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Evidence of Pellagra on 19th Century Human Crania From Northern Italy by Combining Stable Isotope and Paleopathological Analyses

Nicola Carrara[1] | Gregorio Dal Sasso[2] | Anna Addis[3] | Anna Domanico[1] | Nereo Preto[4] | Elisa Saler[4] | Telmo Pievani[5] | Gilberto Artioli[4] | Cinzia Scaggion[6]

[1]Museum of Nature and Humankind-Anthropology Section, University of Padova, Padova, Italy | [2]Institute of Geosciences and Earth Resources, Italian National Research Council-CNR, Padova, Italy | [3]Carl Zeiss S.p.A. with sole shareholder, ZEISS Group, Milan, Italy | [4]Department of Geosciences, University of Padova, Padova, Italy | [5]Department of Biology, University of Padova, Padova, Italy | [6]Department of Chemical and Geological Sciences, University of Modena and Reggio Emilia, Modena, Italy

Correspondence: Cinzia Scaggion (cinzia.scaggion@unimore.it)

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ABSTRACT

Pellagra is a disease caused by a nutritional deficiency, with fatal outcome due to multiple-organ failure, that affected European rural areas until the early decades of the 20th century, especially Veneto region (Italy). At the skeletal level, previous studies pointed out that pathological signs left by the disease are generic and typical of many forms of avitaminosis, not useful to recognize the deaths by pellagra in archaeological contests. Here, a detailed paleopathological study was conducted on skulls of individuals dating to the late 19th-early 20th century, for which the health state and causes of death have been well-documented at the time. Individuals severely affected by pellagra and non-pellagrous individuals were investigated; differential analysis was conducted considering pathologies that leaves on skeletal tissue similar anomalies, such as tuberculosis meningitis, scurvy, and meningioma. By integrating the skeletal alterations reported in literature and the intracranial alterations found in this study, we provide recommendations on a framework that could be used to demonstrate diagnostic validity in cases of severe vitamin B3 deficiency. Peculiar lesions that have been found contrasted with lesions linked to other pathologies and those indicated in the literature, and they could prove fundamental to ensure the identification of pellagra. Finally, pathological evidence observed in pellagrous skulls was compared with diet reconstruction, carried out on stable C and N isotope analysis, highlighting a poor-to-moderate protein consumption and possible fasting or nutritional stress, together with a large input from C4 plants, as maize. We think that this work can contribute to the understanding of adaptations and variability among past communities by more confidently identifying severe niacin deficiency. The framework allows for greater consistency in diagnostic certainty, facilitating greater comparability in research.

1 | Introduction

Pellagra (meaning "rough skin") is a disease caused by a deficiency of niacin (vitamin B-3 or vitamin PP; nicotinic acid) and/or L-tryptophan, an essential amino acid for vitamin biosynthesis and for the normal maintenance of cellular processes (Jaworek et al. 2021; Prabhu, Dawe, and Mponda 2021). Pellagra occurs due to a prolonged unbalanced diet based on the (almost) exclusive consumption (monophagia) of corn (*Zea mays* L., 1753, originally from the Americas) as a staple food

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(Brenton and Paine 2007; Carpenter 1983). Corn is known to have a low protein quality, as it lacks essential amino acids, in particular tryptophan, while the niacin present in the cereal is linked to niacin glycoside molecules (Chamlagain et al. 2020), which must be converted into free niacin to be absorbed by the body.

Through the alkaline treatment of corn with the practice of nixtamalization, a practice traditionally employed by Native Americans for the preparation of corn (Hegyi, Schwartz, and Hegyi 2004; Pelton and McLean 2000), niacin and other nutrients were made available and assimilable for the human body.

However, despite this practice, some populations who were heavily dependent on maize as their main source of nutrition still suffered from pellagra. Lack of awareness about the causes of the disease coupled to the socio-economic crisis and the consequent severe limitations on food resources and quality protein sources, as well as the limited knowledge of nixtamalization, may have been the reasons for the spread of this pathological condition. The history of pellagra dates back to the 18th century, and its spread was particularly significant in rural areas of several European countries such as France, Spain, Portugal, Greece, Italy, but also worldwide as attested in the United States, and in Africa (Jaworek et al. 2021; Rajakumar 2000; Viljoen, Bipath, and Tosh 2021). In the United States, Spain, and Italy, pellagra has been a significant concern throughout history, especially during the 19th and early 20th centuries (Ginnaio 2012; Jaworek et al. 2021). Italy was one of the most severely affected countries, particularly the rural areas of Veneto region (North-Eastern Italy). The majority of patients was interned in mental institutions (Gentilcore and Priani 2023), and specifically, due to this emergency, it was in Mogliano Veneto (Veneto, Italy) at "Villa Torni" that the first Pellagra Asylum was established in 1882 (Ginnaio 2012).

Pellagra is known as the 4D's disease, which perfectly describes the progression of the disease: dermatitis, diarrhea, and dementia, which can ultimately lead to the premature death from multiple organ failure (Hegyi, Schwartz, and Hegyi 2004; Williams and Hill 2020). The disease manifests itself with numerous symptoms: at the epithelial level, it causes a loss of elasticity, thickening, peeling, photosensitivity, hyperkeratinization, and hyperpigmentation of the skin with the formation of wounds and cicatrized blisters on the neck, face, back of the hands, and feet and arms (Hegyi, Schwartz, and Hegyi 2004). With skin problems, symptoms linked to digestive disorders appear, such as stomatitis, glossitis, nausea, vomiting, diarrhea, and finally cerebro-spinal disorders arise with encephalopathy, dementia, acute delirium syndrome, mania, and marasmus (Oldham and Ivkovic 2012).

None of these symptoms directly involved the skeletal system, so that the skeletal degenerations associated with pellagra were poorly described in the medical literature (Gillman and Gillman 1951). To date, at a skeletal level, nondistinctive and generic signs of the disease have been identified such as osteoporosis, periostitis, porotic hyperostosis, enamel hypoplasia, dental caries, and tooth loss linked to severe alveolar resorption, which may be attributed to many forms of avitaminosis or different pathological conditions (Brenton and Paine 2007; Ortner 2011; Paine and Brenton 2006).

In this research, we aim at further investigating the occurrence of specific pathological signs at the skeletal level to be associated with the insurgence of pellagra by analyzing the exceptional osteological collection preserved at the Museum of Nature and Humankind of the Padova University, Anthropology section. A detailed paleopathological study was carried out on the Tedeschi craniological Collection (Carrara, Scaggion, and Holland 2018), composed of individuals that died in the late 19th–early 20th century and for whom the causes of death are known and well-documented, including several cases of pellagra (certainly attested for 19% of the skeletal collection). As for comparison, the study on pellagrous crania was compared with that on skulls from the same collection of individuals that died from pathologies unrelated to pellagra (here labeled as non-pellagrins—NP). Differential analysis was conducted considering a list of pathologies that, due to similarity in skeletal anomalies, would have complicated the diagnosis. Pathological signs observed in pellagrous crania were compared with those found in the skulls of contemporary (or neighboring) Venetian individuals (NP), mainly coming from hospitals or mental institutions with unknown causes of death or for other pathologies not related to pellagra.

Further, confirming the onset of the disease, and correlating pathological observations with nutritional deficiencies, the diet of pellagrous and non-pellagrous patients was investigated by analyzing the C ($\delta^{13}C$) and N ($\delta^{15}N$) stable isotopes. Stable isotope analyses have been widely used to reconstruct the diet of past populations (Vogel and Merwe 1977), as consumer's tissues reflect the isotopic composition of ingested food. The determination of $\delta^{13}C$ is particularly informative on the consumption of C3 plants (e.g., wheat, rice, barley, oats, and potatoes) or C4 plants (e.g., corn, sorghum) (Wang et al. 2012). In fact, the plants defined as C3 and C4, identifying two different carbon fixation pathways, are characterized by a marked difference in the C isotopic signature of their tissues, with $\delta^{13}C$ values between −20‰ and −34‰ for the C3 and between −9‰ and −16‰ for C4 plants. The determination of $\delta^{15}N$, which is indicative of protein consumption and trophic levels, together with that of $\delta^{13}C$, can shed light on the type of diet, for example, predominantly from marine or terrestrial food sources (Schoeninger and DeNiro 1984). Bone collagen reflects the isotopic composition of food sources, considering isotopic enrichment through trophic levels; enrichment between the diet and bone collagen is estimated at ca. 5‰ and 3‰ for $\delta^{13}C$ and $\delta^{15}N$, respectively. Nevertheless, beside the diet, other factors may concur in raising $\delta^{15}N$ values, such as physiological and nutritional stresses (Hertz et al. 2015; Walter et al. 2020).

The presence of skeletal signs consistent with pellagra can represent a valuable reference, enabling one to directly detect the presence of the disease also in archaeological contexts, coupling the paleopathological evidence with archaeobotanical and archaeological findings related to the domestication and processing of maize and to diet reconstruction through stable isotope analyses, providing useful hints on the level of reliance on maize consumption (Goodman, Dufour, and Pelto 2000).

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2 | Material and Methods

2.1 | Samples

The sample set consists of 44 crania collected by Enrico Tedeschi, dated from the end of the19th century and the beginning of 20th century (Carrara, Scaggion, and Holland 2018). Besides sex, the origin, cause of death, and age at death are known for almost all the individuals from historical documents. For the present study, two groups were investigated (Table S1): the first one (labeled P = pellagrins) is constituted by 26 crania (12 females and 14 males with age at death ranging between 26 and 76 years) belonged to people that died for pellagra, the second one (labeled NP) by 18 individuals (six females and 13 males with age at death ranging between 25 and 69 years) with unknown or different causes of death. Most of the pellagrous crania belong to people that died in the Ferrara psychiatric asylum (a province in Emilia-Romagna, severely affected by pellagra), at that time directed by Clodomiro Bonfigli (Bonfigli 1881; Ginnaio and Jacobs 2011). Table S1 presents the causes of death as reported in original 20th century autopsy records. Terms such as "nervous disease," "pellagrous frenosis," "mania," "acute delirium," "persecution paranoia," and "marasmus" were frequently employed to describe clinical manifestations and complications associated with advanced pellagra. Autopsy reports often included the term "pellagrous frenosis (marasmus)" to indicate patients with severe mental and nervous disorders (*pellagrous frenosis*) concomitant with severe malnutrition (*marasmus*). At that time, this terminology emphasized both the neurological and nutritional aspects of the disease, underscoring how chronic malnutrition and vitamin deficiency played critical roles in the pathogenesis and progression of pellagra leading to mortality. Group NP, however, is more heterogeneous as most of the selected samples come from mental hospitals, civil hospitals, and cemeteries in northern Italy, belonging to individuals that lived between the end of the 19th century and the beginning of the 20th century. The P group was investigated from the paleopathological point of view, having care to observe the pathological signs and/or anomalies they presented, comparing them with other pathologies, which present similar skeletal alterations, useful for differential analysis. Group NP serves as reference for the identification of specific signs attributable to pellagra identified in the P group, taking into account both diet reconstruction through stable C and N isotope and paleopathological analyses in individuals suffering from known and unknown pathologies.

2.2 | Paleopathological Observation Methods

The crania of groups P and NP were investigated from the paleopathological point of view following the recommendations of established guidelines (Aufderheide and Rodriguez-Martin 2011; Baxarias and Herrerin 2008; Brenton and Paine 2007a; Ortner and Putschar 1981; Waldron 2008), and 10 pathological lesions were observed and reported in Table S2. All the observations on skulls were made following these guidelines: (i) only one observer performs the analysis; (ii) blinded observations were made, without knowing sample number, sex, age, and cause of death; (iii) repeated observations were carried out 2 or 3 months apart; (iv) a third round of observations was made on detailed digital photos. Ortner's procedures and methods were followed as a guide for paleopathological description, and a gross skeletal differential diagnosis was performed accordingly (Ortner 2003). First, the presence, location, and morphology of the observed pathology were thoroughly described, determining whether these pathological signs are *ante-mortem* or *post-mortem*. *Ante-mortem* pathologies are smooth and rounded along lesion edges (because of osteoblastic repair activity) (Ortner 2008; Ortner 2003), and *post-mortem* ones are jagged, irregular, and sharp. Another method to distinguish between *ante-mortem* and *post-mortem* changes is bone coloration: skeletal elements affected by *post-mortem* changes vary in coloration than those of other elements, while *ante-mortem* and *peri-mortem* alterations present coloration that is the same as the rest of the skeleton (Ortner 2008; Ortner 2003) .

The intact skulls that had not undergone a craniotomy in historical times were investigated using nondestructive methods with an industrial endoscopic device (40 × 80 pixel resolution, with its own light and a focal length of 4–100 mm), entering through the *foramen magnum*. Utilizing an endoscopic instrument through the *foramen magnum* of the occipital bone allows for a comprehensive examination of the cranial vault, covering a large portion of the endocranial surface. This method enables the detection of various paleopathological changes linked to both infectious diseases, such as tuberculosis (Hershkovitz et al. 2002; Spekker et al. 2021; Spekker et al. 2020a; Spekker et al. 2020b) and noninfectious conditions, including tumors (e.g., meningioma) (Brothwell and Brothwell 2016) and vitamin deficiencies (e.g., scurvy) (Snoddy et al. 2018). Additionally, it can identify other conditions such as *hyperostosis frontalis interna* (Hershkovitz et al. 1999; Szeniczey et al. 2019) or normal variations like *arachnoid fossae* caused by the protrusion of the arachnoid mater (arachnoid/Pacchionian granulations) (Koduri and Tubbs 2023). The frequency of pathological signs observed in pellagrous and non-pellagrous samples was statistically analyzed through the Fisher's exact test (Fisher 1922) to determine whether there is a statistically significant association between the presence/absence of each pathological sign and the manifestation of pellagra. Fisher's exact test was calculated on 2 × 2 contingency tables reporting the frequency of occurrence/absence of each pathological sign within the P and NP groups.

2.3 | Sample Preparation for C-N Stable Isotope Analysis

For each selected skull (18 non-pellagrous and 18 pellagrous crania, see Table S3), a small fragment from the occipital bone was sampled with an 8-mm Ø corer operating at low speed, avoiding sample overheating. Collagen was extracted with a common acid–base–acid method, here briefly summarized (Passariello et al. 2012). For each bone sample, an aliquot of about 20 mg was crushed to powder (sieved below 300 μm mesh) in an agate mortar. The inorganic fraction was dissolved using three subsequent acid treatments with 0.6 N HCl at room temperature for 2, 24 and 1 h, respectively. After each treatment, the residue was rinsed three times in MilliQ ultrapure water and centrifuged. The sample was then treated with a solution 0.1 M NaOH to remove other organic contaminants. Once rinsed in MilliQ water, collagen was further treated

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with 0.6 N HCl and then rinsed in MilliQ water until reaching neutral pH. After centrifugation, the sample was freeze-dried overnight under vacuum. $\delta^{13}C$ and $\delta^{15}N$ analyses were carried out on a Thermo Scientific Delta V Advantage Isotope Ratio Mass Spectrometer in continuous flow mode coupled to a Flash 2000 Elemental Analyzer and a ConFlo IV interface. Because of raw signal intensity optimization, separate sample aliquots were weighted for $\delta^{13}C$ (0.065 mg) and $\delta^{15}N$ (0.3 mg) analyses, placed in tin capsules and then in the sample holder. Samples were run in duplicates. Blank correction was done by measuring empty blank capsules, and results were normalized to the standard VPDB scale (for carbon) and Air N2 (for nitrogen) by using international standards (IAEA-CH-7, IAEA-CH-6 for $\delta^{13}C$; IAEA-N-1 for $\delta^{15}N$). Reproducibility in this lab is estimated by the continuous analysis of internal standards, treated as unknown samples (a sucrose from C3 plants for $\delta^{13}C$ and IVA 33802174 for $\delta^{15}N$). The $\delta^{13}C$ standard yielded a standard deviation of 0.16‰ over the period of the analyses, while the reproducibility of $\delta^{15}N$, also expressed as standard deviation, was of 0.3‰.

The C/N ratio of collagen samples was measured using the readings of the TCD detector of the Flash 2000 Elemental Analyzer, by comparison with standards of known C and N content (i.e., urea and acetanilide), which were ran along with the sample.

3 | Results

3.1 | Paleopathological Results and Differential Diagnosis of Pellagrous Skulls

Pathological signs observed on pellagrous and non-pellagrous individuals are discussed and explained here. In this differential diagnosis, the considered pathological signs observed on the skulls can be common to various pathologies including tuberculosis meningitis, meningioma, and scurvy.

These are the conditions that could most likely complicate diagnosis. For each skeletal anomaly detected, the possible triggering causes were evaluated, determining the degree of involvement of pellagra in the development of each one. Table S2 reports a complete list of most frequent pathological signs observed in pellagrous and non-pellagrous skulls divided by sex and age classes according to the registry of personal information. Besides the occurrence frequency of pathological signs (summed up in Table S6), the Fisher's exact test, performed on each pathological sign identified in P and NP groups, indicates a statistically significant correlation between the occurrence of S.E.S., meninges (vascular impressions), alveolar atrophy, zygomatic process, and the manifestation of pellagra. Below we list an accurate description of the patterns of skeletal anomalies observed and their anatomical distribution, providing the most feasible diagnosis.

3.1.1 | *Serpens Endocrania Symmetrica* (S.E.S)

Signs of a particular alteration are identified on the endocranial surface area(s) and along the sagittal sinus (Hershkovitz et al. 2002; Spekker et al. 2020a; Spekker et al. 2020b), which is defined, in the paleopathological literature, as *Serpens Endocrania Symmetrica*, abbreviated to S.E.S. (Hershkovitz et al. 2002).

The affected endocranial area of calvarium is characterized by porosity, pitting, small serpentine channels, and slight or marked discolored bone area; the lesions involve neither the *diploë* nor the external plate of the skull but only the endocranial surface. Approximately 69.2% of the examined pellagrous skulls (eight male; 10 female between 36 and 71 years) presents S.E.S. lesion; of these, the 53.8% involved the sagittal sinus, while in 57.7% of cases, the lesions were accompanied by deep vessel impressions-associated with the *arachnoid foveae* (Figure 1). In the remaining 26.9%, the endocranial alterations (90% bilateral) are found along the anterior, middle, and posterior cranial fossae involving the frontal, parietal, sphenoid, and occipital bones, similar to those reported in Spekker et al. (2020a). Within the series of skulls examined that present S.E.S, in 19.2% of cases, there are large plaques (sometimes even isolated) of new bone deposit without sclerotic aspect on the outer table and endocranial surface of the calvarium and cranial base (Figure 2).

3.1.2 | Endocranial Abnormalities

In 26 skulls of individuals who died of pellagra, chronic lesions are localized on the base of cranium, that is, sclerotic lesions and bone remodeling localized on *dorsum sellæ* (11 skulls) and *clivus* (11 skulls). The *clivus* is an anatomical surface located at the base of the skull. It is a sloping groove, which extends from the *sella turcica*, where the pituitary gland is located, to the front of the occiput, the rear portion of the skull. This structure houses various anatomical structures and performs different functions; the *clivus*, in fact, offers a space for the passage of the spinal cord (Hofmann and Prescher 2012).

The *sella turcica* (pituitary fossa), on the other hand, is a bony depression located in the upper part of the base of the skull, containing the pituitary gland.

In 42.3% of the skulls observed, the bony surface of the *clivus* presents a vast osteosclerotic tissue with an irregular, often striated, and macroporous pattern of a roughly circular shape with well-defined borders and perfectly circumscribed margins, which involves the *dorsum sellæ* (Figure 3), generally characterized by bone remodeling and erosion. In the five of the cases examined (19.2%), one osteolytic lesion (ca. 0.5 cm) characterized by irregular shape with perfectly circumscribed margins affected the *sella turcica* (Figure 4). In 50% and 61.5% of cases, *aracnoid foveae* depression and meningeal vascular impressions were observed, respectively. The skulls (11.5% of) examined (OS479; OS493; OS497) show a severe chronic endocranial infection involving the frontal bone, characterized by intense periosteal bone proliferation with the apposition of new compact bone formation and microporosity (*woven* bone). Of these, only two cases (OS479; OS491) also involved the median ridge of bone that projects from the cribriform plate of the ethmoid bone (*crista galli*) (Figure 5). The others, such as OS493 and OS497, present mild inflammation of the endocranium at the level of the frontal bone, characterized by microporosity and

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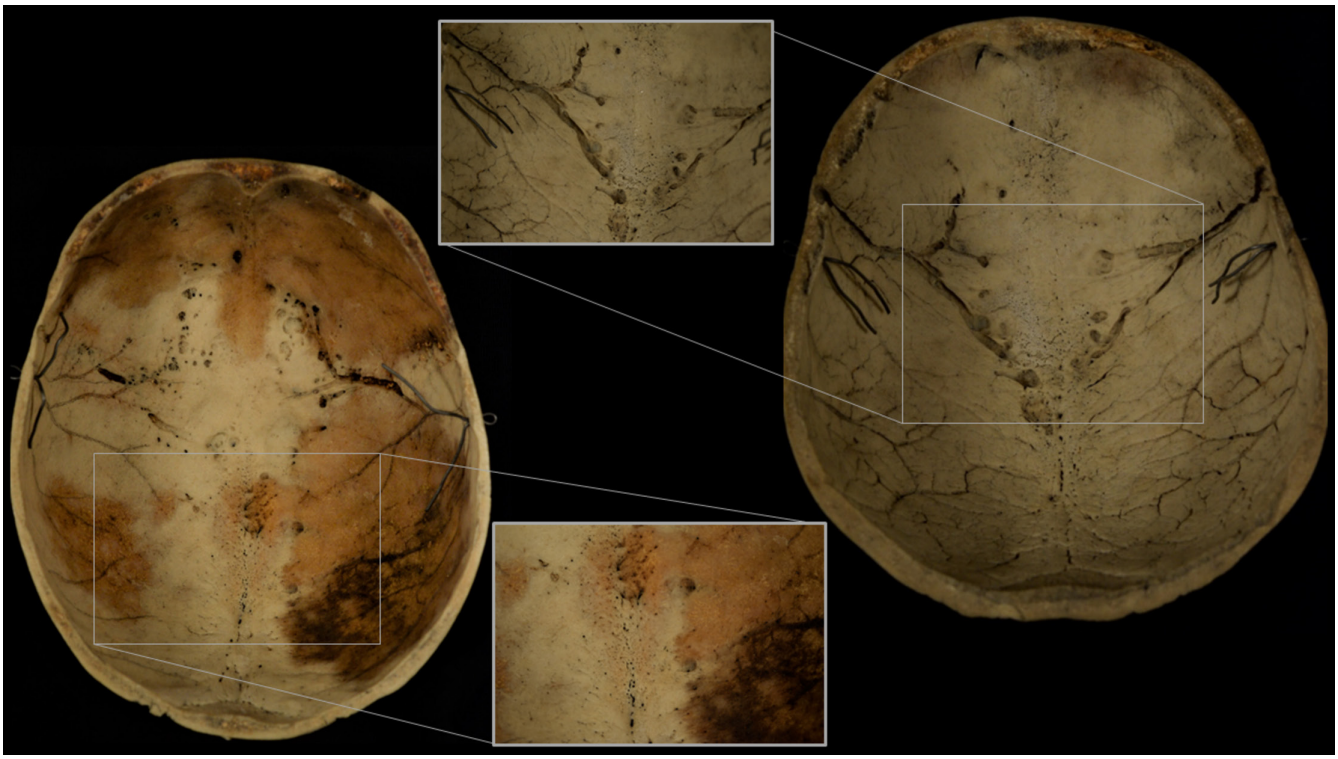

FIGURE 1 | The figures show serpentine endocranial lesions defined as *Serpens Symmetrical Endocrania*, located along the sagittal suture. These serpentine lesions are followed by marked impressions of meningeal vessels and impressions of the *arachnoid foveae*. [Colour figure can be viewed at wileyonlinelibrary.com]

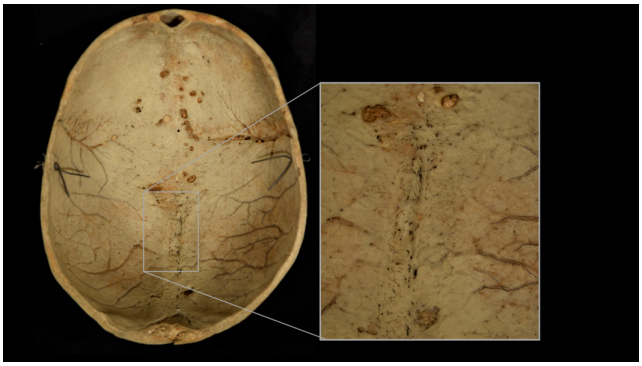

FIGURE 2 | The skull shows arachnoid impressions, marked impressions of the middle meningeal vessels and intracranial periostitis with bony plaques localized along the sagittal suture. [Colour figure can be viewed at wileyonlinelibrary.com]

granular imprints on the orbital part, as described in Spekker et al. (2020b).

3.1.3 | Porotic Hyperostosis, Greater Wing of the Sphenoid, and *Hyperostosis Cranialis Interna*

Porotic hyperostoses (*cribra orbitalia*, observed in seven skulls, and *cribra cranii*, observed in 14 skulls) are common stress indicators of chronic anemia, and widespread porosity of the skull, and are an indication of general inflammation of the scalp. Different degrees of porosity are indicated according to the scale of Brothwell (Brothwell 1981); therefore, it is necessary to distinguish the areas of the external surface of the cranial vault affected. In general, the grade of the *cribra cranii* observed in 10 out of 14 cases is porotic (grade 1), while in the remaining four skulls, it is cribrotic (grade 2), mainly involving the parietal bone bilaterally.

Of the 14 skulls showing *cribra cranii*, only five also present *cribra orbitalia* (grade 2, predominantly). The porotic hyperostosis here found is witnessed only in the form of simple cribrosity affecting the external cranial theca, while in only 11.5% of the cases, the pathology involved an increase in the thickness of the cranial theca (*hyperostosis*). Other lesions attributed to metabolic issues included *hyperostosis cranialis interna* (excessive endosteal bone growth in the cranium (Srinivasan et al. 2023) and porosity of the sphenoid bone. The first pathological condition is observed in two cases (OS479; OS491), while only in the OS499 skull, the sclerosing bone dysplasia affecting the skull base and the calvaria was localized at the level of the frontal bone (*hyperostosis frontalis interna*). Furthermore, severe bilateral cribrotic lesions were observed, involving the articular tubercle of the zygomatic process of the temporal bone (Figure 6) in the skulls OS479, OS484, and OS938. In the same location, bilateral abnormal microporosities were noted in OS493 and OS497, while OS492, OS937, OS490, and OS491 exhibited unilateral microporosities. These alterations affected 34.6% of the examined cases.

Twelve of the examined skulls (46.15% of cases) exhibited abnormal porosity localized in cortex of the greater wing of the sphenoid bone, bilaterally. Abnormal porosity is identified as a

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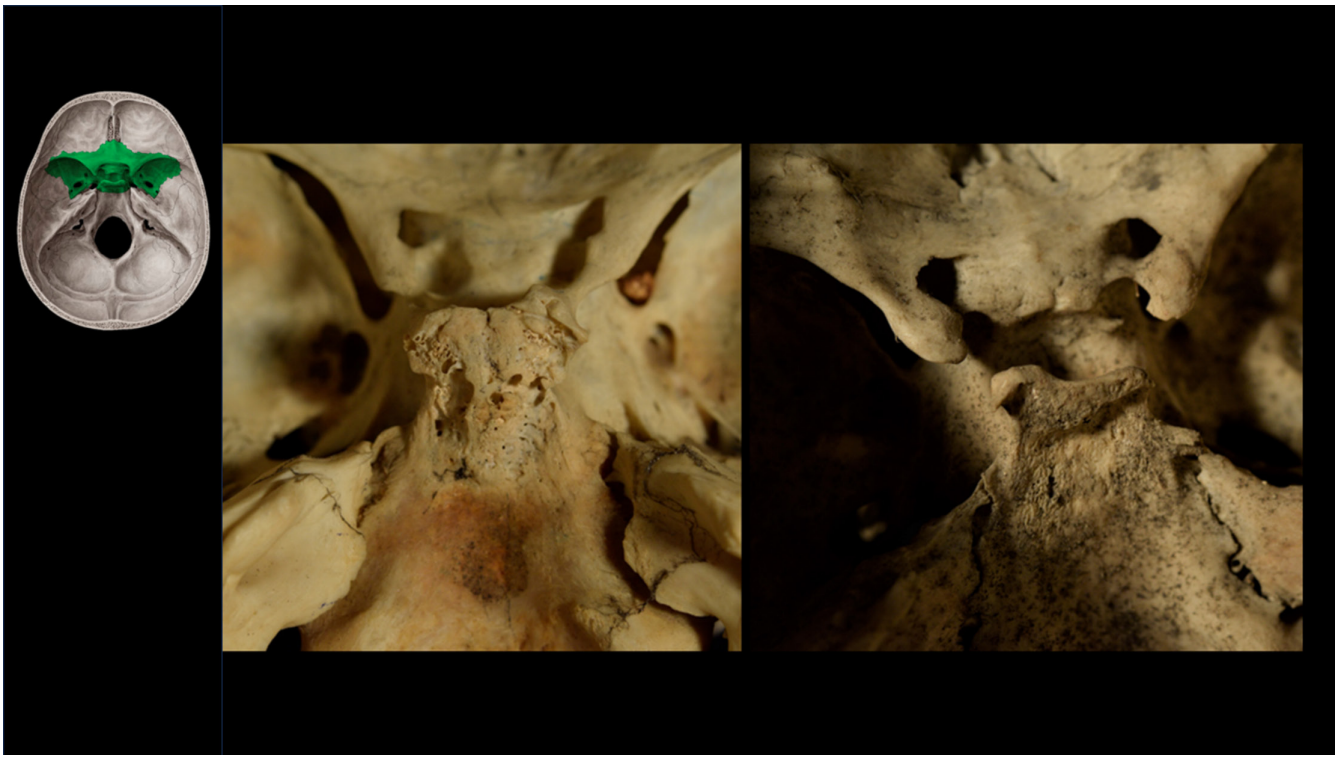

FIGURE 3 | Remodeling and erosion of the bone tissue of the *dorsum sellæ* and *clivus* in the sphenoidal bone region. [Colour figure can be viewed at wileyonlinelibrary.com]

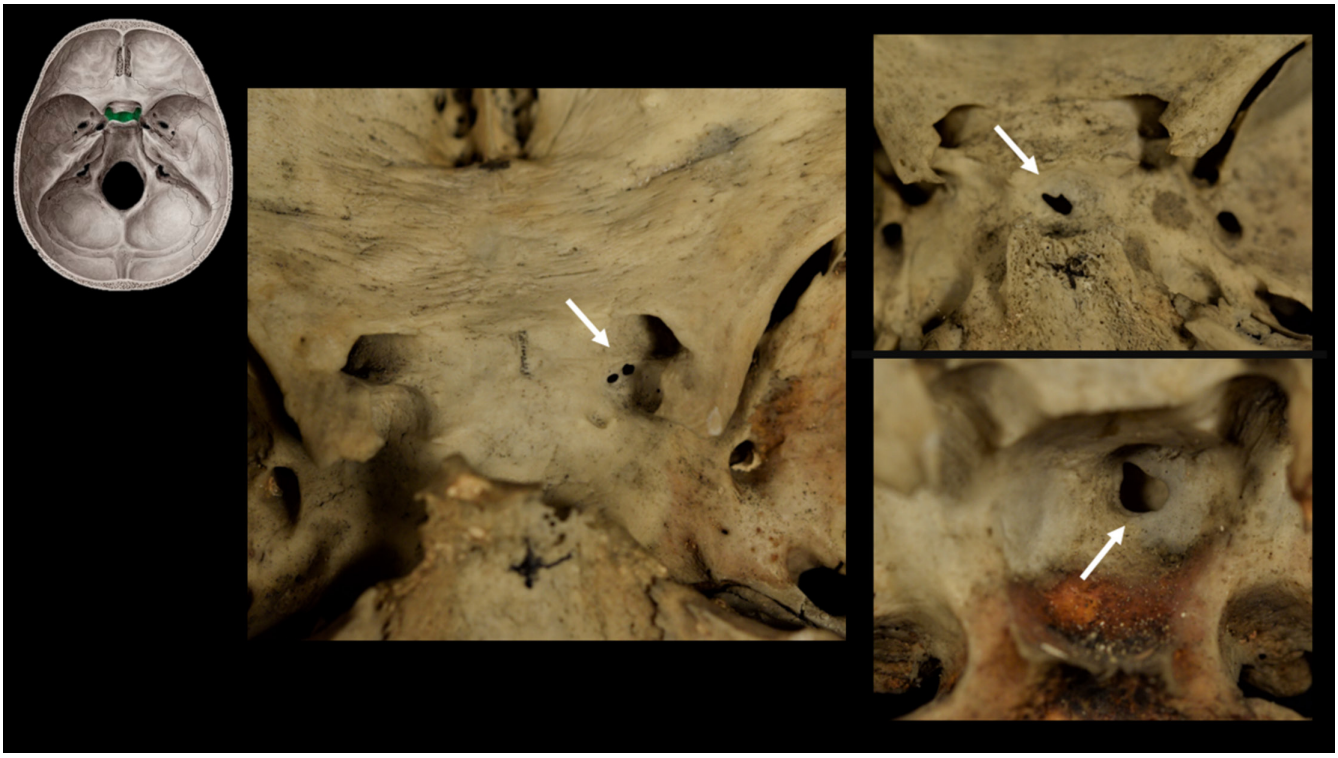

FIGURE 4 | The figure shows the pituitary fossa (or *sella turcica*) of three cranial samples characterized by osteolytic lesions of irregular shape and size with defined margins. [Colour figure can be viewed at wileyonlinelibrary.com]

pathological condition of the cortical bone, that is covered by holes, up to 1 mm in diameter, penetrating the lamellar bone surface (Ortner and Ericksen 1997). However, in the individual OS1460, a porosity of non-uniform in size and larger than 1 mm Ø was observed (Figure 7). Worthy of note, abnormal porosity was observed in the basilar part of occipital bone in 57.7% of the individuals, and, only in two cases, the cortical bone appears strongly remodeled (Figure 8).

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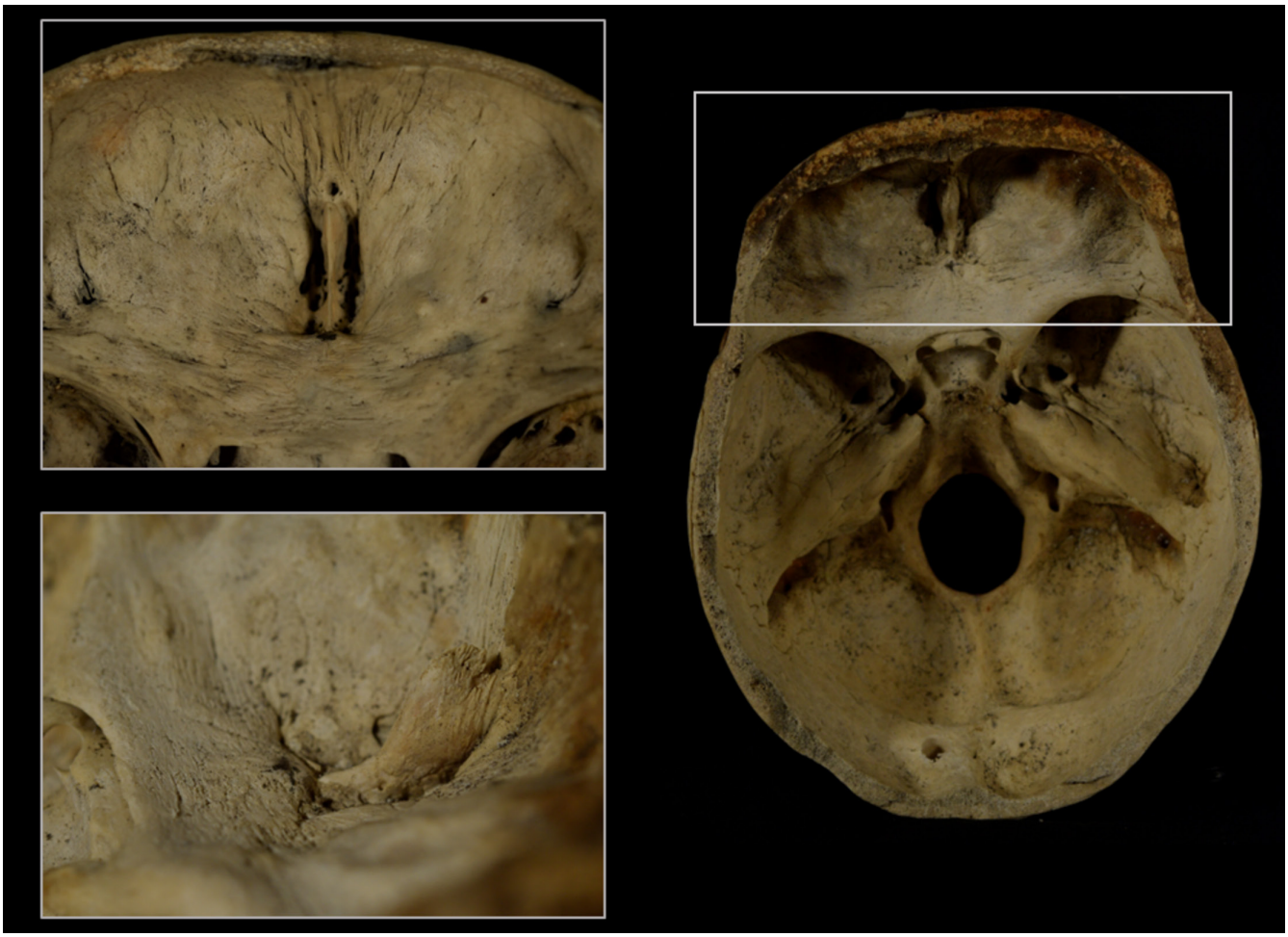

FIGURE 5 | The figure shows endocranial inflammation involving frontal bone. [Colour figure can be viewed at wileyonlinelibrary.com]

Usually, this lesion on the external surfaces of the greater wings is considered a pathognomic lesion of scurvy (Ortner and Putschar 1981; Ortner 2011; Ortner and Ericksen 1997).

3.1.4 | Hard Palate, Dental, and Oral Disease

According to the literature (Brenton and Paine 2007; Paine and Brenton 2006), the incidence of alveolar bone loss, dental caries, enamel hypoplasia, *cribra orbitalia*, and cranial pitting in crania affected by pellagra is high. Considering the skulls here examined, hard palate porosity, alveolar absorption, abscesses, and caries were present in 50%, 96.1%, and 80.7% of the cases, respectively.

3.2 | Cranial Anomalies for Non-Pellagrous Individuals

This section reports the pathological signs, and their degree of alteration, identified in the selected NP skulls . Table S2 shows the complete list of observed signs. Here too, as in Section 3.1, the skeletal anomalies are listed, carefully described and reporting their anatomical distribution. Not all the considered skulls previously underwent cranial vault opening, and this limited the direct investigation of the endocranial surface for some specimens. Although the use of the endoscope facilitated the observations, for many of these skulls (33.3%), the investigation remains complex due to the presence of encrusted sediments on the endocranial bone surface.

Of the 18 skulls examined, four out of these (OS3492; OS394; OS482; OS1492) have lesions attributable to tuberculosis or intrathoracic diseases such as S.E.S lesions (Hershkovitz et al. 2002; Spekker et al. 2020a), but only two crania of these exhibit marked impressions of meningeal vessels. The 39% of the skulls shows alteration of the *dorsum sellæ* and only 22.2% of the clivus. Of the NP group skulls selected, in 33.3% of the cases, abnormal porosity was observed in the basilar part of occipital bone, while in 44.4%, it also affected the great wing of the sphenoid, bilaterally. Porotic hyperostosis was observed in six out of 18 skulls: cribrotic *cribra orbitalia*, was observed in two skulls (grades 1–2, bilaterally), and *cribra cranii* was observed in five skulls. The identified *cribra cranii* is predominantly grade 1 (Brothwell 1981) porotic type and involves the parietal bones bilaterally; only for OS1444, it is of grade 2 (Brothwell 1981), and in OS1349 and OS1444, it is widespread over part of the frontal bone. Dental caries and oral infections, alveolar atrophy and hard palate porosity were detected in 72.2%, 66.6%, and 55.5% of the cases, respectively. Among the other pathological lesions observed, only OS482, who died from chronic

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FIGURE 6 | Cribrotic lesion of the bone tissue located on the articular tubercle of the zygomatic process. [Colour figure can be viewed at wileyonlinelibrary.com]

FIGURE 7 | Surface of the greater wing of the sphenoid bone presenting micro- and macro-porosity (bilateral) in an individual suffering from nervous disease (OS1460). [Colour figure can be viewed at wileyonlinelibrary.com]

dementia-tuberculosis, presents *internal cranial hyperostosis* (Srinivasan et al. 2023).

3.3 | $\delta^{13}C$ and $\delta^{15}N$ Stable Isotope Analysis

The sample set was preliminarily screened for the preservation of collagen by measuring the molar C/N ratio of all samples, which resulted of 3.25 ± 0.18 on average (the uncertainty is given as standard deviation), that is, within the range of well-preserved collagens. None of the samples yielded a C/N ratio outside of the range 2.9–3.6 (Schoeninger and DeNiro 1984), implying that collagen is well preserved in all samples. Hence, all samples are included in the following description and discussions.

By comparing the results of C and N stable isotope analyses, $\delta^{13}C$ values range from −19.26‰ to −10.71‰ and from −19.11‰ to −12.11‰, whereas $\delta^{15}N$ values range from 8.14‰ to 12.05‰ and from 8.46‰ to 11.98‰ for NPs and Ps, respectively (Table S4; Figure 9). Even though a clear separation of the two group of samples is not evident based on the range and mean values, the kernel density estimation (KDE) may represent a

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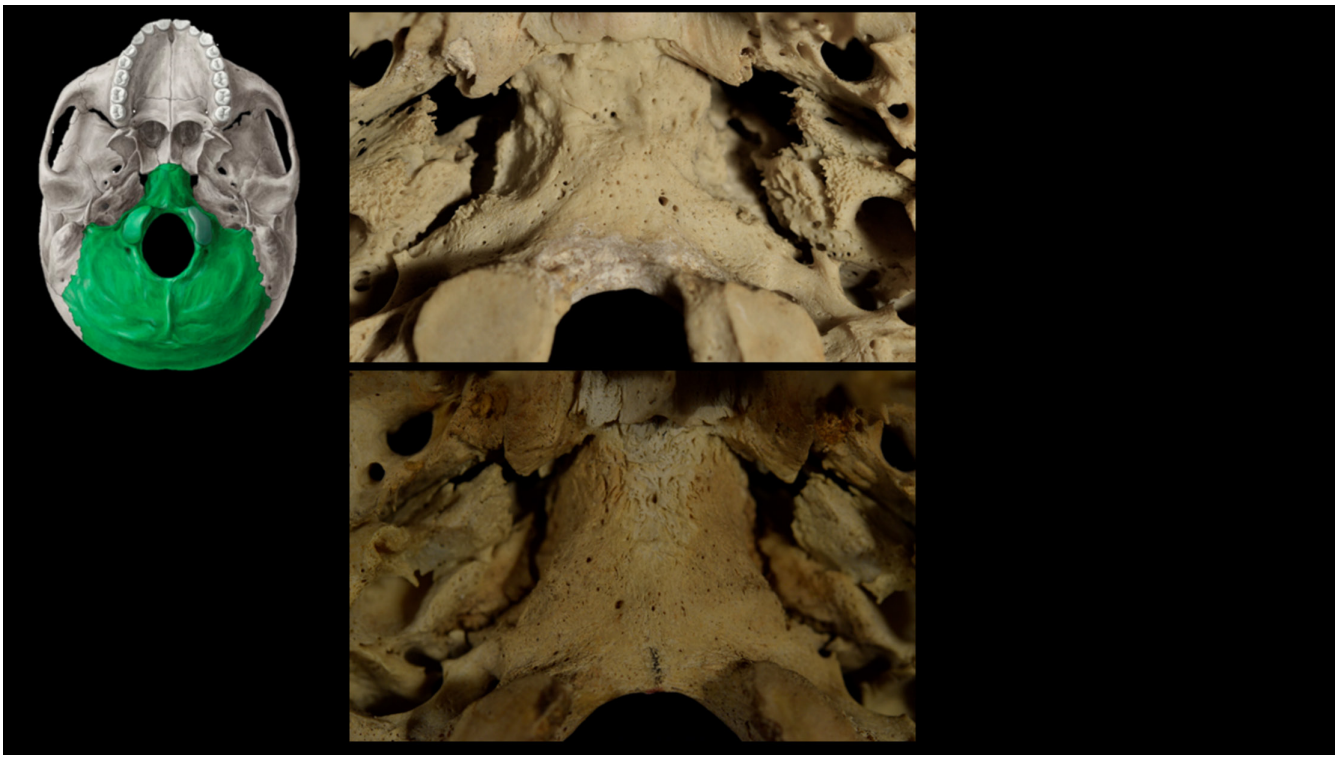

FIGURE 8 | Cortical anterior surface of the basilar part of occipital bone showing porous and remodeled bone. [Colour figure can be viewed at wileyonlinelibrary.com]

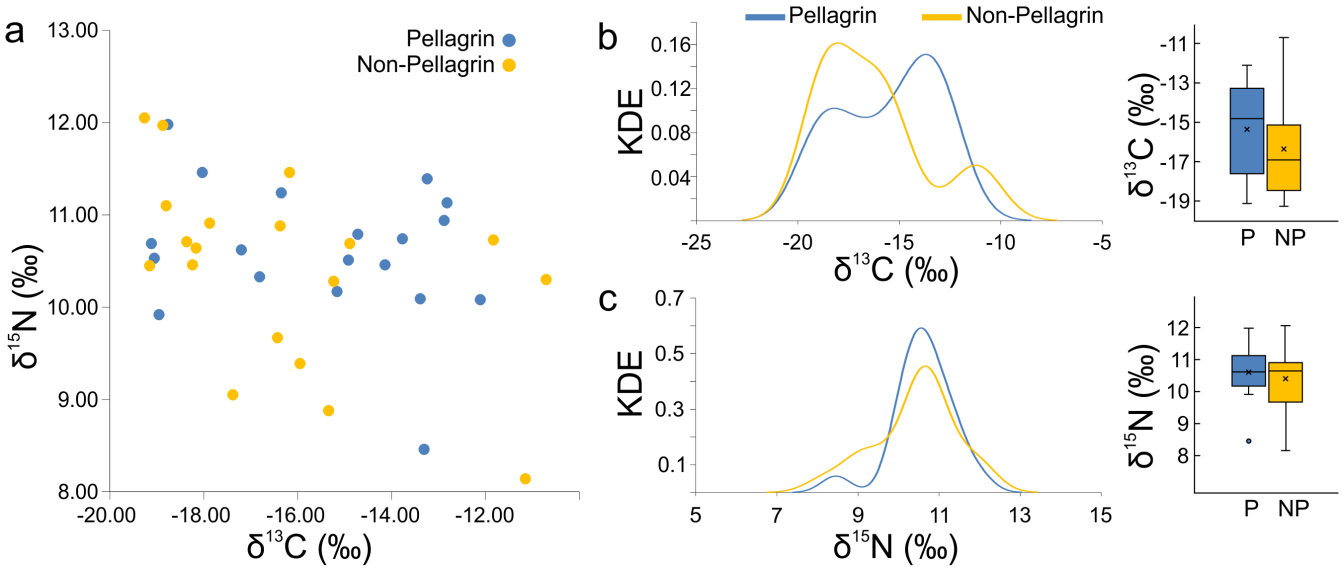

FIGURE 9 | (a) Scatter plot of $\delta^{13}C$ against $\delta^{15}N$ values obtained for pellagrin (blue) and non-pellagrous (yellow) samples. Kernel density estimation (KDE) and boxplot of (b) $\delta^{13}C$ values and (c) $\delta^{15}N$ values for pellagrous (blue) and non-pellagrous (yellow) samples. [Colour figure can be viewed at wileyonlinelibrary.com]

convenient tool for data representation and interpretation. A KDE function was calculated for both $\delta^{13}C$ and $\delta^{15}N$ data for non-pellagrous and pellagrous samples (Figure 9) (software available at www.rsc.org/amc by the Analytical Methods Committee of the Royal Society of Chemistry) by replacing each experimental value with a normal function centered on the same value and with a standard deviation depending on the smoothing parameter *h*, which is statistically determined (Silverman 1986). The KDE function is then obtained by normalizing to a unit area the sum of each normal distribution, thus representing the density function for the two groups of samples without any assumption for their distributions Figure 9. The KDE functions of $\delta^{15}N$ values for non-pellagrous and pellagrous samples are very similar, with frequency distributions peaked at about 10.50 ‰. Conversely, the frequency distribution of $\delta^{13}C$ values for pellagrous samples differs from

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that of non-pellagrous samples, as a more pronounced peak occurs at higher values. This is also highlighted by box plots representing the distribution of $\delta^{13}C$ and $\delta^{15}N$ values for the two set of samples (Figure 9).

4 | Discussion

4.1 | Differential Analysis

Lesions examined during paleopathological analysis could be caused by various diseases such as chronic meningitis, neoplasia, scurvy, and even tuberculosis (Table S5).

4.1.1 | Meningioma

Meningioma is the most common non-primary intracranial tumor of arachnoid origin in adults. In 1922, Harvey Cushing first used the term "meningioma" to describe a series of brain and spinal cord tumors that develop near the meninges (Brown et al. 2023; Cushing 1922). It is a neoplasm derived from the arachnoid cap cells of the leptomeninges, and it is the most common intracranial tumor (Brown et al. 2023; Cook and Danforth 2022; Waldron 2008).

This neoplasia is the most common benign tumor of the central nervous system and can cause various lesions on the skull such as cranial bone hyperostosis, vascular and aracnoidal depressions and impressions, and sclerotic lesions (Cook and Danforth 2022; Zada and Jensen 2016). Patients affected by meningioma can present progressive headaches, vertigo, paralysis, epilepsy, behavioral/cognitive change, seizures, and neurological deficits such as localized weakness, homonymous hemianopsia (Brown et al. 2023), symptoms that are similar to those caused by the pellagrous condition (Oldham and Ivkovic 2012). The age of maximum incidence of cancer is around 40–60 years with an increasing incidence over 65 years (Ostrom et al. 2015). In adults, meningiomas predominantly affect women, with an F:M ratio of 2:1 for intracranial tumors (Commins, Atkinson, and Burnett 2007). Meningioma is excluded from the differential analysis as the presence of porotic hyperostosis involving the external table of the calvaria is generally found. This pathognomic sign of the benign tumor was not found in the majority of cases here examined, as only three individuals (OS479; OS491; OS499) present the hyperostosis involving the external table.

4.1.2 | Tuberculous Meningitis

Tuberculous meningitis (TBM) (Manyelo et al. 2021; Marx and Chan 2011) is the most common form of intracranial tuberculosis and usually refers to infection of the leptomeninges, affecting more frequently children and adolescents rather than adults (Miftode et al. 2015). Aracnoidal impressions near blood vessels on the inner surface of the skull have been considered to be pathognomonic of TBM (Spekker et al. 2020a; Spekker et al. 2020b). Other characteristic lesions of the disease are the intracranial porosity associated to small serpentine canals involving the frontal, parietal, and occipital bones bilaterally, without involving the temporal and sphenoid bones (*Serpens Symmetrical Endocrania*). These lesions can be associated with TBM, but they are not pathognomic of the disease. TBM is a secondary form of tuberculosis and generally appears in people with intrathoracic tuberculosis (Hershkovitz et al. 2002; Manyelo et al. 2021). Despite the absence of post-cranial districts, direct observation of the skulls enables one to exclude the disease as the porosities and small intracranial canals with a non-serpentine shape are accompanied by the presence of plates of newly formed compact bone tissue and new formation of porous subperiosteal bone, generally located along the sagittal and frontal bone.

This type of alteration does not appear in TBM cases.

4.1.3 | Scurvy

Scurvy is a condition caused by a severe and prolonged vitamin C deficiency and can be caused by a poor diet based on cereals, lacking in vitamin C (Mays 2014; Ortner 2003).

Nonspecific signs of the disease are generic and include porosity on maxillary palate, slight *cribra orbitalia* e *cribra cranii*, porosity of the greater wing of the sphenoid, and serious alveolar resorption with teeth loss and caries (Ortner 2003; Ortner and Ericksen 1997; Snoddy et al. 2018). In most of the analyzed skulls, no hyperostosis of the cranial vault was observed in the parietal and/or squamous temporal bone, as well as abnormal porosity on the anterior-medial surface of the zygomatic bone and on the internal surface of the mandibular rami and coronoid process. The endocranial alterations, highlighted in the literature, on individuals suffering from scurvy are mainly porosities, usually caused by hematoma, as reported in Barlow (1883) in an autopsy of a scurvy individual. In the cases here examined, no ectocranial trauma was observed in correspondence with the intracranial inflammatory lesions. Indeed, subdural hematomas are a clinically reported complication of scorbutic hemorrhage (Ingalls 1936).

Despite scurvy is still a disease to be investigated at a skeletal level in archaeological contexts, the intracranial inflammation (sometimes associated to the bone remodeling of *clivus*), meningeal and arachnoidal imprints, presence of plaques of newly formed compact bone tissue, and porous subperiosteal new bone formation on sagittal and frontal bone could be tentatively attributed for cases of pellagra with non-specific signs such as dental caries, severe alveolar absorption, slight *criba cranii*, and sphenoidal porosity.

4.2 | Diet Reconstruction

Considering both NPs and Ps, the relatively low $\delta^{15}N$ values despite the significant variation range of $\delta^{13}C$ values are compatible with a diet characterized by moderate input of terrestrial or freshwater animal protein, but poor in marine sources (Curto et al. 2019; Schoeninger and DeNiro 1984). The lack of marked differences in the frequency distributions of $\delta^{15}N$ values between non-pellagrous and pellagrous samples suggests that the extent of protein consumption did not influence the onset of

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the disease. On the other hand, the intragroup $\delta^{15}N$ variability reflects a poor to moderate protein consumption in the diet of the analyzed individuals, highlighting significant differences in their lifestyle and accessibility to diverse food resources (Holder et al. 2017; Reitsema and Vercellotti 2012; Scorrano et al. 2014). Nevertheless, the actual protein consumption may be lower if considering that a slight $\delta^{15}N$ enrichment can be caused by fasting or nutritional stress (Hertz et al. 2015; Walter et al. 2020).

The wide range of variability of $\delta^{13}C$ values indicates a substantially different diet among individuals belonging to the same group. Intragroup variability ranges from a predominantly C3-based diet, for the most negative values, to a mixed diet with increasingly higher input from C4 plants, reasonably linked to maize consumption, for the less negative values (Holder et al. 2017; Rumolo et al. 2020). Notably, the KDE analysis and the box plot of $\delta^{13}C$ values (Figure 9) show that the P group is mostly represented by individuals with a higher C4 plant input in their diet with respect to the NP. This is particularly relevant, showing that the isotopic signature of bone collagen, indicating a prolonged maize consumption, could be linked to the diagnosis of pellagra. Nevertheless, moderate to predominant C4 plant input in the diet of non-pellagrous individuals, as well as poor protein consumption, is not unexpected considering that all the individuals here analyzed were living in the same geographical area (the northern part of Italy) where maize has been a staple-food for the majority of the population, and within socio-economic conditions experienced by the lower social classes living at the end of the 19th century and beginning of the 20th century. Table S4 reports stable isotope data for non-pellagrous and pellagrous samples.

4.3 | Comparison Between Pathological Observation and Diet

From the point of view of paleopathological–anthropological observation, the solutions to the enigma of pathognomic signs of pellagra may be within reach. In the 1883, the forensic doctor Giuseppe Silvio Tonnini in the article "Spinal disorders in pellagrins. Clinical and anatomical study" describes a series of symptoms and clinical signs associated with pellagra, such as asymmetry of the spinal axis, hyperemia, softening, pigmentation of the cells of the anterior and posterior horns, and degeneration of the lateral cords (Tonnini 1883). The psychiatrist Ernesto Belmondo, first director of the provincial psychiatric hospital of Padova (Veneto, Italy) in 1906, confirmed Tonnini's clinical observations. Belmondo dedicated part of his studies to the examination of spinal cord lesions in patients suffering from pellagra (Belmondo 1889). During his studies, he observed and described, in acute cases of pellagra, meningoencephalomyelitis (Belmondo 1889).

Meningomyelitis is an inflammatory disease caused by various bacterial or viral infections that involves the spinal cord and transmitted to the meninges (Coyle 1999; Young 2016). It can be limited to the spinal cord or affecting the entire central nervous system (meningoencephalomyelitis) (Coyle 1999; Young 2016). When pellagra progresses to an advanced stage and involves the central nervous system, it can lead to inflammation of the meninges, brain, and spinal cord. Moreover, nutritional deficiency–induced lesions in the brainstem and cerebellum are reported by Piercecchi-Marti et al. (2004). In the cited study, neuronal lesions involving the pontine nuclei and cerebellar dentate nuclei, as well as the cranial nerve nuclei (third, sixth, seventh, and eighth), reticular, and arcuate nuclei, were identified. Additionally, noteworthy for our study are the alterations involving the cerebral cortex and the central mesencephalic gray matter (Piercecchi-Marti et al. 2004). Symptoms of meningoencephalomyelitis in relation to pellagra may include confusion, delirium, headache, muscle weakness, progressive paralysis, insomnia, and convulsions (Young 2016). From the observation of skulls of the NP group emerges that the pathologies with the highest incidence are porosity of the large wing of the sphenoid as well as oral infections. The isotopic results of this group would confirm a C4 plant-based but not monophagic diet. These data would confirm that the high incidence of oral infections is due, in addition to poor oral hygiene, to the predominant intake of carbohydrates. It is worth mentioning that information on the diet retrieved by C-N stable isotopes of bone collagen is averaged over the last ~10 years of life of the individual, because of the lifelong process of bone remodeling that entirely replaces skeletal tissues in ca. 10 years. Therefore, diet reconstruction provides information on long-term nutritional behavior within a timeframe that may differ to that spanning from the onset and manifestation of pellagra to the death of the individual. For these reasons, a certain degree of discrepancies between the recorded dietary C4 plant input and the manifestation of pellagra may occur and has to be taken into account in the discussion when linking pathological signs and the attested onset of the disease to diet reconstruction.

As previously discussed, considering the societal and economic conditions of the analyzed individuals, poor protein consumption and prominent maize consumption are not surprising. If we compare paleopathological observations with the isotopic signature, individual OS1492 shows a predominantly maize-based diet and pathological signs that were identified as diagnostic of pellagra, despite the reported cause of death is tuberculosis/madness. Indeed, on the bases of both diet information and pathological analysis, we cannot exclude the occurrence of a severe hypovitaminosis. The other two NP samples OS1437 and OS1601, besides the above mentioned OS1492, that show an isotopic signal strongly linked to maize consumption, do not present any pathological signs linked to endocranial alterations, thus, the presence of the disease could be excluded. If we consider that the samples investigated came from mental asylums and civil hospitals, the medical observations of the patient as well as the clinical course and the remedies adopted for the treatment are reported in the files preserved in the archives of two of the largest Venetian mental asylums (San Servolo (1842) and San Clemente (1873), Venice) (Gentilcore and Priani 2023). As reported in Gentilcore and Priani (2023), among the products administered most frequently to pellagrous patients to combat the disease were, for example, tamarindus decoction, lemonade, dairy products, and meat broth as well as purgatives and emetics. It could be assumed that these remedies were widely used among hospitals and sanatoriums and this could explain our isotopic data collected.

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5 | Limitations of the Study

The endoscope did not permit an accurate examination of the endocranial vault due to the limitations of the instrument, which prevented the acquisition of high-definition images. The primary technical parameters of the endoscope, such as camera resolution, significantly influenced the results. Many of the non-craniotomized skulls from cemeteries exhibited encrustations of soil sediments as well as erosive diagenetic alterations on the periosteal surface, complicating the observation process. Nevertheless, the use of the endoscope enhanced general paleopathological observations without causing destruction to skeletal material. Another limitation concerns the composition of the osteological collection, as it predominantly consists of cranial remains and lacks post-cranial remains, thereby significantly restricting the paleopathological investigation. This study aims to serve as a foundation for necessary comparative studies with other historical populations, as a starting point towards understanding pathological diagnoses linked to Pellagra, providing more general information about the health status of ancient populations and allowing for further studies.

6 | Conclusions

In conclusion, in severe cases of pellagra, for its diagnosis in ancient skeletal and archaeological collections, the useful pathological signs at the cranial level could be bone alterations of the *clivus*, *dorsum sellæ* followed by S.E.S, meningeal vascular impressions, and articular tubercle of the zygomatic process of the temporal bone associated with nonspecific signs such as dental caries, severe alveolar absorption, *criba cranii*, sphenoid, and hard palate porosity. We hope that these considerations can favor diagnostic observation by allowing greater consistency in the certainty of the diagnosis, facilitating greater comparability in research. Furthermore, we hope that this work contributes to the understanding of adaptations and variability among past communities by more confidently identifying severe niacin deficiency.

Author Contributions

Nicola Carrara: conceptualization, data curation, resources, writing – review and editing. **Gregorio Dal Sasso:** data curation, formal analysis, investigation, visualization, validation, writing – original draft, writing – review and editing. **Anna Addis:** investigation, formal analysis, validation. **Anna Domanico:** investigation, formal analysis. **Nereo Preto:** formal analysis (supporting), investigation (supporting), resources, validation, writing – review and editing. **Elisa Saler:** investigation, data curation. **Telmo Pievani:** conceptualization, supervision, funding acquisition, writing – review and editing. **Gilberto Artioli:** conceptualization, supervision, funding acquisition, writing – review and editing. **Cinzia Scaggion:** conceptualization, investigation, data curation, validation, visualization, formal analysis, writing – original draft, writing – review and editing.

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Data Availability Statement

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

References

Aufderheide, A. C., and C. Rodriguez-Martin. 2011. *The Cambridge Encyclopedia of Human Paleopathology (Cambridge).* Cambridge: Cambridge University Press.

Barlow, T. 1883. "On Cases Described as "Acute Rickets" Which Are Probably a Combination of Scurvy and Rickets, the Scurvy Being an Essential, and the Rickets a Variable, Element." *Journal of the Royal Society of Medicine* MCT-66, no. 1: 159–219. https://doi.org/10.1177/095952878306600112.

Baxarias, J., and J. Herrerin. 2008. *The Handbook Atlas of Paleopathology.* Zaragoza: Zaragoza: Editorial Pórtico.

Belmondo, E. 1889. *Le alterazioni anatomiche del midollo spinale nella Pellagra*. Riforma Medica.

Bonfigli, C. 1881. *I pellagrosi accolti nel manicomio provinciale di Ferrara durante l'anno 1879.* Vol. 128. Ferrara: Bozzetti Clinici Da Servire Allo Studio Della Pellagra.

Brenton, B. P., and R. R. Paine. 2007. "Reevaluating the Health and Nutritional Status of Maize-Dependent Populations: Evidence for the Impact of Pellagra on Human Skeletons From South Africa." *Ecology of Food and Nutrition* 46, no. 5–6: 345–360. https://doi.org/10.1080/03670240701486545.

Brothwell, D. R. 1981. *Digging up Bones*. Ithaca, New York: Oxford University Press.

Brothwell, M., and D. Brothwell. 2016. "Evidence for Ancient Meningiomas and a Probable Case From Medieval Tarbat, Scotland." *International Journal of Paleopathology* 13: 65–69. https://doi.org/10.1016/j.ijpp.2016.01.004.

Brown, N. J., Z. Pennington, C. C. Kuo, et al. 2023. "Meningioma: A Biography-Tumor Forever Tied to the Origins and "Soul of Neurosurgery"." *World Neurosurgery* 178: 191–201. https://doi.org/10.1016/j.wneu.2023.07.126.

Carpenter, K. J. 1983. "The Relationship of Pellagra to Corn and the Low Availability of Niacin in Cereals." *Nutrition Today* 54: 197–222. https://doi.org/10.1007/978-3-0348-6540-1_12.

Carrara, N., C. Scaggion, and E. Holland. 2018. "The Tedeschi Collection: A Collection of Documented and Undocumented Human Skeletal Remains at the Museum of Anthropology, Padua University (Italy)." *American Journal of Physical Anthropology* 166, no. 4: 930–933. https://doi.org/10.1002/ajpa.23471.

Chamlagain, B., S. Rautio, M. Edelmann, V. Ollilainen, and V. Piironen. 2020. "Niacin Contents of Cereal-Milling Products in Food-Composition Databases Need to Be Updated." *Journal of Food Composition and Analysis* 91: 103518. https://doi.org/10.1016/j.jfca.2020.103518.

Commins, D. L., R. D. Atkinson, and M. E. Burnett. 2007. "Review of Meningioma Histopathology." *Joirnal of Neurosurgery* 23, no. n. 4: E3. https://doi.org/10.3171/FOC-07/10/E3.

Cook, D. C., and M. E. Danforth. 2022. "Meningiomas in Ancient Human Populations." *Cancers* 14, no. 4: 1058. https://doi.org/10.3390/cancers14041058.

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Coyle, P. K. 1999. "Overview of Acute and Chronic Meningitis." *Neurologic Clinics* 17, no. 4: 691–710. https://doi.org/10.1016/S0733-8619(05)70162–6.

Curto, A., P. Mahoney, A.-F. Maurer, C. Barrocas-Dias, T. Fernandes, and G. E. Fahy. 2019. "Diet and Disease in Tomar, Portugal: Comparing Stable Carbon and Nitrogen Isotope Ratios Between Skeletons With and Without Signs of Infectious Disease." *Journal of Archaeological Science* 105: 59–69. https://doi.org/10.1016/j.jas.2019.03.005.

Cushing, H. 1922. "The Meningiomas (Dural Endotheliomas): Their Source, and Favoured Seats of Origin." *Brain* 45, no. 2: 282–316. https://doi.org/10.1093/brain/45.2.282.

Fisher, R. A. 1922. "On the Interpretation of χ^2 From Contingency Tables, and the Calculation of P." *Journal of the Royal Statistical Society* 85, no. 1: 87. https://doi.org/10.2307/2340521.

Gentilcore, D., and E. Priani. 2023. "Experiencing the Asylum." https://doi.org/10.1007/978-3-031-22496-6_8.

Gillman, J., and T. Gillman. 1951. "Perspectives in Human Malnutrition: A Contribution to the Biology of Disease From a Clinical and Pathological Study of Chronic Malnutrition and Pellagra in the African."

Ginnaio, M. 2012. "La pellagre en Italie à la fin du XIXe siècle : les effets d'une maladie de carence." *Population* 66, no. 3: 671–698. https://doi.org/10.3917/popu.1103.0671.

Ginnaio, M., and A. Jacobs. 2011. "Pellagra in Late Nineteenth Century Italy: Effects of a Deficiency Disease." *Population* 66, no. 3/4: 583–609 Retrieved from https://www.jstor.org/stable/41488615.

Goodman, A., D. L. Dufour, and G. H. Pelto. 2000. "Nutritional Anthropology: Biocultural Perspectives on Food and Nutrition."

Hegyi, J., R. A. Schwartz, and V. Hegyi. 2004. "Pellagra: Dermatitis, Dementia, and Diarrhea." *International Journal of Dermatology* 43, no. 1: 1–5. https://doi.org/10.1111/j.1365-4632.2004.01959.x.

Hershkovitz, I., C. M. Greenwald, B. Latimer, et al. 2002. "Serpens Endocrania Symmetrica (SES): A New Term and a Possible Clue for Identifying Intrathoracic Disease in Skeletal Populations." *American Journal of Physical Anthropology* 118, no. 3: 201–216. https://doi.org/10.1002/ajpa.10077.

Hershkovitz, I., C. Greenwald, B. M. Rothschild, et al. 1999. "Hyperostosis Frontalis Interna: An Anthropological Perspective." *American Journal of Physical Anthropology* 109, no. 3: 303–325. https://doi.org/10.1002/(SICI)1096–8644(199907)109:3<303::AID-AJPA3>3.0.CO;2-I.

Hertz, E., M. Trudel, M. K. Cox, and A. Mazumder. 2015. "Effects of Fasting and Nutritional Restriction on the Isotopic Ratios of Nitrogen and Carbon: A Meta-Analysis." *Ecology and Evolution* 5, no. 21: 4829–4839. https://doi.org/10.1002/ece3.1738.

Hofmann, E., and A. Prescher. 2012. "The Clivus." *Clinical Neuroradiology* 22, no. 2: 123–139. https://doi.org/10.1007/s00062-011-0083-4.

Holder, S., T. L. Dupras, R. Jankauskas, L. Williams, and J. Schultz. 2017. "Reconstructing Diet in Napoleon's Grand Army Using Stable Carbon and Nitrogen Isotope Analysis." *American Journal of Physical Anthropology* 163, no. 1: 53–63. https://doi.org/10.1002/ajpa.23184.

Ingalls, T. 1936. "The Role of Scurvy in the Etiology of Chronic Subdural Hematoma." *New England Journal of Medicine* 215, no. 27: 1279–1281. https://doi.org/10.1056/NEJM193612312152704.

Jaworek, A. K., A. Łazarczyk, P. Hałubiec, M. Leończyk, F. Staszewski, and A. Wojas-Pelc. 2021. "The History of Pellagra." *Dermatology Review* 108, no. 6: 554–566. https://doi.org/10.5114/dr.2021.114610.

Koduri, M. M., and R. S. Tubbs. 2023. "Anatomy of the Arachnoid Granulations." In *Cerebrospinal Fluid and Subarachnoid Space*, edited by R. S. Tubbs, 153–168. Elsevier. https://doi.org/10.1016/B978-0-12-819509-3.00016-X.

Manyelo, C. M., R. S. Solomons, G. Walzl, and N. N. Chegou. 2021. "Tuberculous Meningitis: Pathogenesis, Immune Responses, Diagnostic Challenges, and the Potential of Biomarker-Based Approaches." *Journal of Clinical Microbiology* 59, no. 3: e01771–e01720. https://doi.org/10.1128/JCM.01771–20.

Marx, G. E., and E. D. Chan. 2011. "Tuberculous Meningitis: Diagnosis and Treatment Overview." *Tuberculosis Research and Treatment* 2011: 1–9. https://doi.org/10.1155/2011/798764.

Mays, S. 2014. "The Palaeopathology of Scurvy in Europe." *International Journal of Paleopathology* 5: 55–62. https://doi.org/10.1016/j.ijpp.2013.09.001.

Miftode, E. G., O. S. Dorneanu, D. A. Leca, et al. 2015. "Tuberculous Meningitis in Children and Adults: A 10-Year Retrospective Comparative Analysis." *PLoS ONE* 10, no. 7: e0133477. https://doi.org/10.1371/journal.pone.0133477.

Oldham, M. A., and A. Ivkovic. 2012. "Pellagrous Encephalopathy Presenting as Alcohol Withdrawal Delirium: A Case Series and Literature Review." *Addiction Science & Clinical Practice* 7, no. 1: 12. https://doi.org/10.1186/1940-0640-7-12.

Ortner, D. 2008. "Differential Diagnosis of Skeletal Lesions in Infectious Disease." In *Advances in Human Paleopathology*, edited by S. Pinhasi and R. Mays, 191–214. Chichester: John Wiley and Sons Ltd.

Ortner, D. J. 2003. *Identification of Pathological Conditions in Human Skeletal Remains*. Elsevier. https://doi.org/10.1016/B978-0-12-528628-2.X5037-6.

Ortner, D. J. 2011. "Human Skeletal Paleopathology." *International Journal of Paleopathology* 1, no. 1: 4–11. https://doi.org/10.1016/j.ijpp.2011.01.002.

Ortner, D. J., and M. F. Ericksen. 1997. "Bone Changes in the Human Skull Probably Resulting From Scurvy in Infancy and Childhood." *International Journal of Osteoarchaeology* 7, no. 3: 212–220. https://doi.org/10.1002/(SICI)1099–1212(199705)7:3<212::AID-OA346>3.0.CO;2–5.

Ortner, D. J., and W. G. J. Putschar. 1981. *Identification of Pathological Conditions in Human Skeletal Remains*. Washington: Smithsonian Institution Press.

Ostrom, Q. T., H. Gittleman, J. Fulop, et al. 2015. "CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2008–2012." *Neuro-Oncology* 17, no. suppl 4: iv1–iv62. https://doi.org/10.1093/neuonc/nov189.

Paine, P. R., and B. Brenton. 2006. "The Paleopathology of Pellagra: Investigating the Impact of Prehistoric and Historical Dietary Transitions to Maize." *Journal of Anthropological Sciences* 84: 125–135.

Passariello, I., P. Simone, J. Tandoh, et al. 2012. "Characterization of Different Chemical Procedures for ^{14} C Dating of Buried, Cremated, and Modern Bone Samples at Circe." *Radiocarbon* 54, no. 3–4: 867–877. https://doi.org/10.1017/S0033822200047512.

Pelton, J. T., and L. R. McLean. 2000. "Spectroscopic Methods for Analysis of Protein Secondary Structure." *Analytical Biochemistry* 277, no. 2: 167–176. https://doi.org/10.1006/abio.1999.4320.

Piercecchi-Marti, M.-D., A.-L. Pélissier-Alicot, G. Leonetti, J.-P. Tervé, F. Cianfarani, and J.-F. Pellissier. 2004. "Pellagra." *American Journal of Forensic Medicine & Pathology* 25, no. 4: 342–344. https://doi.org/10.1097/01.paf.0000136589.28903.e5.

Prabhu, D., R. S. Dawe, and K. Mponda. 2021. "Pellagra a Review Exploring Causes and Mechanisms, Including Isoniazid-Induced Pellagra." *Photodermatology, Photoimmunology & Photomedicine* 37, no. 2: 99–104. https://doi.org/10.1111/phpp.12659.

Rajakumar, K. 2000. "Pellagra in the United States: A Historical Perspective." *Southern Medical Journal* 93, no. 3: 272–277 Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10728513.

10991212, 2025, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/oa.3400 by University Of Padova Center Di, Wiley Online Library on [15/04/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Reitsema, L. J., and G. Vercellotti. 2012. "Stable Isotope Evidence for Sex- and Status-Based Variations in Diet and Life History at Medieval Trino Vercellese, Italy." *American Journal of Physical Anthropology* 148, no. 4: 589–600. https://doi.org/10.1002/ajpa.22085.

Rumolo, A., G. Forstenpointner, P. Rumolo, and R. Jung. 2020. "Palaeodiet Reconstruction Inferred by Stable Isotopes Analysis of Faunal and Human Remains at Bronze age Punta di Zambrone (Calabria, Italy)." *International Journal of Osteoarchaeology* 30, no. 1: 90–98. https://doi.org/10.1002/oa.2836.

Schoeninger, M. J., and M. J. DeNiro. 1984. "Nitrogen and Carbon Isotopic Composition of Bone Collagen From Marine and Terrestrial Animals." *Geochimica et Cosmochimica Acta* 48, no. 4: 625–639. https://doi.org/10.1016/0016–7037(84)90091–7.

Scorrano, G., M. Brilli, C. Martínez-Labarga, et al. 2014. "Palaeodiet Reconstruction in a Woman With Probable Celiac Disease: A Stable Isotope Analysis of Bone Remains From the Archaeological Site of Cosa (Italy)." *American Journal of Physical Anthropology* 154, no. 3: 349–356. https://doi.org/10.1002/ajpa.22517.

Silverman, B. W. 1986. "Density Estimation for Statistics and Data Analysis." In *Monographs on Statistics and Applied Probability*. London, Great Britain: Chapman and Hall.

Snoddy, A. M. E., H. R. Buckley, G. E. Elliott, V. G. Standen, B. T. Arriaza, and S. E. Halcrow. 2018. "Macroscopic Features of Scurvy in Human Skeletal Remains: A Literature Synthesis and Diagnostic Guide." *American Journal of Physical Anthropology* 167, no. 4: 876–895. https://doi.org/10.1002/ajpa.23699.

Spekker, O., D. R. Hunt, W. Berthon, et al. 2021. "Tracking Down the White Plague. Chapter Three: Revision of Endocranial Abnormally Pronounced Digital Impressions as Paleopathological Diagnostic Criteria for Tuberculous Meningitis." *PLoS ONE* 16, no. 3: e0249020. https://doi.org/10.1371/journal.pone.0249020.

Spekker, O., D. R. Hunt, L. Paja, E. Molnár, G. Pálfi, and M. Schultz. 2020a. "Tracking Down the White Plague: The Skeletal Evidence of Tuberculous Meningitis in the Robert J. Terry Anatomical Skeletal Collection." *PLOS ONE* 15, no. 3: e0230418. https://doi.org/10.1371/journal.pone.0230418.

Spekker, O., M. Schultz, L. Paja, et al. 2020b. "Tracking Down the White Plague. Chapter Two: The Role of Endocranial Abnormal Blood Vessel Impressions and Periosteal Appositions in the Paleopathological Diagnosis of Tuberculous Meningitis." *PLoS ONE* 15, no. 9: e0238444. https://doi.org/10.1371/journal.pone.0238444.

Srinivasan, W., W. Thorell, T. L. McCumber, M. Vilburn, and E. L. Snow. 2023. "Hyperostosis Cranialis Interna and an Ectopic Ossification on the Endosteal Dura Deep to the Trigeminal Ganglion: Case Analysis and Clinical Implications." *Translational Research in Anatomy* 30: 100239. https://doi.org/10.1016/j.tria.2023.100239.

Szeniczey, T., A. Marcsik, Z. Ács, et al. 2019. "Hyperostosis Frontalis Interna in Ancient Populations From the Carpathian Basin — A Possible Relationship Between Lifestyle and Risk of Development." *International Journal of Paleopathology* 24: 108–118. https://doi.org/10.1016/j.ijpp.2018.10.003.

Tonnini, G. S. 1883. "I disturbi spinali nei pazzi pellagrosi. Anatomia pathologica." *Rivista sperimentale di freniatria e medicina legale delle alienazioni mentali* 9, no. 208: 10.

Viljoen, M., P. Bipath, and C. Tosh. 2021. "Pellagra in South Africa From 1897 to 2019: A Scoping Review." *Public Health Nutrition* 24, no. 8: 2062–2076. https://doi.org/10.1017/S1368980021001336.

Vogel, J. C., and N. J. Van Der Merwe. 1977. "Isotopic Evidence for Early Maize Cultivation in new York State." *American Antiquity* 42, no. 2: 238–242. https://doi.org/10.2307/278984.

Waldron, T. 2008. *Palaeopathology*. Frist Edit ed. New York: Cambridge University Press.

Walter, B. S., S. N. DeWitte, T. Dupras, and J. Beaumont. 2020. "Assessment of Nutritional Stress in Famine Burials Using Stable Isotope Analysis." *American Journal of Physical Anthropology* 172, no. 2: 214–226. https://doi.org/10.1002/ajpa.24054.

Wang, C., L. Guo, Y. Li, and Z. Wang. 2012. "Systematic Comparison of C3 and C4 Plants Based on Metabolic Network Analysis." *BMC Systems Biology* 6, no. Suppl 2: S9. https://doi.org/10.1186/1752-0509-6-S2-S9.

Williams, A. C., and L. J. Hill. 2020. "The 4 D's of Pellagra and Progress." *International Journal of Tryptophan Research* 13: 117864692091015. https://doi.org/10.1177/1178646920910159.

Young, R. 2016. "Meningoencephalitis." In *American Academy of Pediatrics AAP Textbook of Pediatric Care*, 2nd ed., 2309–2315. American Academy of Pediatrics. https://doi.org/10.1542/9781610020473-part07-ch290.

Zada, G., and R. L. Jensen. 2016. "Meningiomas: An Update on Diagnostic and Therapeutic Approaches." *Neurosurgery Clinics of North America* 27, no. 2: xiii. https://doi.org/10.1016/j.nec.2016.02.001.

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