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RESEARCH ARTICLE

The distal femoral epiphysis used as a fetal maturity marker: Implications of extant medical data for bioarcheological analysis

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Abstract

The distal epiphysis of the femur is classically reported as a marker of fetal maturity and is thus identified in a bioarcheological context as an indicator that an individual died at or around the time of birth; it thus provides crucial information in the creation of the biological profile and associated burial practices. The aim of the present study was to re-evaluate this use by investigating an extant sample to assess (i) the age-related frequencies of both distal femoral and proximal tibial epiphyses and (ii) the influence of factors such as sex, vitality, and morbidity on the maturation of both epiphyses. The study was conducted on medical CT scans acquired in utero and ex utero between 2008 and 2017 in the hospital of Marseille (France). The final sample included 248 individuals aged between 26 and 42 completed gestational weeks (GW). Based on the results obtained in this study, 11% of the individuals from the sample aged between 26 and 33 completed GW had already developed a distal femoral epiphysis, whereas individuals aged between 38 and 42 GW had already developed both femoral and tibial epiphyses. According to these observations and current obstetrical practice, this maturation indicator cannot therefore be considered a precise estimator of whether a fetus is at term or not in an archeological context. Similarly, no delayed ossification was found among individuals who did not survive to 42 GW, or among those with severe developmental abnormalities, which does not support the hypothesis that delayed epiphysis maturation of the distal femur may be a morbidity marker for this age group in past populations.

KEYWORDS

children, full-term pregnancy, funerary practices, morbidity criterion, morbidity indicator, neonatal death, osteological maturation, perinatal period

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1 | INTRODUCTION

The distal femoral epiphysis (DFE), or so-called “point de Béclard” in French literature, is the first of the long bone epiphyses to ossify and appears before the proximal tibial epiphysis (PTE) (Paturet, 1951). Around birth, the DFE consists of a rounded or oval nucleus with pitting and osseous circumvolutions. These epiphyses are maturation indicators marking the different stages of progression of bone maturation. They appear in a constant and defined order, which makes the infracranial sequence of maturation useful for age estimation of immature individuals (i.e., Coqueugniot et al., 2010; Cunningham et al., 2016).

Since the DFE was previously reported to be present in a majority of individuals at birth (i.e., Adair & Scammon, 1921; Flecker, 1996), its presence has been classically considered a marker of fetal maturity in skeletonized archeological remains, indicating that the individual died around 40 gestational weeks (GW; Knight, 1996; Scheuer, 2002). In current obstetrical and forensic practices, the absence and nonstandard dimensions of DFE are, however, routinely used as a predictive factor for several pediatric and maternal conditions such as hypothyroidism or hyperthyroidism (i.e., Savino et al., 2011). Given the high sensitivity of bone maturation to hormonal fluctuations, this epiphysis is indeed not considered as a constant indicator of term but instead as a variable for the analysis of health status.

The aims of this paper were to investigate (i) the validity of the use of the DFE as a precise full-term gestational marker in a bioarcheological context, based on the scoring of both the DFE and the PTE in an extant documented cohort, and (ii) the hypothesis that a delay in epiphysis maturation in this area may be associated with major developmental anomalies and could therefore be considered as a morbidity criterion for this age group in past populations. For this purpose, this study is based on an extant sample consisting of medical CT scans of fetuses and newborns and therefore not subjected to poor preservation and adverse taphonomic processes.

2 | MATERIAL AND METHODS

2.1 | Initial study sample

The study sample initially included 364 anonymized individuals aged between 26 completed GW and 2 postpartum months. All of them underwent in utero or ex utero CT scan examination. In utero CT scans were performed on fetuses referred for additional medical examinations (i.e., suspicion of developmental abnormalities, growth retardation, and maternal pathology). Ex utero CT scans were performed during foetopathological examination following medical abortions or fetal deaths in utero and still-born.

After discarding 116 individuals due to poor scan resolution or methodological incompatibility (see Section 4.1), the final study sample consisted of 248 individuals aged between 26 and 42 completed GW.

3 | METHODS

3.1 | CT analysis

Medical CT scans were performed with a helical CT scanner (Somatom Sensation Cardiac 64; Siemens, Erlangen, Germany, voltage 100–140 kVp, amperage 50–150 mA, and thickness 0.75–1 mm) between 2008 and 2017 in the Assistance Publique des Hôpitaux de Marseille (AP-HM; Marseille, France) and collected in the Digital Imaging and Communications in Medicine (DICOM) format after anonymization from the Picture Archiving and Communication System (PACS).

The presence or absence of both distal femoral epiphyses and proximal tibial epiphyses were scored on three-dimensional bone surface reconstructions (isosurfaces; Figure 1) based on DICOMs using the software ©Avizo Fire 8.1, following a protocol designed to minimize scoring bias due to the fluctuating accuracy of reconstructions. Segmentation was produced by thresholding (Otsu, 1979), which permitted selection of the bone tissues to be visualized. The quality of the isosurfaces produced in the initial sample was variable, depending on the need to limit the exposure of the fetus and mother to X-rays. The 3D reconstructions based on examinations performed ex utero directly on the fetus or newborn had a higher accuracy than those performed while the fetus was still in utero. In some cases, a loss of precision of the skeletal contours occurred, as well as the presence of “noise” that could sometimes interfere with the observations.

To ensure the reliability of the frequencies obtained and to best guarantee that the absence of the DFE on the isosurfaces would in fact correspond to an absence of the DFE in an individual, successive observations were made by testing between three and 10 thresholds per individual. Individuals whose scan resolution did not permit obvious identification of the ossification nuclei were discarded from the initial study sample (Figure 2).

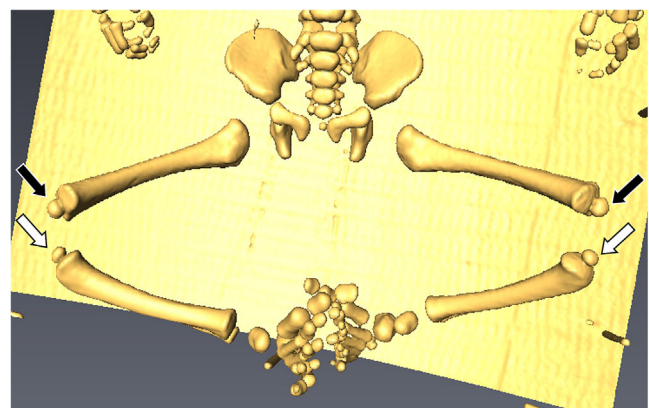
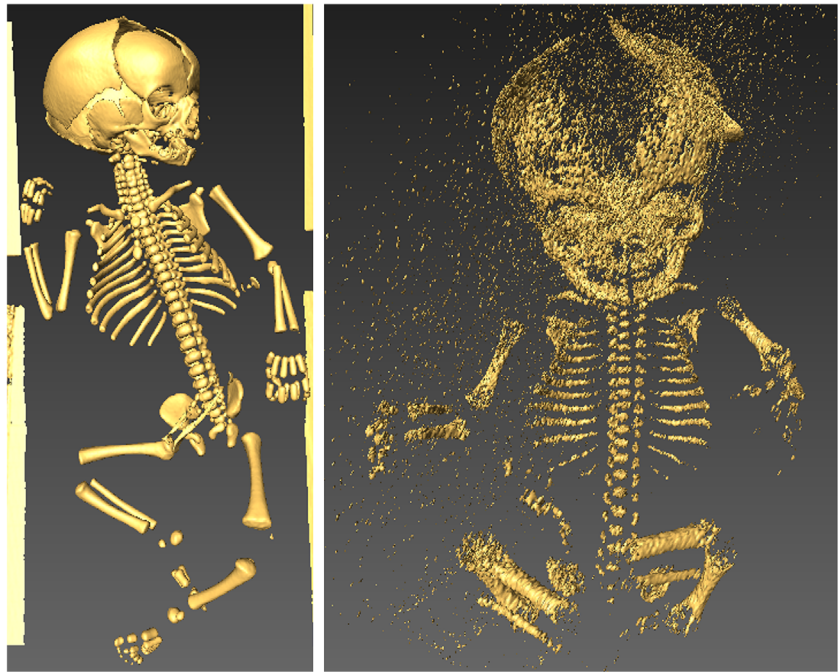


FIGURE 1 Example of distal femoral epiphyses (black arrows) and proximal tibial epiphyses (white arrows) of individual M34 who died at the age of 39 GW and underwent ex utero CT scan for autopsy. [Colour figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1002/ajpa.25240)]

FIGURE 2 Variability of isosurface quality in the virtual sample, left: individual M333, who died at the age of 30 gestational weeks and underwent ex utero CT scan at autopsy, right: individual M995, who was scanned in utero and was discarded from the study sample. [Colour figure can be viewed at wileyonlinelibrary.com]



3.2 | Statistical analysis

First, the symmetry between left and right sides was assessed by computing a raw percentage of concordance along with a Cohen's kappa (Cohen, 1960; Appendix 3 in the Supporting Information). Because the symmetry was almost perfect, all subsequent analyses were performed using the left side only. A Fisher's exact test was performed to assess the relationship between the number of ossification points (on the left side) and the age subgroup (Appendix 4 in the Supporting Information). Then, mosaic plots (Friendly, 1994) were used to represent and assess the relationship between maturation state, age subgroups, and three other covariates (respectively sex, vitality status at 8 postpartum weeks, and morbidity; Figures S3, S4, S5, and S6). Log-linear models (Christensen, 2006) were then built to test the influence of each of these three covariates on the number of ossification points (Appendix 5.2 in the Supporting Information). An alternative procedure using logistic regressions instead of log-linear models resulted in the same conclusions (Appendix 5.3 in the Supporting Information). All analyses were performed using R 4.2.0 (R Core Team, 2022); the corresponding R code is available as Supporting Information.

4 | RESULTS

4.1 | Final study sample

Among the 364 individuals from the initial sample, 116 were discarded because of poor scan resolution (see Section 3) or methodological incompatibility with respect to age assessment. Live-born individuals whose ages were estimated in weeks of gestation could

not be pooled with the individuals whose age were assessed in postnatal weeks without mention of the actual gestation time. The final study sample consisted therefore of 248 individuals aged between 26 and 42 completed GW. Two fetuses had two successive in utero CT scans; only the data acquired during the second scan were considered. The sample included three twin pregnancies; each twin was considered independently from the other.

Information from the medical records was available after anonymization, including age (100% of the individuals), sex (81% of the individuals), vitality at the upper limit of the initial cohort, that is, 2 postpartum months (99.6% of the individuals), and information on health status (medical reasons supporting CT scan examination, medical commentaries, and post-examination diagnosis, 99.2% of the individuals). These medical data permitted morbidity status to be established (normal vs. with anomalies) by distinguishing between the individuals identified as having significant developmental abnormalities that could have compromised their survival in the short or medium term (such as severe dysmorphic signs, agenesis of bone segments or organs, spinal anomalies, *osteogenesis imperfecta*, significant developmental anomalies) on the one hand, and those with no or minor anomalies (i.e., shortening or discrete curvatures of the diaphysis) on the other hand. Individuals for whom no medical information on their health status was available were not classified.

As expected, considering the nature of the study sample and the fact in utero CT scans are only performed in cases of extensive medical examination (unlike routine ultrasound scans), more than a half of the individuals from the final sample ($n = 125/247$) died before 2 months postpartum and 57% of the final cohort ($n = 140/246$) were identified as having significant developmental abnormalities.

4.2 | Symmetrical and asymmetrical development

Cases of symmetrical development were by far most predominant (98.8%; Table 1), and asymmetric cases never presented more than one ossification stage apart (i.e., the situation where an individual would have two nuclei on one side and none on the other never occurred).

Cohen's kappa value is 0.969, corresponding to an almost perfect symmetry between left and right sides (Appendix 3 in the Supporting Information).

4.3 | Frequencies of ossification nuclei among age groups

A majority of the individuals aged between 24 and 34 GW (89%) presented no ossification nucleus at the femoro-tibial joint (Table 2 and Figures 3 and S4), but 11% showed evidence of the DFE. On the left side, half of the individuals aged between 35 and 37 GW had no ossification nuclei, whereas 39% of them had the DFE, and 11% had both DFE and PTE. Between 38 and 42 GW, about a quarter of the sample had no ossification nuclei, only 56% had the DFE, and 20% had both DFE and PTE. These differences in the distribution of ossification nuclei according to age subgroups were, as expected, highly significant according to Fisher's exact test ($p_{\text{value}} = 9.5e-16$). These frequencies confirm the great inter-individual variability in the ossification of these epiphyses.

4.4 | Distribution of ossification nuclei according to sex and age subgroups

On the left side, 91% of the females and 89% of the males aged between 24 and 34 GW presented no ossification nucleus at the femoro-tibial joint, 5% of the females had the DFE versus 9% of the males, and none of them had both DFE and PTE (Table 3 and Figures 4 and S5). Among the individuals aged between 35 and 37 GW, 37% of the females and 50% of the males had no ossification nucleus at the femoro-tibial joint, 37% of the females had the DFE versus 45% of the males, and 25% of the females versus 4% of the males had both DFE and PTE. Among the individuals aged between 38 and 42 GW, 3% of the females and 17% of the males presented no ossification nucleus at the femoro-tibial joint, 50% of the females had one nucleus versus 60% of the males, and 30% of the females versus 17% of the males had both DFE and PTE.

TABLE 1 Confusion matrix between left and right sides.

	0	1	2
0	186	2	0
1	1	49	0
2	0	0	10

Neither log-linear models nor logistic regressions showed a significant effect of sex on the maturation of ossification nuclei (Cf. full details in Supporting Information). These results do not support the hypothesis of differential maturation of DFE and PTE according to sex in this sample.

4.5 | Distribution of ossification nuclei by age subgroups and vitality status

On the left side and among the individuals aged between 24 and 34 GW, 87% of the live versus 93% of the deceased individuals presented no ossification nucleus at the femoro-tibial joint, 13% of the live versus 7% of the deceased had the DFE, and none of them had both DFE and PTE (Table 4 and Figures 5 and S6). Among the individuals aged between 35 and 37 GW, 55% of the live versus 45% of the deceased individuals presented no ossification nucleus at the femoro-

TABLE 2 Contingency table for age subgroups and number of ossification nuclei.

	Side	Age subgroup	Number of ossification nuclei		
			0	1	2
Left		(25,34]	160	19	0
		(34,37]	22	17	5
		(37,42]	6	14	5
Right		(25,34]	161	19	0
		(34,37]	20	18	5
		(37,42]	7	13	5

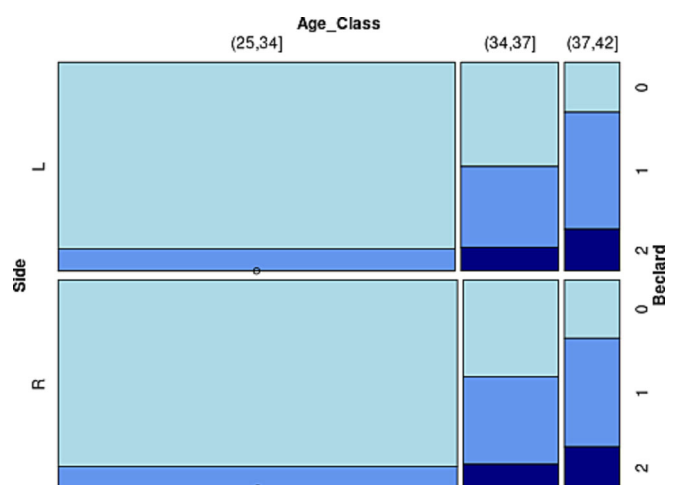
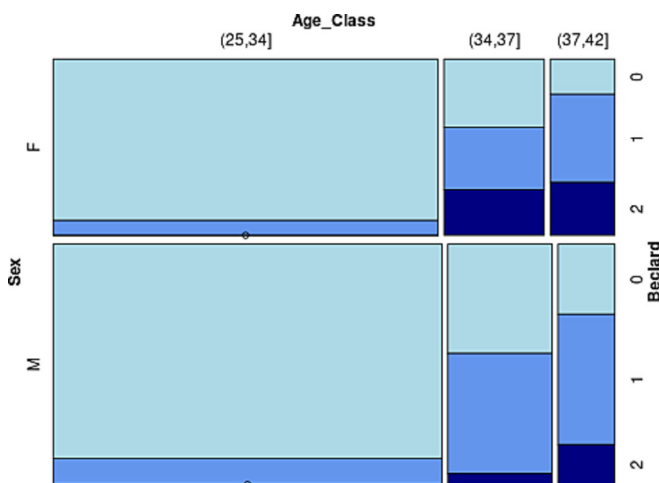


FIGURE 3 Representation of the frequencies of ossification nuclei among age groups as a mosaic plot (where the area of each tile corresponding to the combination of a given side, a given age class, and a given stage is proportional to the number of observations within this category; Table S1). [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Contingency table for the relationship between sex, age subgroup, and number of ossification nuclei.

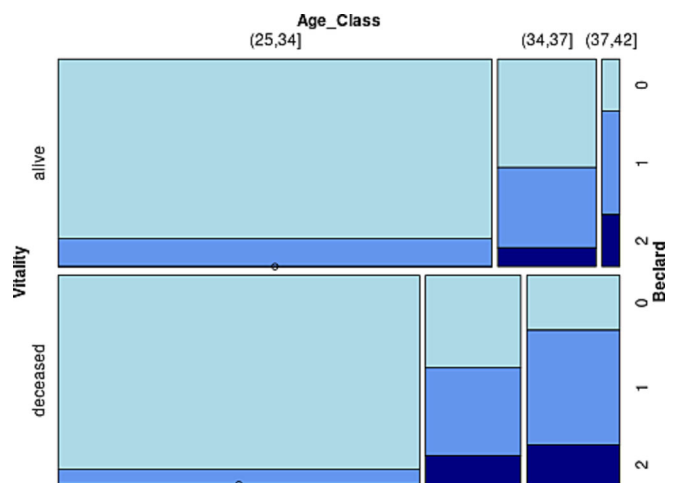
Sex	Side	Age subgroup	Number of ossification nuclei		
			0	1	2
Female	Left	(25,34]	54	5	0
		(34,37]	6	6	4
		(37,42]	2	5	3
	Right	(25,34]	55	5	0
		(34,37]	6	5	4
		(37,42]	2	5	3
Male	Left	(25,34]	73	9	0
		(34,37]	11	10	1
		(37,42]	3	7	2
	Right	(25,34]	73	9	0
		(34,37]	9	12	1
		(37,42]	4	6	2

**FIGURE 4** Representation of the frequencies of ossification nuclei among age groups and according to sex as a mosaic plot (where the area of each tile corresponding to the combination of a given side, a given age class, and a given stage is proportional to the number of observations within this category; Table S3). [Colour figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.com)]

tibial joint, 36% of the live versus 41% of the deceased had the DFE, and 9% of the live versus 14% of the deceased individuals had both DFE and PTE. Among the individuals aged between 38 and 42 GW, 25% of the live versus 24% of the deceased individuals presented no ossification nucleus at the femoro-tibial joint, 50% of the live versus 57% of the deceased had the DFE, and 25% of the live versus 19% of the deceased had both DFE and PTE. No significant influence of vitality status on the maturation of ossification nuclei could be found using log-linear models (Cf. Supporting Information). Based on these results, no differential maturation of DFE and PTE was identified between the individuals who died before 8 postpartum weeks and the individuals who were alive at this point.

TABLE 4 Contingency table for the relationship between age subgroup, vitality status, and number of ossification nuclei.

Side	Age subgroup	Vitality	Number of ossification nuclei		
			0	1	2
Left	(25,34]	Alive	84	13	0
		Deceased	75	6	0
	(34,37]	Alive	12	8	2
		Deceased	10	9	3
	(37,42]	Alive	1	2	1
		Deceased	5	12	4
Right	(25,34]	Alive	84	13	0
		Deceased	76	6	0
	(34,37]	Alive	11	9	2
		Deceased	9	9	3
	(37,42]	Alive	1	2	1
		Deceased	6	11	4

**FIGURE 5** Representation of the frequencies of ossification nuclei among age groups and according to vitality status as a mosaic plot (where the area of each tile corresponding to the combination of a given side, a given age class, and a given stage is proportional to the number of observations within this category; Table S4). [Colour figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.com)]

4.6 | Distribution of ossification nuclei by age subgroups and health status

On the left side and among the individuals aged between 24 and 34 GW, 92% of the individuals with anomalies versus 86% of the normal individuals presented no ossification nuclei at the femoro-tibial joint, 8% of the individuals with anomalies versus 14% of the deceased had the DFE, and none had both DFE and PTE (Table 5 and Figures 6 and S7). Among the individuals aged between 35 and 37 GW, 46% of the individuals with anomalies versus 56% of the normal individuals presented no ossification nucleus at the femoro-tibial joint, 42% of the individuals with anomalies versus 33% of the normal

TABLE 5 Contingency table for the relationship between age subgroup, morbidity, and number of ossification nuclei.

Side	Age subgroup	Morbidity	Number of ossification nuclei		
			0	1	2
Left	(25,34]	Anomalies	85	7	0
		Normal	73	12	0
	(34,37]	Anomalies	12	11	3
		Normal	10	6	2
	(37,42]	Anomalies	5	12	4
		Normal	1	2	1
Right	(25,34]	Anomalies	86	7	0
		Normal	73	12	0
	(34,37]	Anomalies	11	11	3
		Normal	9	7	2
	(37,42]	Anomalies	6	11	4
		Normal	1	2	1

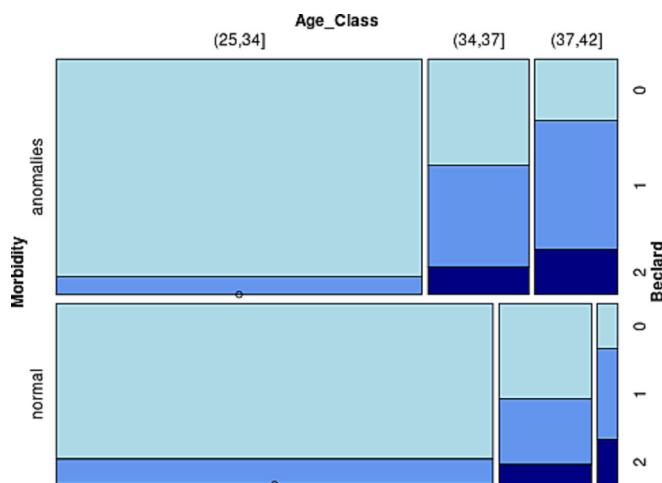


FIGURE 6 Representation of the frequencies of ossification nuclei among age groups and according to health status as a mosaic plot (where the area of each tile corresponding to the combination of a given side, a given age class, and a given stage is proportional to the number of observations within this category; Table S5). [Colour figure can be viewed at wileyonlinelibrary.com]

individuals had the DFE, and 11% of the individuals with anomalies versus 11% of the normal individuals had both DFE and PTE. Among the individuals aged between 38 and 42 GW, 24% of the individuals with anomalies versus 25% of the normal individuals presented no ossification nucleus at the femoro-tibial joint, 57% of the individuals with anomalies versus 50% of the normal individuals had the DFE, and 19% of the individuals with anomalies versus 25% of the normal individuals had both DFE and PTE.

The influence of health status on the maturation of ossification nuclei was tested using log-linear models, comparing between individuals identified as having major developmental abnormalities and individuals without major abnormalities or only minor anomalies (Table 5)

(Cf. Supporting Information). The effect of health status was, again, not significant. Delayed maturation of both ossification nuclei was therefore not identified among the individuals with major anomalies.

5 | DISCUSSION AND CONCLUSIONS

Collecting large samples of individuals aged around the time of birth is necessary to investigate the biological variability of this age group and examine life courses and mortuary practices in past population. This process is, however, challenging in both archeological and medical contexts, with both ethical and practical concerns.

In extant cohorts of fetal and postnatal individuals, ultrasound is the routine examination method and does not permit accurate observation of bone tissues, unlike CT scans, which are much less commonly employed. CT scans are only prescribed in cases of suspected medical conditions justifying the irradiation of the fetus or newborn. Bone maturation can also be evaluated via radiological examination or a direct observation during autopsy. The few collections available for bioanthropological studies therefore consist mainly of scans performed as part of the medical monitoring of the pregnancy, in cases of perinatal death, or for medical or natural pregnancy termination, resulting in biases with respect to the nature of the sample. The mode of data acquisition (autopsy, radiology, or CT scan) may also influence the scoring of these features, similarly to what is documented between direct or radiographic acquisition of metric data (Adalian, 2001). However, although the direct analysis of archeological bone remains is challenged by taphonomic and preservation issues, the study of CT scans carried out on complete individuals remains a real asset for the study of very small bone elements such as immature epiphyses.

According to the results obtained in this study, the presence of the DFE in the sample appears to be variable between the fetal period and 42 GW. Among the youngest individuals (from 22 to 34 GW), more than 1 in 10 had already developed the DFE. Moreover, at full-term pregnancy (between 38 and 42 GW), about a quarter of the sample had no ossification nuclei, more than half had developed the DFE, and less than a quarter had developed both DFE and PTE. These outcomes do not support the hypothesis that the DFE can be used as a precise marker for age-at-death assessment in individuals who died during the perinatal period from past populations.

Sex-based differences in bone growth and maturation have also been documented (Garn et al., 1966; Scheuer & Black, 2000). During the post-natal period, maturation would appear to be faster in females than in males (Brodeur et al., 1981; Pyle & Hoerr, 1955), with, for example, the hand bones of female individuals ossifying earlier when compared with those of males between the ages of 3 postpartum months and 14 years of age (Pryor, 1908 cited by Flecker, 1996). These general sex-based maturation differences could also be identified as early as the fetal period and throughout intrauterine life (Pryor, 1908 cited by Flecker, 1996; Choi & Trotter, 1970; Pedersen, 1982). Because sex diagnosis of immature individuals, particularly the youngest ones, still remains very scarce in

bioarcheological contexts, these sex-based differences in bone maturation should be specifically considered for biological study. The DFE has therefore sometimes been identified on average 2 weeks earlier in female than in male infants (Scheuer & Black, 2000), whereas other studies do not find any significant sexual dimorphism regarding the maturation of the knee epiphyses (Leshem et al., 2002; Savino et al., 2011). Our observations in the extant sample are consistent with the latter conclusions.

The DFE is routinely used as an indicator for health status and morbidity in obstetrical and forensic practice since conditions such as hypothyroidism are associated with delayed bone maturation and smaller DFE dimensions (Knight, 1996; Paturet, 1951; Savino et al., 2011; Scheuer, 2002). However, no significant delayed DFE ossification with respect to age was observed in the extant sample between the group of individuals who died before 2 postpartum months and the group of those who survived, neither between the group with diverse severe developmental anomalies nor those with normal health status. Thus, the observation in the extant sample does not support the hypothesis that delayed epiphysis maturation in the knee is a sufficiently sensitive indicator to be used as a nonspecific morbidity indicator for this age group in past populations, unlike other osteological markers such as the supernumerary cervical rib (Partiot, 2018; Partiot et al., 2020) or fluctuating asymmetries (Partiot et al., 2021).

The current study has some limitations when applied to bioarcheological samples because the nucleus may be missed during excavation or may not be preserved at all because of taphonomic processes. It is therefore not systematically considered for in studies of skeletal maturation, which limits the impact of our results on age estimation. However, the increasing development of the principles of archeoethnology (Duday, 2009; Duday et al., 1990) and the care given to recovering these small bony elements will aid the identification and recovery of more preserved DFE in the future. More studies are also to be implemented in other cohorts, first to investigate more precisely the limitations produced by the observation of this epiphysis using medical scanners, and second to evaluate its potential relevance as indicators of morbidity for more specific conditions, such as hypothyroidism in past populations.

AUTHOR CONTRIBUTIONS

Mélissa Niel, Clémence Delteil, Emmanuelle Lesieur, Kathia Chaumoitre, Marie-Dominique Piercecchi, and Pascal Adalian gathered the CT scans and elaborated the database with individual information. Pascal Adalian supervised the study. Caroline Partiot conceptualized the study, acquired data from the CT scans, analyzed them, and wrote the initial manuscript draft with important contributions from FS in the statistical analysis, writing, and visualization of the outcomes. All authors contributed to the final review and editing of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no known competing interests or personal relationships that could have appeared to influence the work reported in this paper.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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