineralisation (Brickley et al., 2020). As such, metabolic diseases such as rickets and scurvy can also be responsible for the porous appearance of bones, including the orbital roof (Brickley et al., 2020). While these different types of porous lesions would have a similar appearance, they can be distinguished through careful examination, though not in all cases (Brickley et al., 2020). The fact that these other, common childhood conditions can also cause a porous appearance may therefore be an alternative explanation for the high prevalence of cribra orbitalia in individuals under 20 years seen here. However, it is interesting to note that in the Netherlands the prevalence of cribra orbitalia appears to be correlated with geographic location. Earlier research by the author showed that the orbital lesion was statistically significantly more common in both rural and urban sites located near the coastal areas, which may be related to the presence of malaria in these regions (Schats, 2015). The potential link between cribra orbitalia, geographic location, and malaria was suggested earlier for the UK by Gowland and Western (2012) as well. While a spatial analysis of the current cribrous data has not been undertaken yet, considering that several of the skeletal collections in the current study are from the Dutch coastal region, anaemia caused by a malaria infection might be a viable hypothesis for some of the observed cases. Computed tomography of the lesions areas could provide information on if marrow hyperplasia, and therefore anaemia, is present (e.g., Exner et al., 2004; Naveed et al., 2012; Rivera and Lahr, 2017; Saint-Martin et al., 2015).

Cribra humeri and cribra femora have not garnered the same research interest as cribra orbitalia and are infrequently included in studies focusing on past health and stress. Moreover, the investigations that examine these lesions generally only study non-adults (Djurić et al., 2008, 2010; Miquel-Feucht et al., 1999). Although this is understandable considering the strong association with age also found in this research, it limits the availability of comparative data for this study. Garcia and colleagues studied the prevalence of all three lesions in adults and non-adults, of which both post-cranial lesions are markedly more common in individuals under 18 years (Garcia et al., 2002). Erkelens (2017) focused on the prevalence of cribra femora in adults and non-adults in two post-medieval Dutch skeletal collections and observed the lesion in all age groups (total 36.2%), but also noted a clear correlation with age with the lesion being more prevalent in the younger age categories. They found cribra femora to be most prevalent in the child category (3–12 years: 93%) (Erkelens, 2017), as is the case in this study. Erkelens noted a difference in prevalence between the two populations she studied, cribra femora being more frequently observed in the coastal region, which could fit with the malaria hypothesis posed for cribra orbitalia (Erkelens, 2017). Although the frequency data is not split by age and sex, this pattern is supported by the research of Smith-Guzmán (2015b), who noted a higher prevalence of cribra humeri and femora in the endemic malaria sample they investigated (23.6% and 38.5% versus 4.5% and 0.0% respectively).

Even though the individuals older than 20 years are far less affected by all three skeletal lesions, solely looking at the adults does reveal interesting patterns. While cribra orbitalia and cribra femora are equally observed in males and females, cribra humeri appears to affect females disproportionally and the risk for females of developing this lesion in 3.79 times higher. This difference is difficult to interpret, as there are no direct morphological and physiological explanations for this observation. It may be related to a differential stress and disease experience by females that started already at a young age, as was for example found in the prevalence of rickets in the post-medieval Netherlands, where girls were more commonly affected by a vitamin D deficiency (Veselka et al., 2018). Yet, there are no sex differences observed for the other two studied lesions, which may have been expected if females experienced more stress. As research on this particular humeral porous lesion in adults is limited, comparisons with other studies are difficult. Erkelens (2017) did study all three lesions in adults and non-adults but found no cases of cribra humeri in the two Dutch collections she studied. More research on this lesion and its prevalence in other skeletal collections, on adults and non-adults, needs to be conducted. It would be particularly interesting to investigate if a sex difference in prevalence for the lesions exists in the non-adults. For this study in particular, it also has to be taken into account that there are more young females than young males in the sample, 54.8% and 39.6% respectively. Although this difference in sample size is not statistically significant, it may have contributed to the high prevalence of cribra humeri in females.

Another notable pattern is found in the adult age distribution of the three lesions. The post-cranial lesions, cribra humeri and femora, are both significantly more common in younger adults and increasing age is associated with a decrease in risk of developing the lesions, supporting the observations in previous research. Yet, this age pattern is not mirrored in the cribra orbitalia prevalence, as this lesion is found equally in both adult age groups. This observation, also noted by Smith-Guzmán, potentially counters the assumption that cribra orbitalia is only formed in childhood (Smith-Guzmán, 2015b). More likely, however, is that this finding is the result of differential rates of remodelling in the skeleton. Although there are studies that suggest that bone turnover is higher in the cranium compared to the long bones (Goldberg et al., 2016), others suggest that because the skull is under less mechanical stress, remodelling of the cranial vault may progress at a slower rate (García Gil et al., 2016). Additionally, with increasing age the cortical bone of the cranium becomes thinner (Lillie et al., 2016), potentially making cribra orbitalia, if caused by marrow hyperplasia associated with anaemia, visible over longer periods of time, despite the likely fact that the lesion formed in childhood. If this is indeed the case, then cribra orbitalia is a better indicator of childhood stress in adults than both cribra humeri and

cribra femora.

5.2. Co-occurrence and association of cribriotic lesions

While the lesions display macroscopically, microscopically, and radiographically similar characteristics (Miquel-Feucht et al., 1999) and demonstrate a comparable age distribution, this study showed that the lesions are unlikely to co-occur in the medieval/early modern Netherlands. All three lesions only co-occur in 3.9% of individuals and only in 1.1% of adults, indicating that, for adults, the lesions are substantially more likely to occur independently than together. The rate of co-occurrence is higher for non-adults (13.2%). The study by Miquel-Feucht et al., which introduced the concept of 'cribrous syndrome', only observed co-occurrence of all three lesions in five cases (Miquel-Feucht et al., 1999), but it is unfortunately not clear for how many individuals all three skeletal locations could be observed. Compared to other research, the co-occurrence rates found in the current study are substantially lower. Djurić and colleagues demonstrated that the three lesions co-occurred in 33.3% (5/15) of their non-adults sample (0–14 years) (Djurić et al., 2008). In a later study focusing on adolescents, Djurić et al. reported a slightly lower co-occurrence rate of 27.3% (unclear for how many individuals the three lesions were observable) (Djurić et al., 2010). The fewer instances of co-occurrence in this investigation may be due to slight methodological differences or to differences in the age compositions of the samples. Additionally, local environmental and geographical variations may have resulted in different risks for developing these pathological lesions. Moreover, differences in relative prevalence of the lesions could have also influenced the co-occurrence rates in the used comparative studies. Interestingly, the prevalence rates for cribra orbitalia and cribra femora in this study are similar to the rates found in Djurić et al. (2008). Cribra humeri is however less common in the non-adult sample presented, which likely explains the marked difference in co-occurrence with the current study.

The lesions commonly occur in pairs, with cribra orbitalia-femora and cribra humeri-femora being the most likely to occur together. Yet, the associations between the lesions are not statistically significant, except for the cribra humeri-femora association in non-adults. Cribra humeri does not occur without cribra femora being present. This is similar to what has been found at the Prat de la Riba Necropolis in Spain (Garcia et al., 2002). Here, an 100% association was also found between cribra humeri and femora (Garcia et al., 2002). Smith-Guzmán (2015b) also found the lesions to be correlated in a malaria endemic sample. This may suggest that they are caused by a shared pathological process, potentially anaemia, yet, a comparable pattern would be expected if these lesions are related to the normal growth process. The metaphyses of the humerus and femur are areas which experience significant growth and development (Brickley et al., 2020). As this physiological process is often associated with increased porosity in the areas of growth, it may explain the high prevalence of porous lesions in the proximal humerus and femur in non-adult individuals, and therefore their association. This does however not explain peak in prevalence of cribrous lesions between 4 and 12 years seen in the current study, as growth is most intense during the first two years of life (Ribot and Roberts, 1996). Potentially, the growth spurt associated with puberty may have resulted in this increased porosity in the metaphyses of the humerus and femur in this child age group (Lewis et al., 2016). The common, yet not statistically significant, co-occurrence of cribra orbitalia with cribra femora in adults can potentially be explained by the high prevalence rate of the femoral lesion in the current research: if prevalence of one of the lesions is high, co-occurrence is more likely (Brickley et al., 2018). In most of the studies discussed here, including the current one, cribra humeri appears to be an outlier with regard to prevalence, occurring substantially less often than cribra orbitalia and cribra femora (with Durić et al. (2008 and 2010) being an exception), making it therefore also less likely for all three lesions to co-occur. This may suggest that cribra humeri is caused by a different process, disease or otherwise, than the other two lesions. At the same time, some of the difference in prevalence and co-occurrence could be explained by anatomical variations in the lesions areas. Differences in rates of bone growth and remodelling, and variation in bone mechanics may contribute to the variation in prevalence observed here; it is possible that the lesions form more difficult or remodel quicker. Studies show that variation in growth velocity between different long bones exist, the lower limb bones are larger and have therefore greater growth velocity (Smith and Buschang, 2004). To what extent this variation influences the presence, development or visibility of porous lesions in the proximal humerus and femur requires further research. Additionally, if the hypothesis that marrow expansion is responsible for the three lesions is correct, then it is to be expected that in areas with thicker cortical bone it takes longer for the lesions to become visible macroscopically. Clinical studies show that the sub-capital cortical bone of the femur is thinner than the cortical bone of the neck of the humerus (Boyce and Bloebaum, 1993; Helfen et al., 2017), which may explain why cribra humeri is less frequently observed than the femoral lesion. However, it must be noted that these cortical thickness studies were performed on adults and not on non-adult individuals, which may therefore not explain the pattern seen in the younger individuals of this study.

5.3. Cribrous syndrome?

The results discussed here do not support the presence of a cribrous syndrome as co-occurrence of all three lesions is infrequent. Although the observed patterns are somewhat more convincing for non-adults, it is unlikely that cribra orbitalia, humeri, and femora co-occur. A similar age distribution is noted for the three lesions, yet, this pattern is not necessarily indicative of a causative link, i.e., a shared aetiology. It is possible that the lesions are caused by different processes, pathological or otherwise, impacting children (4–12 years) the most. The significant association between cribra humeri and femora in non-adults does suggest that these two lesions are associated, suggesting a common cause. This may be a pathological condition, such as anaemia or another childhood illness. Several studies do seem to support the link with malaria endemic areas (Erkelens, 2017; Smith-Guzmán, 2015b). The differences in the prevalence of individual lesions may then be explained by variations in bone remodelling and cortical thickness in the lesion areas. However, it cannot be ruled out that these humeral and femoral porous lesions are the result of normal growth in childhood and are therefore likely to co-occur. Moreover, as cribra femora is highly prevalent in non-adults (81.1%), co-occurrence is to be expected. Yet, it is interesting that this is not the case for cribra orbitalia. Thus, even though the lesions demonstrate macroscopically, microscopically, and radiographically similar characteristics and the data presented here demonstrated a comparable age distribution, this study cannot confirm the presence of a cribrous syndrome.

6. Conclusions

This study has examined the prevalence, co-occurrence, and association of three cribriotic lesions and their relationship with sex and age-at-death. All three lesions demonstrated a strong relationship with age, as they are all more common in non-adults, with a peak in the 4–12 years age group. Cribra orbitalia, while also occurring more frequently in non-adults, appears to be less strongly related to age-at-death than the other two lesions, occurring commonly in older adults as well. While the lesions have been grouped within a cribrous syndrome, co-occurrence of all three lesions is infrequent, especially for adults. As such, this research cannot support the hypothesis that all three lesions are caused by the same pathological process. The correlation between cribra humeri-femora is interesting and may suggest a common cause for the two post-cranial lesions, which is supported by other studies, although the possibility that these lesions are the result of the normal growth cannot be excluded. More research into the occurrence of the post-cranial defects in general and specifically into associated factors is necessary to

fully understand their occurrence and development. This study has underlined the complex nature of cribrous lesions and the importance of looking beyond co-occurrence rates. The results demonstrate that even if skeletal lesions are similar in appearance, a shared aetiology cannot be assumed. This research highlighted that the development of lesions is multifactorial, with age, bone growth and remodelling, potentially red marrow distribution, and cortical thickness being particularly important. Future research on cribrous lesions on a larger non-adult sample, limited in age range, would be able to help in addressing and limiting the factors associated with lesion development and allow for more insights in these cribrous skeletal lesions.

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