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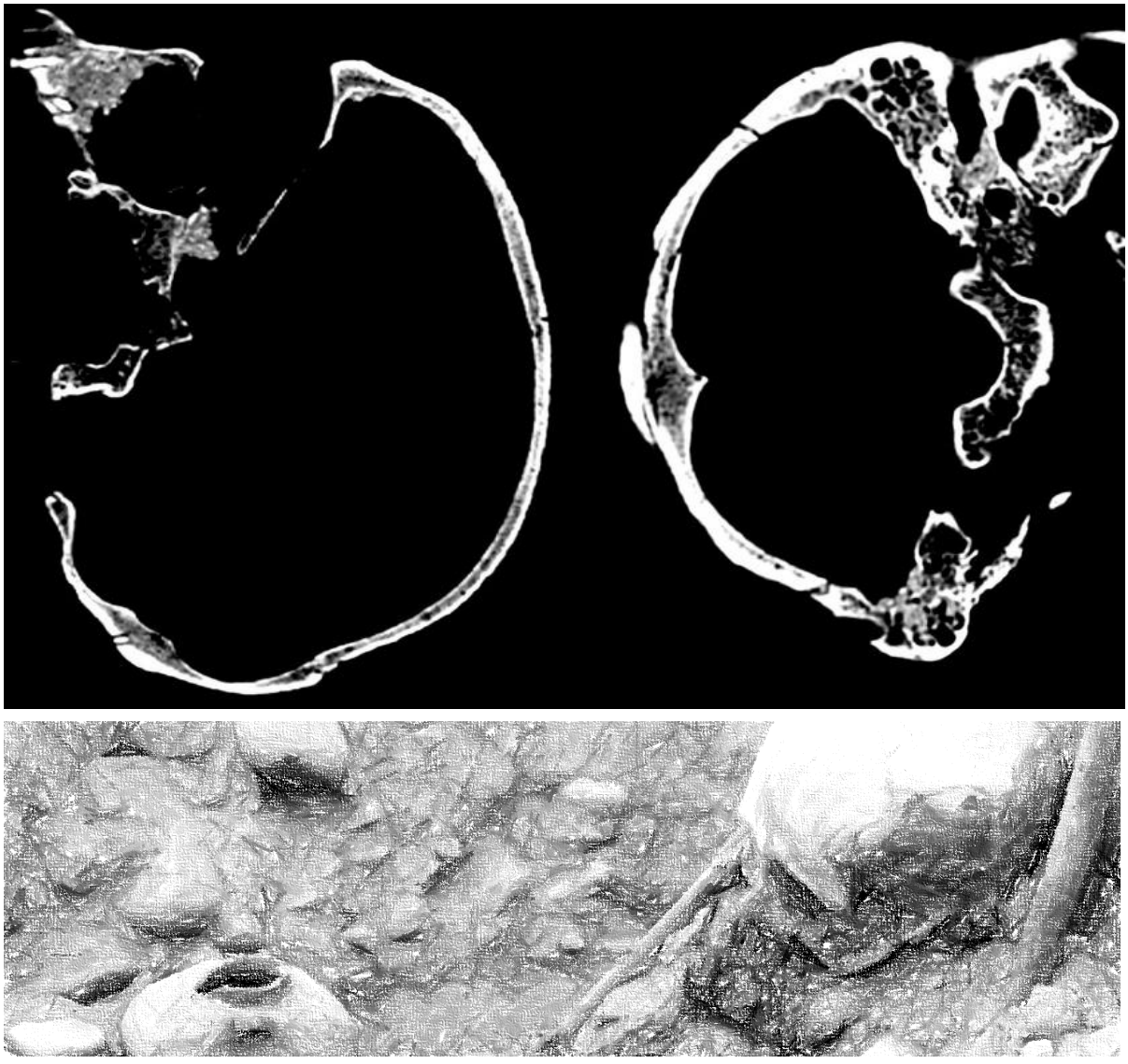

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Cover image taken from Đukić et al. The case of hip dysplasia of an adult from the Late Antiquity site of Velebit (Serbia). p. 73-80

About the journal:

Journal of Bioanthropology is a multi and interdisciplinary scientific journal that focuses on scientific research in the field of biological anthropology, bioarchaeology, biomechanics, biomedicine, ergonomics, forensics, genetics, human evolution, molecular anthropology, public health and related subjects. Official language of the Journal is English.

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Submitted manuscripts will generally be reviewed by two to three experts who will be asked to evaluate whether the manuscript is scientifically sound and coherent, whether it duplicates already published work, and whether or not the manuscript is sufficiently clear for publication. Reviewers will also be asked to indicate how interesting and significant the research is. The Editors will reach a decision based on these reports and, where necessary, they will consult with members of the Editorial Board.

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We are Celebrating Bioanthropology – We are Celebrating Ourselves!

Damir Marjanović

Editor-in-Chief

First Issue December 20th, 2021

Editorial

Here we are! We are celebrating the release of the first issue of our new journal. Journal of Bioanthropology is a multi and interdisciplinary scientific journal that focuses on scientific research in the field of biological anthropology, bioarchaeology, biomechanics, biomedicine, ergonomics, forensics, genetics, human evolution, molecular anthropology, public health and related subjects.

Compared to other scientific disciplines, anthropology boasts a huge number of admirers, who are probably not even aware that since their first significant observation of the environment in childhood they have somehow become amateur bioanthropologists. Namely, by knowing themselves as individuals and individual parts of the body, putting feet in the mouth, sucking a finger, pushing a finger into an eye, ear or nose, each member of *Homo sapiens* made a small bioanthropological experiment of getting to know the human body. These were certainly the first steps towards gathering bioanthropological knowledge about oneself, but also about the biological characteristics of our species. This is the first step in which man studies himself as a biological object and in which he compares himself with his environment and tries to classify himself in a specific biotype, population, species or, what worries pastors, a race.

Each member of the species *Homo sapiens* has taken a small course in bioanthropology on daily scale, whether it is shaving or putting make-up on. Namely, when a mostly male, based on previously analyzed anthropometric parameters and points, removes hair from his face with precise and learned moves that avoid the traps of his phenotype that would put him in a situation to cut, he only confirms his knowledge of his body, more precisely his face. On the other hand, every mostly female who in the car at a red light, with experienced and trained moves, occasionally glancing at the smallest possible mirror, perfectly applies makeup prepared in the passenger seat within a few seconds, proves that she is a real expert not only in knowing her face. and its anthropometric points and measures on it than ergonomics, as an anthropological discipline, because it clearly adapted its movements to the cramped space of the car. Every measurement of height, weight, length of hair, nails, every

determination of whether the chair fits the dimensions of the customer, whether the bed will be wide enough for two who should sleep on it and trying on shoes or clothes, it's all part of knowing your phenotype, everything it is, even at the amateur level, applied bioanthropology.

Finally, the moment the average human specimen takes one last look at the mirror in the morning before leaving the apartment, wanting to conclude whether one is satisfied with its appearance, they automatically observe accurately and arbitrarily selected parts of their phenotype (results of interaction between genotype and environment) and analyze the variants of selected traits, they are applying bioanthropology in the most basic way. However, at the moment one concludes that they like or dislike something, or if one is satisfied or disappointed with their appearance, one meets the limit of the bioanthropological cognition and has delved well into the socioanthropological "part of oneself". Yes, one is starting to be amateur socioanthropologist, but we will talk about that some other time.

Therefore, I have no doubt that this new Journal of Bioanthropology will attract a wide range of readers (as well as authors) from those who live bioanthropology as scientists, to those who are intrigued by this science and who follow the latest knowledge about themselves as members of this fascinating species *Homo sapiens*.

Prof. Damir Marjanović, Editor-in-Chief

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Phenotypic association of seven observed traits of hand complex

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Abstract

This paper provides an overview of the seven possible hand-related traits, with an idea to estimate the statistical phenotypic association between them. The traits observed in this study were: midphalangeal hair, Hitchhiker's thumb, extensibility of proximal joint of thumb, digital index, nail shape, crooked fifth finger and hand clasping. The mentioned characteristics were observed in 7431 unrelated subjects, with approximately equal gender distribution. For each case, three groups were formed: total, male and female. The subjects were evenly distributed throughout Bosnia and Herzegovina's various geographical regions, and they properly represent the country's national and ethnic composition. The Chi-squared test was used to determine the statistical significance of the association between these traits, while Fisher's exact test was utilized as an extra test to analyze the association between each pair of observed features. Also, Chi-squared test was applied for observing differences in the frequencies of the phenotypic characteristics of the hand between the genders. Following traits were shown to have a statistically significant association: midphalangeal hair-Hitchhiker's thumb, midphalangeal hair - digital index, midphalangeal hair - nail shape, midphalangeal hair - crooked fifth finger, Hitchhiker's thumb- extensibility of proximal joint of thumb, digital index - nail shape, digital index -crooked fifth finger, midphalangeal hair - hand clasping, crooked fifth finger - hand clasping. Analysis of differences in the frequencies of the observed phenotypic traits of the hand according to the genders showed statistical significance for D, Dht, Ref and Lf.

Introduction

In bioanthropological research, the focus was on relatively easily measurable traits, which is why we generally divide them into: dynamic-morphological, static-morphological and biochemical-physical. In most cases, such traits have an oligogenic or polygenic character, and it is not easy to assess the association. Therefore, one of the ways of perceiving the complexity of these traits is the phenotypic association, ie. evaluation of the association of phenotype variants.

Bioanthropological research in Bosnia and Herzegovina began during the Austro-Hungarian Empire in the late 19th century, and the history of such research is presented in Lasic et al. 2016. A number of bioanthropological and genetic studies have been performed in Bosnia and Herzegovina to assess the heterogeneity of local populations as well as the general B&H population (Berberovic 1969; Dogan et al. 2016; Hadziselimovic 1981; Kapur-Pojskic et al. 2014; Kovacevic et al. 2013, 2014; Lasic et al. 2013, 2016, 2020; Marjanovic et al. 2005, 2005a, 2006, 2008; Pojskic et al. 2013). However, most of these works are based on molecular genetic markers, and a smaller part on phenotypic markers.

The assessment of heterogeneity in temporal time was done by Pojskic in 2003, and when it comes to assessing heterogeneity based on the hand phenotype and other phenotypic traits numerous studies were performed by B&H scientists in the last century (Berberovic 1969, 1978; Berberovic et al. 1976; Hadziselimovic 1977, 1981; Hadziselimovic and Terzic 1985; Kaunic and Grin 1963). However, none of these papers included the assessment of the association of different phenotypic

traits. Therefore, this paper presents an overview of the possible seven hand-related traits. Having a large data set, the assumption is that we can estimate the statistical association of hand-related phenotypes.

By reviewing the literature concerning the seven traits regarding complex of hand (Dutta 1965; Glass and Kistler 1953; Lai and Walsh 1965; Munir et al. 2010; Nesic et al. 2010; Phelps 1952;), the mode of inheritance was determined. These papers indicate variations of the stated traits, which in principle means variations of the genetic basis. Most of these traits are controlled by a set of multiple genes [polygenic traits] (Bernstein 1949). From all the above, it can be concluded that the study of the relationship between the phenotypic traits of the hand is very interesting approach in bioanthropology.

Materials and methods

Possible phenotypic association among seven traits regarding complex of hand was observed. Those seven traits were: midphalangeal hair (D), Hitchhiker's thumb (Dht), extensibility of proximal joint of thumb (Pht), digital index (Lf), nail shape (Ln), crooked fifth finger (Ref) and hand clasping (Hc) (Table 1). A total of 7431 unrelated subjects were observed at random for these seven traits regarding complex of hand. Observed subjects were evenly distributed through different geographical regions of Bosnia and Herzegovina and duly represent characteristic national and ethnic composition (Fig.1). Total sample contained approximately equal gender distribution. Out of 7431, for a total of 6985 individuals, gender distribution was observed.

Therefore, in the analysis of frequencies of phenotypic variants and their association, only those samples whose gender association was known were analyzed. For determining statistical significance of association between these traits, Chi-squared test was calculated. As additional test for assessing the association between each pair of observed traits Fisher's exact test was utilized. For calculating these values, MedCalc version 18.10.2 was used. Considered statistical significance level was 0.05. In order to observe the difference in the frequencies of the phenotypic characteristics of the hand between the genders, the Chi-squared test was applied with the considered level of statistical significance $p < 0.05$. In every case, three groups were

Table 1. List of seven observed traits regarding complex of hand

Trait	Abbreviation	Recessive	Variant I	Variant II	Author
Hand clasping	Hc	/	Right-1	Left-2	Lutz, F.E. (1908)
Midphalangeal hair (mid-digital hair)	D	Hairless	No hair-0	Hairy-1	Danforth, C.H. (1921); Bernstein (1949)
Nail shape (Short nails)	Ln	Long nails	Non-flat-0	Flat-1	Gillin (1959)
Crooked fifth finger	Ref	„Normal" phalanx	Abnormally crooked-0	Normal-1	Hefner, R.A. (1929); Hersh, A.H., F. DeMarinis, R.M. Stecher (1953); Dutta (1965)
Digital index	Lf	short (♀♀) and long (♂♂) index finger	Male-short-1; Female-short-0	Male-long-0; Female-long-1	Ecker (1875); Phelps (1952)
„Hitch-hiker's" thumb (Extensibility of distal joint of thumb)	Dht	„Hitch-hiker's" thumb (Hyperextensibility)	Hypoextensibility-0	Hyperextensibility-1	Glass, B., Kistler, J.C. (1953)
Extensibility of proximal joint of thumb	Pht	Hyperextensibility	Hypoextensibility-0	Hyperextensibility-1	Whitney (1942) Gillin (1959)

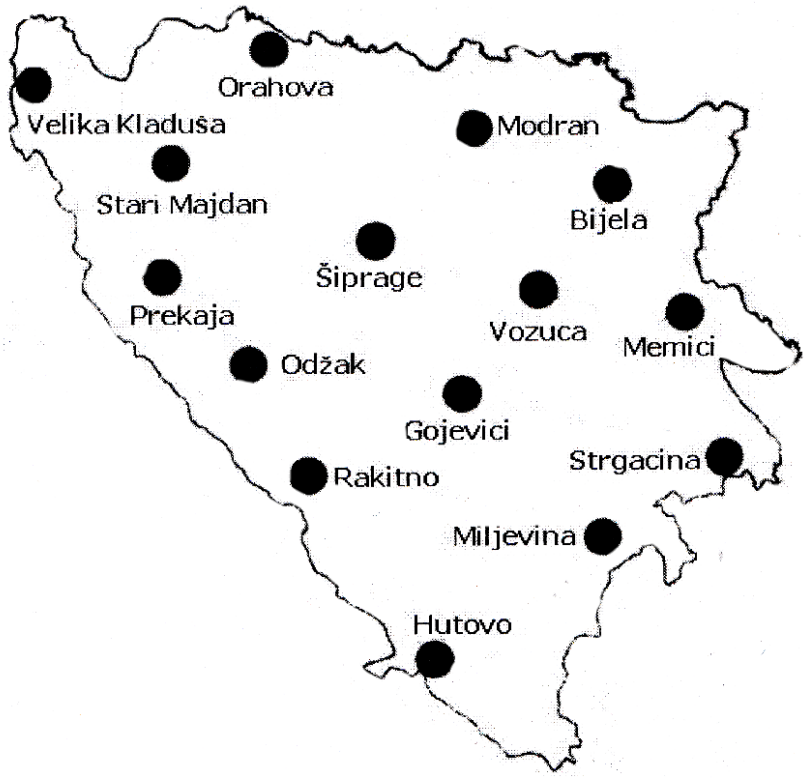

Figure 1 Distribution of observed local populations in Bosnia and Herzegovina

formed: total, male and female groups, in later paragraphs marked with T (total), F (female) and M (male). Since there is a difference in the dominant inheritance of variants of the digital index trait between the genders, the assessment of the possible association of this trait with other observed traits was performed only for gender groups and not for the total population.

Results and Discussion

In table 1 a list of seven observed traits regarding complex of hand with its abbreviation is presented. The results of Fisher exact and Chi-squared test between seven observed traits for all three groups (T, M, F) are presented in tables 2, 3, 4.

The results of the analysis of differences in the frequencies of the observed phenotypic traits of the hand according to the genders showed statistical significance for D ($\chi2=6.019$, $p=0.0142$), Dht ($\chi2=27.569$, $p<0.0001$), Ref ($\chi2=4.180$, $p=0.0409$) and was not observed for Pht ($\chi2=0.856$, $p=0.3548$), Ln ($\chi2=2.867$, $p=0.0904$) and Hc ($\chi2=0.187$, $p=0.6655$). A pronounced statistically significant difference was also observed for Lf ($\chi2=715.546$, $p<0.0001$), given that there is a different dominant phenotype depending on the gender. In our study, it was observed that the frequency of phenotype variants D, Dht and Ref, and expectedly Lf, also had a statistically significant difference between the genders. Thus, in trait D, the balance of phenotypes 0 and 1 in male group is observed, and in female group more pronounced 1 in relation to 0. In the case of Dht, a larger difference was observed in different variants of this trait in female group than in male group, while in the case of Ref, slightly higher difference in phenotype variants is observed in male group rather than female group. As expected, there is a marked difference in Lf, since the dominant phenotype in female group is long index finger, and in male group short index finger.

Statistical significant association was observed between following traits: midphalangeal hair-Hitchhiker's thumb, midphalangeal hair - digital index, midphalangeal hair - nail shape, midphalangeal hair - crooked fifth finger, Hitchhiker's thumb- extensibility of proximal joint of thumb, digital index - nail shape, digital index -crooked fifth finger, midphalangeal hair - hand clasping, crooked fifth finger - hand clasping (Fig.2A, 2B, 2C).

Table 2. Fisher's exact test p-value and Chi squared value for total population in case of seven observed traits of hand complex (upper triangle - χ 2 value; lower triangle - Fisher exact p value; * p<0.05; ** p<0.01; *** p<0.001)

	D	Dht	Lf	Ln	Ref	Pht	Hc
D		7.976**	-	31.343***	19.858***	0.016	4.692*
Dht	0.0050**		-	3.613	0.000	58.979***	0.071
Lf	-	-		-	-	-	-
Ln	0.0000***	0.0612	-		0.006	1.997	1.445
Ref	0.0000***	1.0000	-	0.9501		1.676	3.599
Pht	0.9238	<0.0000***	-	0.1610	0.2079		0.002
Hc	0.0321*	0.7920	-	0.2311	0.0610	0.9746	

[$]Since there is a difference in the dominant inheritance of variants of the digital index trait between the genders, the assessment of the possible association of this trait with other observed traits was performed only for gender groups and not for the total population (-)

Table 3. Fisher's exact test p-value and Chi squared value for male population in case of seven observed traits of hand complex (upper triangle - χ 2 value; lower triangle - Fisher exact p value; * p<0.05; ** p<0.01; *** p<0.001)

	D	Dht	Lf	Ln	Ref	Pht	Hc
D		5.596*	11.485***	10.208**	11.994***	1.224	2.604
Dht	0.0186*		1.994	0.742	0.047	50.504***	0.477
Lf	0.0007***	0.1678		7.184**	41.238***	0.011	0.138
Ln	0.0015**	0.4026	0.0081**		0.454	2.185	1.699
Ref	0.0005***	0.8297	<0.0000***	0.5286		1.596	0.991
Pht	0.2699	<0.0000***	0.9165	0.1412	0.2256		0.341
Hc	0.1082	0.4926	0.7143	0.2021	0.3234	0.5810	

Table 4. Fisher's exact test p-value and Chi squared value for female population in case of seven observed traits of hand complex (upper triangle - χ 2 value; lower triangle - Fisher exact p value; * p<0.05; ** p<0.01; *** p<0.001)

	D	Dht	Lf	Ln	Ref	Pht	Hc
D		3.111	0.008	31.243***	8.286**	0.089	1.371
Dht	0.0802		1.172	3.010	1.404	27.297***	0.242
Lf	0.9397	0.2850		1.874	20.346***	0.006	0.003
Ln	0.0000***	0.0902	0.1759		0.088	0.247	0.092
Ref	0.0045**	0.2516	0.0000***	0.8029		1.607	4.923*
Pht	0.7905	0.0000***	0.9558	0.6459	0.2150		0.718
Hc	0.2468	0.6493	0.9699	0.7881	0.0290*	0.3981	

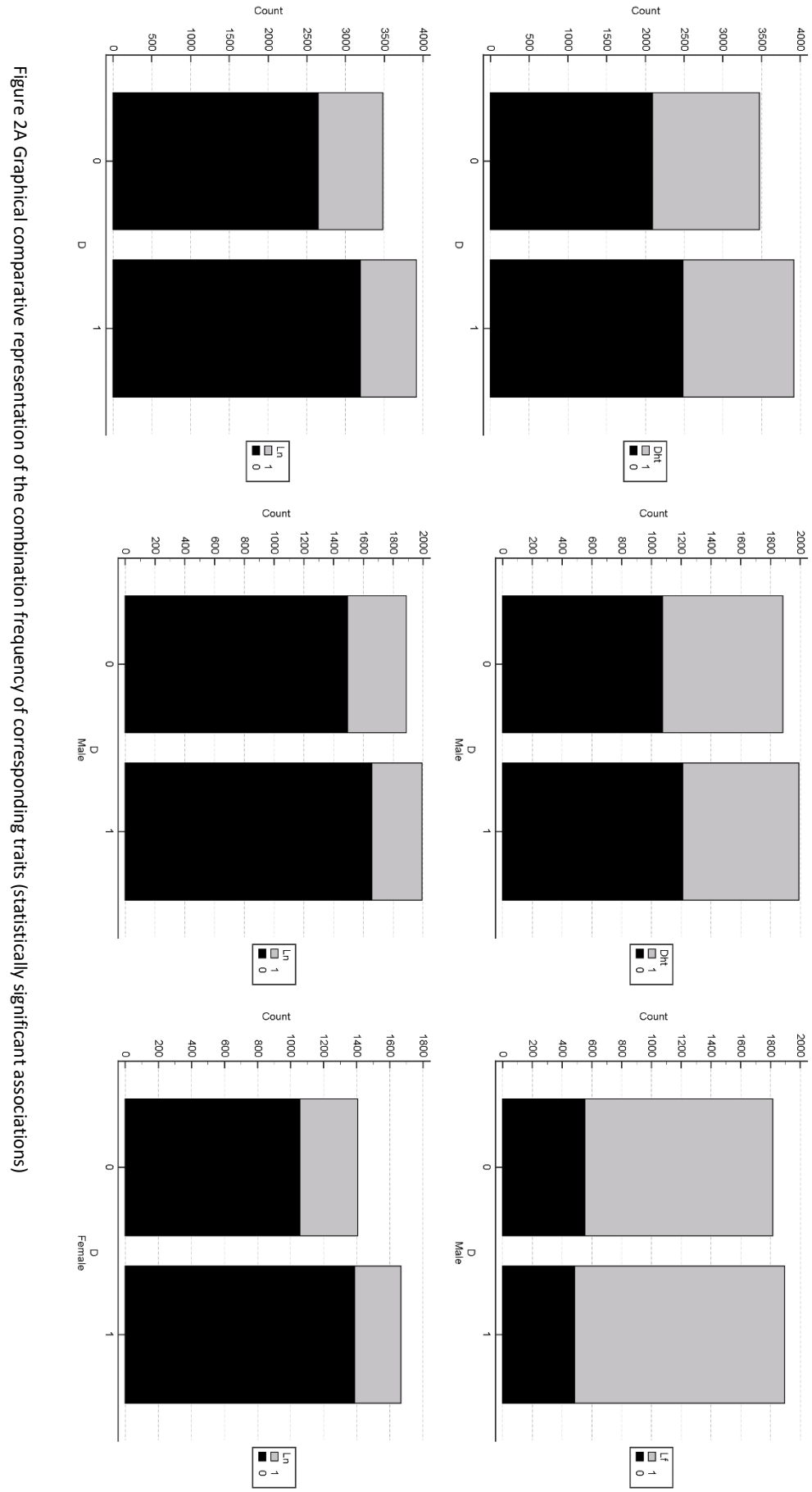

Figure 2A Graphical comparative representation of the combination frequency of corresponding traits (statistically significant associations)

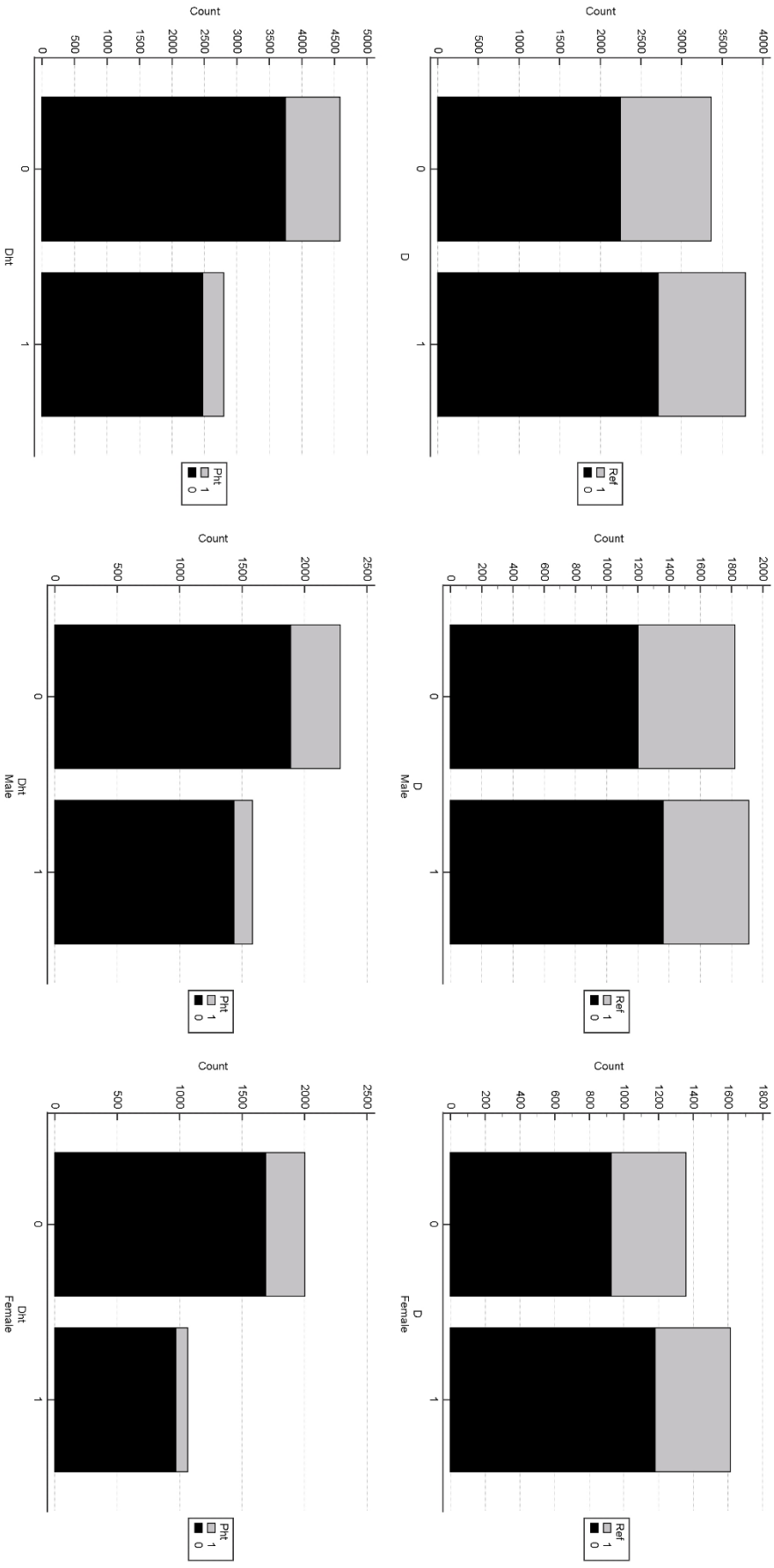

Figure 2B Graphical comparative representation of the combination frequency of corresponding traits (statistically significant associations)

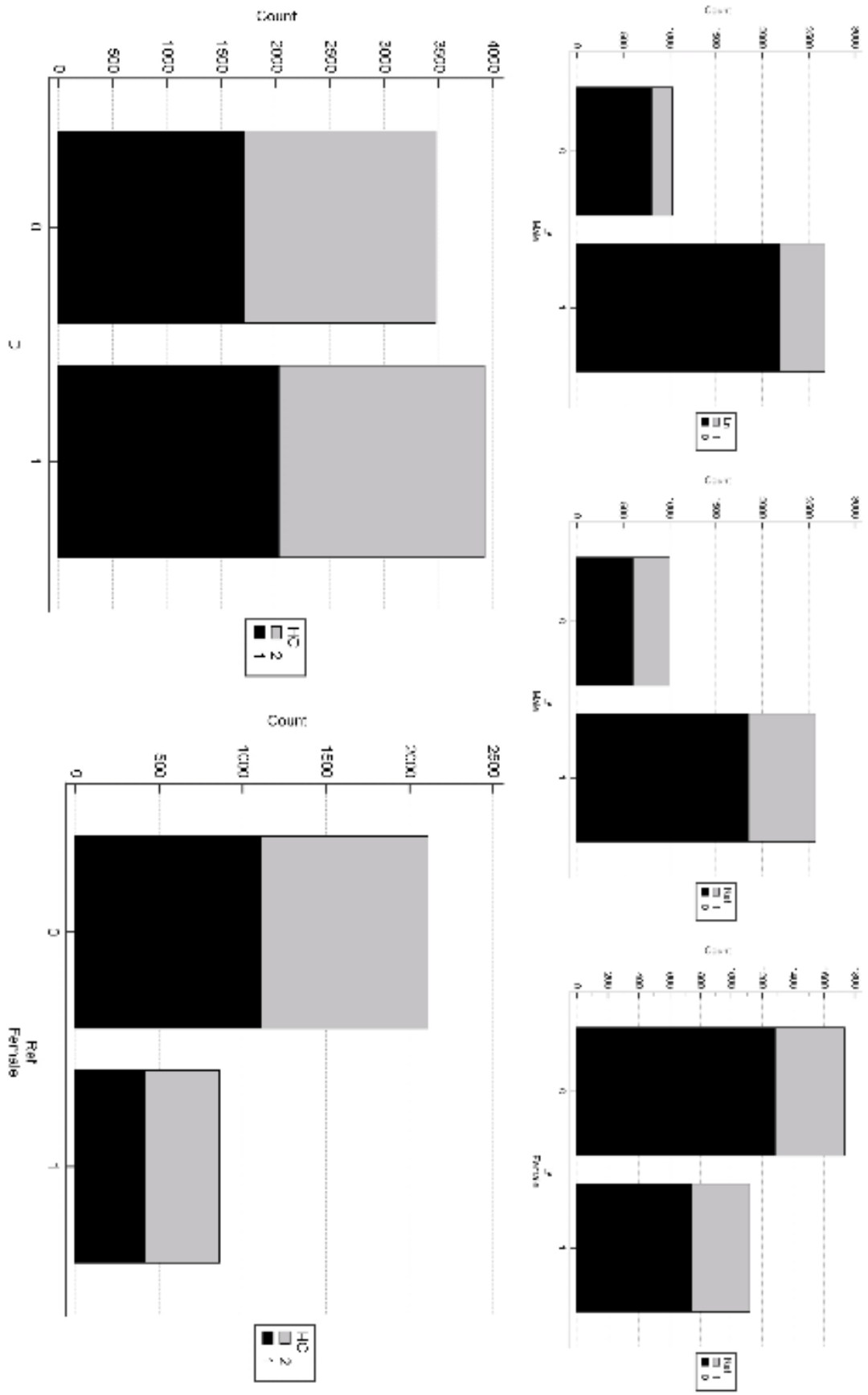

Figure 2C Graphical comparative representation of the combination frequency of corresponding traits (statistically significant associations)

Regarding association between D and Dht, highest significance was observed in total sample (χ2= 7.976; p= 0.0047, Fisher's exact test p=0.004968586). Statistical significance was also observed in group M (χ2= 5.596, p= 0.0180, Fisher's exact test p= 0.018645058). However, regarding F group statistical significance was not observed (χ2=3.111, p=0.0778, Fisher's exact test p=0.080236612). In total sample, the largest proportion of individuals (2489) had hypoextensibility of distal joint of thumb (Hitchhiker's thumb) and presence of midphalangeal hair, and smallest proportion (1378) had hyperextensibility of distal joint of thumb (Hitchhiker's thumb) and absence of midphalangeal hair. In male group, the largest proportion of individuals (1212) had hypoextensibility of distal joint of thumb (Hitchhiker's thumb) and presence of midphalangeal hair, and smallest proportion (779) had hyperextensibility of distal joint of thumb (Hitchhiker's thumb) and presence of midphalangeal hair. In case of association between D and Lf, statistical significance was observed only in group M (χ2=11.485, p= 0.0007, Fisher's exact test p= 0.000760890). In group F (χ2=0.008, p=0.9296, Fisher's exact test p= 0.939756783) statistical significance was not observed. In male group, the largest proportion of individuals (1412) had short index finger and presence of midphalangeal hair, and smallest proportion (484) had long index finger and presence of midphalangeal hair. In cases D and Ln, D and Ref and Dht and Pht statistical significance was observed in all 3 groups T, F, M. Also highest significance in total was observed in these cases, especially Dht and Pht. In group T values are as follows (χ2 =58.979, p=<0.0001, Fisher's exact test p=<0.000000001), group F (χ2 = 27.297, p=<0.0001, Fisher's exact test p=0.000000100) and group M (χ2 = 50.504, p=<0.0001, Fisher's exact test p= <0.000000001). As for Dht and Pht case, in total group, the largest proportion of individuals (3746) had hypoextensibility of proximal joint of thumb and hypoextensibility of distal joint of thumb (Hitchhiker's thumb), and smallest proportion (326) had hyperextensibility of proximal joint of thumb and hyperextensibility of distal joint of thumb (Hitchhiker's thumb). In female group, the largest proportion of individuals (1690) had hypoextensibility of proximal joint of thumb and hypoextensibility of distal joint of thumb (Hitchhiker's thumb), and smallest proportion (95) had hyperextensibility of proximal joint of thumb and hyperextensibility of distal joint of thumb (Hitchhiker's thumb). Also in male group, the largest proportion of individuals (1891) had hypoextensibility of proximal joint of thumb and hypoextensibility of distal joint of thumb (Hitchhiker's thumb), and smallest proportion (148) had hyperextensibility of proximal joint of thumb and hyperextensibility of distal joint of thumb (Hitchhiker's thumb). In case of D and Ln values are: group T (χ2 =31.343, p=<0.0001, Fisher's exact test p= 0.000000025), group F (χ2 = 31.243, p=<0.0001, Fisher's exact test p= 0.000000030) and group M (χ2 =10.208, p=0.0014, Fisher's exact test p=0.001529606). In this example it was obvious to conclude that the lowest statistical significance was observed in group M. In total group, the largest proportion of individuals (3195) had non-flat nail shape and presence of midphalangeal hair, and smallest proportion (728) had flat nail shape and presence of midphalangeal hair. In female group, the largest proportion of individuals (1390) had non-flat nail shape and presence of midphalangeal hair, and smallest proportion (278) had flat nail shape and presence of midphalangeal hair. Also in male group, the largest proportion of individuals (1659) had non-flat nail shape and presence of midphalangeal hair, and smallest proportion (335) had flat nail shape and presence of midphalangeal hair. The last example in which statistical significance was registered in all three groups is D and Ref. In group T values were (χ2=19.858, p=<0.0001, Fisher's exact test p=0.000008737), group F (χ2=8.286, p=0.0040, Fisher's exact test p=0.004519130) and group M (χ2= 11.994, p=0.0005, Fisher's exact test p=0.000545274). Highest statistical significance was observed in group T, followed by group M and group F. In total group, the largest proportion of individuals (2717) had abnormally crooked fifth finger and presence of midphalangeal hair, and smallest proportion (1073) had normal fifth finger and presence of midphalangeal hair. On the other side, in female group, the largest proportion of individuals (1181) also had abnormally crooked fifth finger and presence of midphalangeal hair, however, smallest proportion (430) had normal fifth finger and absence of midphalangeal hair. In male group, the largest proportion of individuals (1364) had abnormally crooked fifth finger and presence of midphalangeal

hair, while smallest proportion (550) had normal fifth finger and presence of midphalangeal hair. Regarding association between Lf and Ln statistical significance was observed only in group M ($\chi2$=7.184, p= 0.0074, Fisher's exact test p=0.008111623), while statistical significance was not observed in group F ($\chi2$=1.874, p=0.1710, Fisher's exact test p=0.175861855). In male group, the largest proportion of individuals (2191) had non-flat nail shape and short index finger, while the smallest proportion (228) had flat nail shape and long index finger. Association of Lf and Ref traits showed statistical significance in groups F ($\chi2$ =20.346, p=<0.0001, Fisher's exact test p=0.000007402) and M ($\chi2$=41.238, p=<0.0001, Fisher's exact test p=<0.000000001). Therefore, it is logical to conclude that highest statistical significance in this case was registered in group M. In female group, the largest proportion of individuals (1285) had abnormally crooked fifth finger and short index finger, and the smallest proportion (378) had normal fifth finger and long index finger. In male group the situation was similar, the largest proportion of individuals (1855) had abnormally crooked fifth finger and short index finger, and the smallest proportion (391) had normal fifth finger and long index finger Regarding association between D and Hc statistical significance was registered only in group T ($\chi2$ = 4.692, p=0.0303, Fisher's exact test p=0.032093967). In groups F ($\chi2$ = 1.371, p=0.2416, Fisher's exact test p=0.246670517) and M ($\chi2$ =2.604, p=0.1066, Fisher's exact test p=0.108240593) statistical significance was not observed. In total group, the largest proportion of individuals (2030) had right side hand clasping and presence of midphalangeal hair, while the smallest proportion of individuals (1711) had also right side hand clasping and absence of midphalangeal hair. In case of association between Ref and Hc statistical significance was observed in group F only ($\chi2$ = 4.923, p=0.0265, Fisher's exact test p=0.028970327). Statistical significance was not registered in groups T ($\chi2$ =3.599, p=0.0578, Fisher's exact test p= 0.060997732) and M ($\chi2$= 0.991, p= 0.3196, Fisher's exact test p=0.323410665). In female group, the largest proportion of individuals (1108) had right side hand clasping and abnormally crooked fifth finger, while the smallest proportion (414) had also right side hand clasping and normal fifth finger.

Statistical significant association was not registered between following traits: Midphalangeal hair-Extensibility of proximal joint of thumb, Hitchhiker's thumb-Digital index, Hitchhiker's thumb-Crooked fifth finger, Digital index-Extensibility of proximal joint of thumb, Nail shape-Crooked fifth finger, Crooked fifth finger-Extensibility of proximal joint of thumb, Extensibility of proximal joint of thumb-Hand clasping, Nail shape-Hand clasping, Digital index-Hand clasping, Hitchhiker's thumb-Hand clasping, Hitchhiker's thumb - nail shape and nail shape - extensibility of proximal joint of thumb. Regarding D and Pht following results were obtained which purely suggests lack of statistical significance among all 3 groups: T ($\chi2$ =0.016, p=0.8999, Fisher's exact test p=0.923847792); F ($\chi2$ =0.089, p=0.7649, Fisher's exact test p=0.790533135); M ($\chi2$ =1.224, p=0.2685, Fisher's exact test p=0.269928151). In case of Dht and Lf statistical significance was not found: F ($\chi2$ =1.172, p=0.2790, Fisher's exact test p= 0.285018113); M ($\chi2$ =1.994, p= 0.1580, Fisher's exact test p= 0.167816247). Statistical significance was also not registered in association between Dht and Ref: T ($\chi2$= 0.000, p=0.9884, Fisher's exact test p= 1.000000000); F ($\chi2$=1.404, p= 0.2360, Fisher's exact test p= 0.251564880); M ($\chi2$= 0.047, p= 0.8283, Fisher's exact test p=0.829697700). In case Lf and Pht statistical significance was not registered: F ($\chi2$= 0.006, p= 0.9391, Fisher's exact test p= 0.955834351); M ($\chi2$= 0.011, p= 0.9152, Fisher's exact test p= 0.916518951). Statistical significance was not found in all three groups regarding association between Ln and Ref: T ($\chi2$= 0.006, p= 0.9371, Fisher's exact test p= 0.950060646); F ($\chi2$= 0.088, p= 0.7672, Fisher's exact test p= 0.802901021); M ($\chi2$= 0.454, p= 0.5004, Fisher's exact test p=0.528605720). Case Ref and Pht was also one of the cases where statistical significance was not observed. Group T showed following results ($\chi2$= 1.676, p= 0.1954, Fisher's exact test p= 0.207934253); group F following results ($\chi2$ = 1.607, p= 0.2049, Fisher's exact test p= 0.215016014) and group M following results ($\chi2$ = 1.596, p= 0.2064, Fisher's exact test p= 0.225658910). Statistical significance between association of Pht and Hc was not registered in all three groups: T ($\chi2$ =0.002, p=0.9610, Fisher's exact test p=0.974636342); F ($\chi2$ =0.718, p=0.3969, Fisher's exact test p=0.398064529); M ($\chi2$ =0.341, p=0.5593, Fisher's exact test

p=0.581037977). In case of Ln and Hc statistical significance was not observed. Group T showed following results ($\chi2$ =1.445, p=0.2294, Fisher's exact test p=0.231078861); group F following results ($\chi2$=0.092, p=0.7611, Fisher's exact test p=0.788142971); group M following results ($\chi2$ =1.699, p=0.1924, Fisher's exact test p=0.202158623). Statistical significance was also not observed in case of association between Lf and Hc in all three groups: F($\chi2$ =0.003, p=0.9556, Fisher's exact test p=0.969964492); M ($\chi2$ = 0.138, p=0.7106, Fisher's exact test p=0.714351184). Regarding Dht and Hc following results were obtained which suggests lack of statistical significance among these traits. Significance was not found in all three groups: T($\chi2$=0.071, p= 0.7902, Fisher's exact test p=0.792048907); F ($\chi2$ = 0.242, p=0.6231, Fisher's exact test p=0.649306981); M ($\chi2$= 0.477, p=0.4898, Fisher's exact test p=0.492630053). In case of association between Dht and Ln statistical significance was not observed in any group: T ($\chi2$= 3.613, p= 0.0573, Fisher's exact test p= 0.061250992); F ($\chi2$=3.010, p=0.0828, Fisher's exact test p=0.090187515); M ($\chi2$= 0.742, p=0.3891, Fisher's exact test p=0.402617708). In case of Ln and Pht, statistical significance was not observed in all three groups: T ($\chi2$=1.997, p=0.1576, Fisher's exact test p=0.161041198); F ($\chi2$=0.247, p=0.6191, Fisher's exact test p=0.645890662); M ($\chi2$=2.185, p=0.1393, Fisher's exact test p=0.141195402).

There are not many papers in the scientific literature that include estimates of the association of morphological phenotypic traits, especially when it comes to hand. Thus, this paper has an additional value because a potential association of phenotypic traits is studied in a large number of unrelated individuals. The reason why it was decided to observe seven traits of hand is the assumption about the possible association of phenotypic traits since it is the same part of the body. The results of this study indicate the association of certain phenotypic traits of hand, distinguishing three different types of results. The first is that a statistically significant association was observed in both the total population and the gender-differentiated populations. The second type of results is statistically significant association observed only in the total population and the third type only in populations determined by gender. Of all the phenotypes in this study, the digital index and its association (Phelps, 1952) were studied the most. One reason is the different inheritance according to gender where female and male group have different dominant and recessive trait (Table 1). It is indicative that in most associations the largest number of individuals had dominant phenotypes for both traits. Only in one case, there was a situation where individuals had dominant-recessive phenotypes in associated traits. Mainly studies on other traits have been done to assess the differentiation of certain phenotypic characteristics with respect to gender association.

Conclusion

The assumption about the phenotypic association of hand traits is related to a total of nine combinations of traits. The phenotypic association of hand traits in gender groups (M and F) was observed in four combinations. It is obvious that the polygenic combinatorics of the genetic background of these traits indicates the connection of a certain number of genes, since they are polygenic traits. Detailed knowledge about the mechanism of inheritance would supplement the understanding of the genetic relationship of certain genes that form the basis of inheritance.

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Variation in Selection Intensities among the Western Coastal Populations of India

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Abstract

Selection is continuously occurring on the living beings and the fittest who are able to reproduce will survive. To measure this selection, the data from 954 women was obtained who belong to different ethnic groups of Gujarat and Maharashtra and various index and components were computed using Crow`s Index and Johnston and Kensinger`s Index. The Crow`s total index value was found to be 0.539. The mortality component was found to be 0.130 and fertility component was found to be 0.363. The contribution of fertility component was greater than the mortality component according to Crow`s Index. Value of total selection index computed using Johnston and Kensinger`s Index is 0.639. The index of selection due to pre-natal mortality and post-natal mortality was observed to be 0.064 and 0.130 respectively. Therefore, it is found that among coastal populations of Gujarat and Maharashtra the selection trend is more due to fertility component than mortality component.

Introduction

Ever since Darwin, the role of natural selection in shaping the various characteristics of life and reproduction across different generations has been central to understanding variation in life and its extent. Natural selection is one of the major forces which cause changes in the genotypic frequencies of a population. Researches have proved that it is a natural force which increases the chance of survival of the fittest and adaptable ones.

Karl Pearson in 1907, examined that Darwinian Theory has application to civilised man and the heavy exemption from life does not means inefficiency (Pearson, 1912). Fitness is important demographic property, a function of reproduction and deaths variables in a population. It has been found that reproductive success in humans depends upon the total amount of progeny that parents contribute to the proceeding generations (Jacquard, 1969). In larger populations, there is a larger gene pool, meaning that it would take more time for natural selection to show its affect and cause fixation of alleles than in a smaller population. However, it is difficult to show direct evidence of such selection by experiments and to measure selection intensity directly. Natural selection does not only depend on the fluctuating fertility, but also depends upon the differential survival of the off-springs up to the reproductive age (Reddy et.al., 1987; Lasker & Kaplan, 1995).

To measure the natural selection effect and its impact, Crow (1958) has provided an index to measure intensity of selection. This index mainly depends on two components first is Intensity of fertility (If) and second is Intensity of mortality (Im). So, this index allows the changes in the fitness to be determined by calculating specific birth and death rates. The Crow index would measure actual selection only, if there is complete heritability and genetic factor solely determine birth and death rate (Jorde and Durbize, 1986), whereas

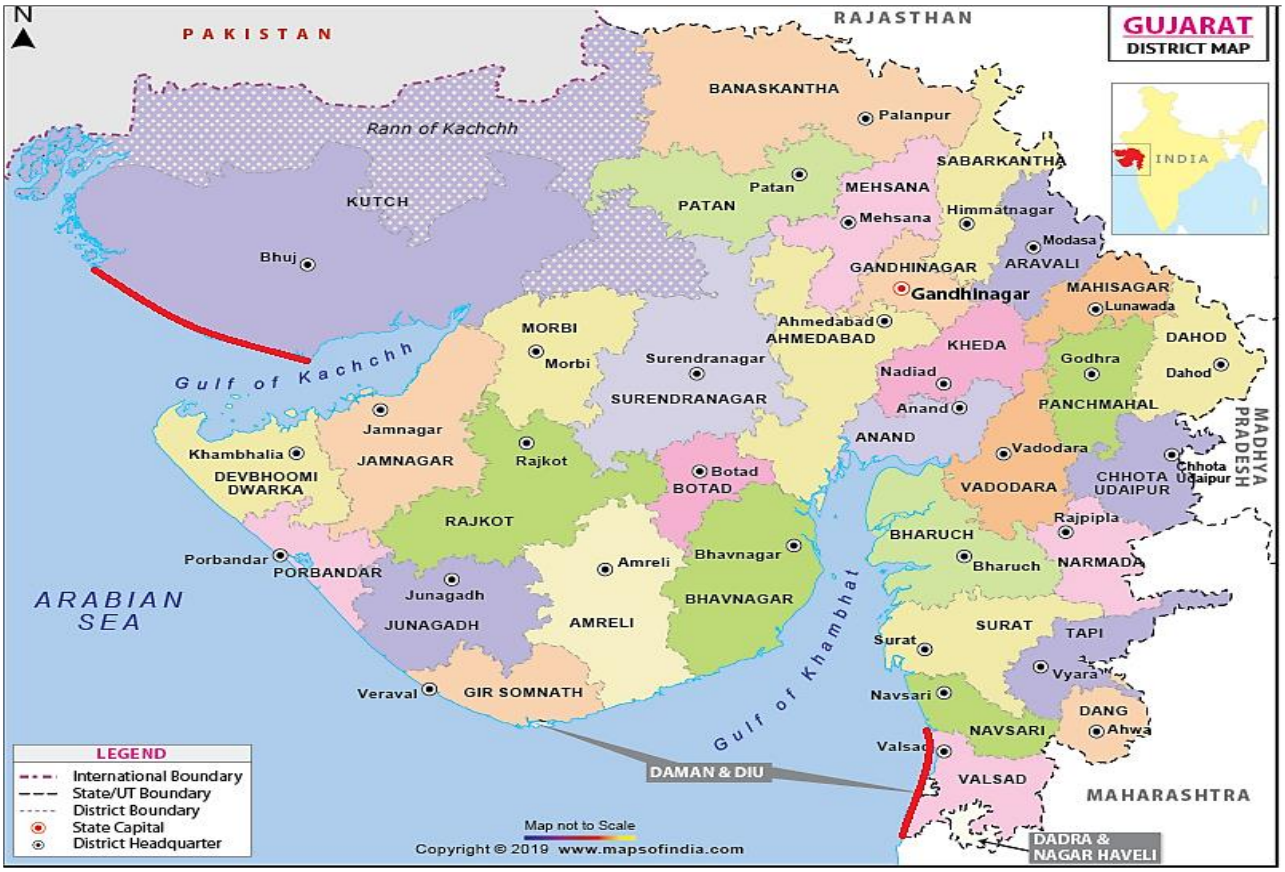
index of value zero indicates no changes in fitness (Livingston and Spuhler, 1965). Later on, this index was improvised by Johnston and Kensinger (Johnston and kensinger, 1971) to measure the third component called prenatal mortality and this index is known as Johnston and Kensinger Index.

Worldwide study on natural selection have shown that socio-economic and socio-cultural environment of a population have major impact on the fertility and mortality components and afterwards on selection (Crow 1958; Spuhler 1962; Johnston and Kensinger 1971; Tripp- Reimer 1980; Jorde and Durbize 1986; Sarkar et al. 1994; Kapoor et al. 2003; Gautam, 2009).

In India, the studies over different population groups have shown that natural selection is playing an important role in demonstrating fertility and mortality differentials among different populations in various environments (Gosh 1970; Murthy and Ramesh 1978; Basu et al. 1988; Barua 1976; Kapoor and Patra 1998; Chengal Reddy and Lakshanudu 1979; Kapoor and kshatriya 2000; Rao and Murty 1984; Gautam 2006, 2009; Reddy and Chopra 1990). India also has a huge coastal boundary divided into Eastern Coastal Zone and Western Coastal Zone with a varying risk factor like cyclone, tsunami, flooding etc. The coastal vulnerability is induced both by human related causes like rise in greenhouse gas (Nicholls et al. 1999; Varekamp 1999) and natural factors like season change. So far, the study among the coastal part of India (Odisha and Goa) is conducted by Kapoor et al. in 2012 which reveals that mortality is predominant factor contributing to selection intensity among coastal populations (Kapoor et al., 2012) whereas fertility is predominant factor among Non-coastal populations (Singh and Kapoor, 2015). Hence, the present investigation was to determine the variation in selection intensities among populations of two states of western coast of India i.e., Gujarat and Maharashtra. This study will also supplement the previous study among the various coastal populations of India and the world.

Methodology

The data for the present study was collected in different phases during year 2017 to 2019, from 81 villages of Gujarat and Maharashtra. These villages



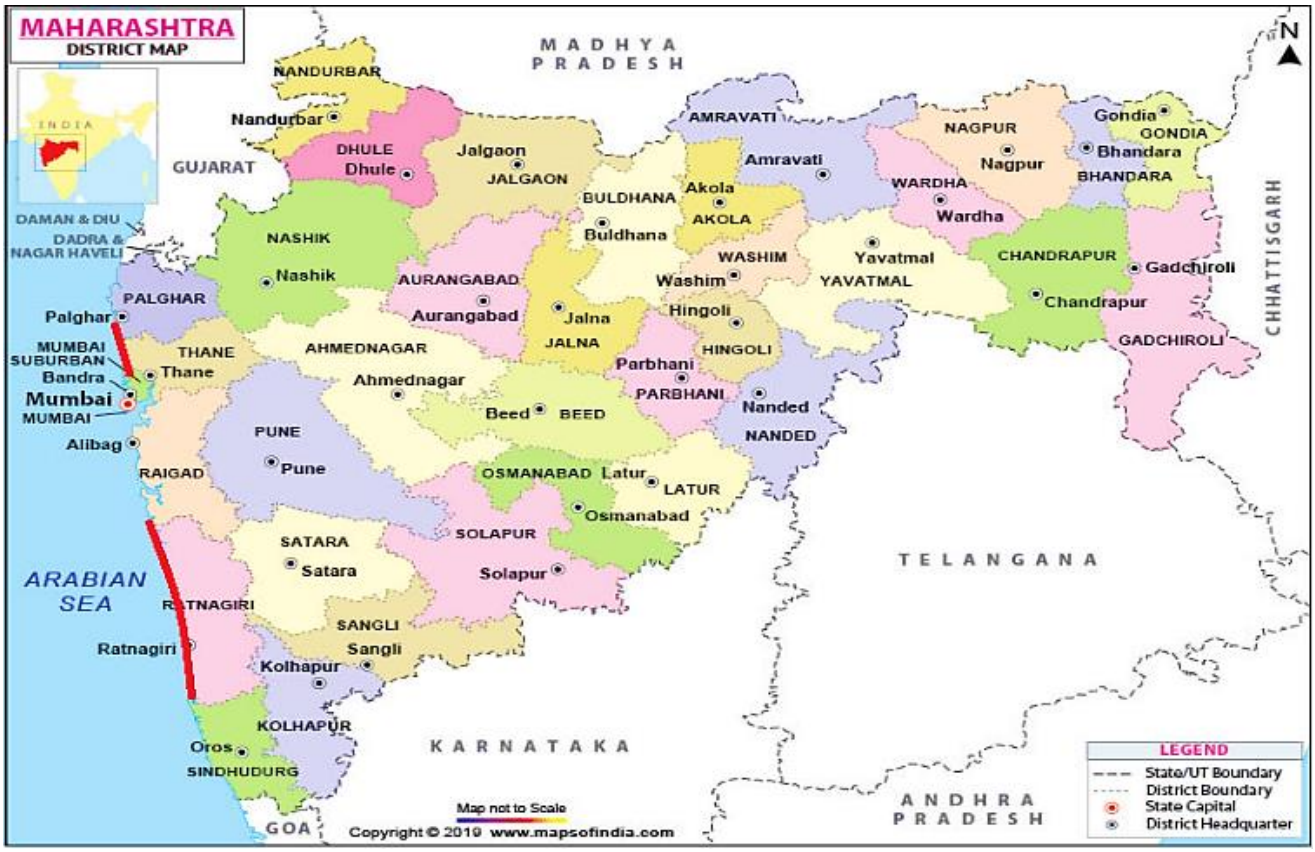


Figure 1 & 2: Study Areas in Gujarat & Maharashtra (Shown in Red Boundary), Source: Maps of India

belong to Kutch and Valsad districts of Gujarat and Ratnagiri and nearby villages of Mumbai districts of Maharashtra (Figure 1 & 2). Demographic data were collected from 954 women aged 40+ years (considered to have completed their fertility) on fertility (pregnancies, live births etc.) and mortality (still births, abortion, child death before 15 years of age etc.). Ethical clearance was obtained from appropriate authorities prior to the commencement of the study. Subjects were informed about the objectives of the study and written consent was obtained from them.

The selection intensity has been computed by using internationally accepted original method devised by Crow in 1958 and later modified formulae by Johnston & Keisinger in 1971.

Results and Discussion

Data on various demographic parameters were collected and tabulated (Table 1). The data involves 954 mothers who experienced 3207 pregnancies during their reproductive life span. Among these pregnancies 3017 were successful birth and 190 were pre-natal deaths. The post-natal death counts 329 of total successful pregnancies. The methodologies devised by Crow (1958) and Johnston & Kensinger (1971) were used to determine total selection indices. The proportion of pre-reproductive deaths varied from 0.162-0.073 and proportion of pre- embryonic deaths varied from 0.096-0.028 (Table 3). The proportion of survivor from birth to reproductive age was highest among Bhoi of Maharashtra (0.927) and lowest among Muslim of Gujarat (0.838). Overall the total index of selection was highest (0.617) among the Machhawa of Maharashtra and lowest (0.388) among the Macchiyaras of Gujarat. In Maharashtra the lowest total index of selection was among Bhoi (0.418) and in Gujarat the highest total intensity of selection was among Koli (0.596) (Table 2). Among all these mentioned populations the selection was operating due to fertility component rather than mortality component. The fertility component contributed more than 70% in total index of selection in all populations,

TABLE 1: Demographic variables Utilizes in calculation of index of total selection for Gujarat and Maharashtra population

Area	Ethnic Groups*	Occupation*	Number of mothers with completed fertility	Total number of pregnancies	Number of children ever born (live births)	Prenatal deaths	Post-natal deaths
Gujarat	Macchiyaras	Fishing/Business	132	477	457	20	36
	Muslim (Mavdari-Bhuj)	Fishing/Boat Makers/Shopkeepers/Miscellaneous works	74	247	234	13	38
	Koli	Miscellaneous jobs including Fishing	113	332	310	22	35
	Bhoi	Miscellaneous jobs including Fishing	107	358	322	36	42
Maharashtra	Manzi/Macchi	Fishing/Business	130	453	435	18	48
	Bhoi (Ratnagiri)	Fishing/Business	130	425	413	12	30
	Koli	Fishing/horticulture	96	337	318	19	30
	Malhar	Fishing and Shop keeping	76	264	247	17	28
	Machhawa	Fishing	96	314	281	33	42
		Total	954	3207	3017	190	329

*Fishing communities are substantially dependent on fisheries resources for their livelihood which are majorly influenced by a wide range of natural, climatic and human factors. These communities are indulged into a wide range of fishing activities including capturing of fishes, their culturing, processing and preserving to selling of fishes and their products in local markets. However, a high degree of dependency on coastal and marine resources makes these communities vulnerable to changes in resource availability and conditions. In order to reduce their higher dependency on fishing sector and to sustain their livelihood, these communities have also adopted altered livelihood activities like small-scale business, shop-keeping, shrimp collection, boat making and other miscellaneous jobs.

Table 2: Selection intensities (based on live births and pre-reproductive mortalities- Crow, 1958)

Area	Ethnic Groups	Occupation	Proportion of pre-reproductive deaths	Proportion of survivors from birth to reproductive age	Index of selection due to mortality	Index of selection due to fertility	Total index of selection	Mean number of live births		Variance of live births	% Fertility Component	% Mortality Component
			P_d	P^a_s	I_m	I_f	$I^a\|$	X	X^2			
Gujarat	Macchiyara	Fishing/Business	0.079	0.921	0.086	0.279	0.388	3.460	11.972	3.340	77.982	22.018
	Muslim (Mavdari-Bhuj)	Fishing/Boat Makers/Shopkeepers/Miscellaneous works	0.162	0.838	0.194	0.319	0.575	3.160	9.986	3.190	66.298	33.702
	Koli	Miscellaneous jobs including Fishing	0.113	0.887	0.127	0.416	0.596	2.740	7.508	3.120	78.636	21.364
	Bhoi	Miscellaneous jobs including Fishing	0.130	0.870	0.150	0.357	0.560	3.010	9.060	3.230	73.214	26.786
Maharashtra	Manzi/ Macchi	Fishing/Business	0.110	0.890	0.124	0.297	0.458	3.350	11.223	3.330	72.893	27.107
	Bhoi (Ratnagiri)	Fishing/Business	0.073	0.927	0.078	0.315	0.418	3.180	10.112	3.190	81.283	18.717
	Koli	Fishing/horticulture	0.094	0.906	0.104	0.599	0.765	3.310	10.956	6.560	86.389	13.611
	Malhar	Fishing and Shop keeping	0.113	0.887	0.128	0.308	0.475	3.250	10.563	3.250	73.077	26.923
	Machhwa	Fishing	0.149	0.851	0.176	0.375	0.617	2.930	8.585	3.220	71.505	28.495

Table 3: Selection intensities (based on pregnancies and Pre-reproductive mortalities including embryonic mortalities-Johnston and Kensinger, 1971)

Area	Ethnic Groups	Occupation	Proportion of pre-reproductive deaths	Proportion of survivors from birth to reproductive age	Proportion of embryonic (prenatal) deaths	Proportion of survivors to birth	Index of selection due to embryonic mortality	Index of selection due to post-natal mortality	Index of selection due to fertility	Total index of selection	Mean number of live births		Variance of live births	Fertility Component %	Post-natal Mortality Component %	Embryonic mortality component %	Total mortality component %
			P_d	P^a_s	P_{ed}	P^b_s	Ia_{me}	Ia_{mc}	I^a_f	I	X	X^2					
Gujarat	Macchiyara	Fishing/Business	0.079	0.921	0.042	0.958	0.044	0.086	0.279	0.449	3.460	11.972	3.340	71.216	19.040	9.744	28.784
	Muslim (Mavdari-Bhuj)	Fishing/Boat Makers/Shopkeepers/Miscellaneous works	0.162	0.838	0.053	0.947	0.056	0.194	0.319	0.663	3.160	9.986	3.190	62.366	29.252	8.382	37.634
	Koli	Miscellaneous jobs including Fishing	0.113	0.887	0.096	0.904	0.107	0.127	0.416	0.766	2.740	7.508	3.120	69.458	16.616	13.926	30.542
	Bhoi	Miscellaneous jobs including Fishing	0.130	0.870	0.073	0.927	0.078	0.150	0.357	0.682	3.010	9.060	3.230	66.530	21.989	11.480	33.470
Maharashtra	Manzi/ Macchi	Fishing/Business	0.110	0.890	0.051	0.949	0.053	0.124	0.297	0.536	3.350	11.223	3.330	66.851	23.161	9.988	33.149
	Bhoi (Ratnagiri)	Fishing/Business	0.073	0.927	0.028	0.972	0.029	0.078	0.315	0.460	3.180	10.112	3.190	76.641	17.039	6.320	23.359
	Koli	Fishing/horticulture	0.094	0.906	0.056	0.944	0.060	0.104	0.599	0.871	3.310	10.956	6.560	81.176	11.963	6.862	18.824
	Malhar	Fishing and Shop keeping	0.113	0.887	0.064	0.936	0.069	0.128	0.308	0.576	3.250	10.563	3.250	65.878	22.182	11.941	34.122
	Machhwa	Fishing	0.149	0.851	0.073	0.927	0.079	0.176	0.375	0.745	2.930	8.585	3.220	65.780	23.604	10.616	34.220

although it varied from 62.37 among Muslim of Gujarat to 81.18 among Koil of Maharashtra. As mentioned in Table-2 the overall contribution of fertility component is 75.70% while of mortality component is 24.30%. The reduction in mortality component was may be due to diseases occurring among the coastal populations. The total selection index was reported to be moderate among these populations, as average total selection index for Indian population was reported to be 0.585 (Gautam, 2009).

The high post-natal mortality in the studied populations may be due to the poor health care (Shyam et al., 2014) and environment provided to them. Environmental conditions contributing high post-natal mortality include inadequate facilities for proper living and more emphasis on the ante-natal care than post-natal care (Mavalankar et al., 2009). Furthermore, the negligence from various vaccinations, unhealthy post-natal care practices, gender related neglect of healthcare seeking due to high expenditure of specialized healthcare services can also be a cause of this high rate of post-natal mortality (Shah and Dwivedi, 2013; Dabade et al., 2013; Chaudhari and Virmani, 2016).

The contribution of fertility component to total selection index in current study is higher than the earlier study of coastal populations study by Kapoor et al in 2012. Their study among the populations of Goa and Odisha shows the fertility component contribution of 66.23% while present study estimate is of 69.54% (Table-3). Similarly, there is a decrease in the embryonic mortality component contribution (9.92%) as compared to their study (13.95%) and there is slight increase in the post-natal mortality component contribution (19.82%-earlier to 20.54%-present). Since both the studies were conducted among the coastal populations so the risk on the life must be same through natural calamities, although the quality of life can be affected by their local government agenda or the policies and facilities available to them in last few years. So, the overall increase in fertility component and decrease in embryonic mortality component shows the continuous increase in the health services in the present study area despite the fact that both area differs so, there must be chance that the variations can be area dependent, but if we consider the progress of coastal areas on overall basis then the increase is efficient and valid.

Conclusion

The study shows that the contribution of fertility component in total selection is more than mortality component. As, this show an inversion from the general past trend of selection among coastal populations and similarity with non-coastal populations. This must be due to improved health care, proper sanitation, reduction or protection from natural hazards etc. Further, a re-analysis of all the studied coastal area after fixed time must be required to trace out the actual selection pattern.

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Syphilis in London's Children's Hospitals (1852 - 1921)

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Abstract

Establishing the palaeoepidemiology of diseases in children is a difficult task due to limited written and physical evidence. Historic admissions records from children's hospitals can provide large data sets allowing insights into this area, rather than just case studies which are what most commonly appear within the palaeopathological literature. An oft ignored aspect of childhood illness is venereal disease due to the social taboo surrounding this topic. This study aimed to investigate the extent of syphilis within Victorian and Edwardian London's children's hospitals and explore the socioeconomic context this disease was occurring within. This was achieved by examining digitised hospital admissions data covering the mid-nineteenth to early twentieth centuries for three children's hospitals. These records revealed a significant spike in admissions for congenital syphilis following World War One. This was likely due to the return of troops from the warfront who had been infected whilst in mainland Europe. It was also found that the upper levels of the working classes accounted for the majority of the admissions, despite these institutions being created to aid the children from the lowest socioeconomic groups. Finally, this paper highlights the need for researchers to also consider the possibility of children having acquired syphilis rather than congenital syphilis when examining such records.

Introduction

The study of venereal diseases (VD) in the past, or sexually transmitted infections in modern medical terminology, allows researchers to examine how human sexuality and health intersect, and how these diseases have evolved and spread through populations. The study of childhood health and disease in the past allows researchers to explore the value that past societies placed upon the youngest and often weakest of their members (Lewis 2018). These areas overlap within the study of congenital syphilis.

Studying congenital syphilis in the past

The skeletal changes that accompany syphilitic infections, both acquired and congenital, are well documented within the palaeopathological literature (Aufderheide and Rodríguez-Martín 1998; Waldron 2009; Lewis 2018; Roberts and Buikstra 2019). However, the study of congenital syphilis in palaeopathology and the history of children's health presents a challenge to researchers. The skeletal remains of non-adults are not commonly recovered during archaeological excavations due to taphonomic factors, poor excavation strategy and technique, as well as issues of misidentification and/or disposal (Lewis 2019). Accordingly, few large-scale archaeological studies of congenital syphilis exist. A Google Scholar search using the search terms "congenital syphilis archaeology" returned 612 results published since 2016. Of these, less than 20 papers discussed cases of congenital syphilis in archaeological/historic human remains, and the majority of these were single case studies, thus highlighting the dearth of studies regarding this topic. Whilst this is not an exhaustive search using multiple combinations of search terms to

capture all possible results, it is highly unlikely that repeating the exercise would identify many more papers. Indeed, Lewis (2018) listed only 18 possible cases of congenital syphilis reported in the palaeopathological literature with the majority being from the Americas.

At present, the authors could only find three reported cases of congenital syphilis within British palaeopathology, all of which were from London. Two cases were from the medieval and post-medieval period (Walker 2012; Walker et al 2015). The third was from the Victorian period and consisted of a singular skull curated in the Pathology Museum of Imperial College London, belonging to a one-year-old girl named Rosa Pike who died in 1886 (Patel and Mitchell 2007). Similarly, the largest reported collection of non-adult syphilitic remains that could be found was a rediscovered historical anatomical collection (Cole et al 2020). This collection originally belonged to the nineteenth century French physician Jules Parrot and consisted of 56 bones, representing a minimum of eight individuals of foetal and neonatal age. These bones were curated by Parrot in the latter half of the nineteenth century from the autopsied remains of syphilitic children, at *l'Hospice des Enfantes Assistés* in Paris, France. Parrot later brought his skeletal collection to the Pathological Society of London and exhibited the bones during a lecture on the skeletal effects of congenital syphilis; the transcript of which was later published in the Lancet (Parrot 1879). Although Dittmar and Mitchell (2016) have shown that medical collections can provide additional contextual information regarding the period in which they were formed, the value of the Parrot collection is arguably more limited than the curated skull of Rosa Pike. The latter was accompanied by an entry card which listed Rosa's name, her symptoms, and her mother's symptoms. This allowed Patel and Mitchell (2007) to identify a birth and death certificate for Rosa and explore her precise life circumstances and illness. In contrast, Cole et al (2020) had no other contextual information beyond what the bones themselves could provide about the individuals they were sourced from, and thus the researchers were limited in regard to what may be deduced about *l'Hospice des Enfantes Assistés* and its patients at the time Parrot was performing autopsies and building his collection.

Where physical evidence is lacking, written evidence may be used to investigate questions of the past. However, few historical records focus on children, and even fewer focus on childhood diseases (Heywood 2017). Historic hospital records are an exception to this and may be used on their own or as a complementary source of data within palaeopathological studies (Hirst 2018). Hospital admission data does not always present an easy alternative due to the time needed to access, examine, and interpret physical records. Instead, the digitisation of records can aid the interpretation of such data, however the resources required to undertake this process (finance, technology, transcribers, etc.) can equally present barriers for both researchers and institutions (Hirst 2018). Additionally, hospital records present some of the same issues as archaeological skeletal assemblages, in that they are not representative of the whole population, as only the sick are represented, and researchers can only examine those records which survive (Waldron 2007).

The Historical Hospital Admission Records Project (HHARP) is an open-source online repository (https://hharp.org) that brings together two-thirds of the surviving admissions registers for nineteenth century children's hospitals in Great Britain (Hawkins 2012). This project formed from a collaboration between Kingston University's Centre for the Historic Record and four children's hospitals within London and Glasgow. The included institutions are, from London: Great Ormond Street Hospital and its convalescent home Cromwell House, the Evelina Hospital, and the Alexandra Hospital for Children with Hip Disease; from Glasgow: The Royal Hospital for Sick Children. The HHARP project includes over 140,000 admission records, covering the period between 1852 and 1921.

This paper uses the HHARP dataset to identify the number of children diagnosed with syphilis that were admitted to the London hospitals, allowing for the examination of trends in admission, age, sex, deaths, and social background. This will provide the largest investigation of historical congenital syphilis currently in the literature, whilst also highlighting a data source

that may prove valuable for research focused upon children's health in the mid-nineteenth to early twentieth centuries.

The Hospitals

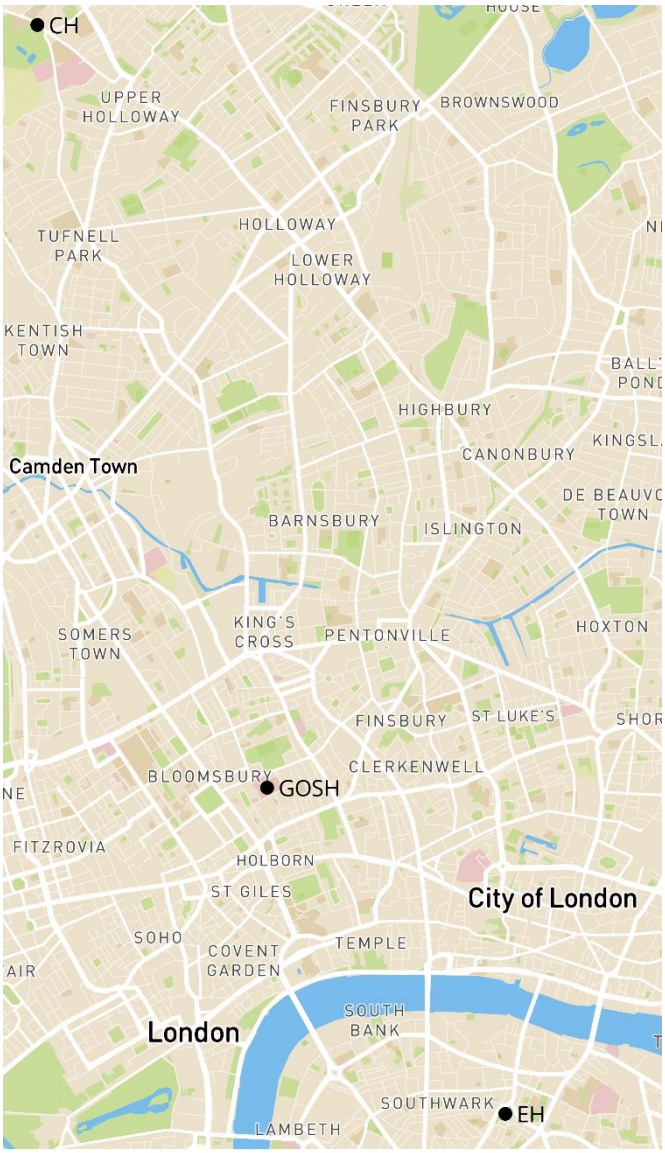

Figure 1: The locations of the two children's hospitals and the convalescent home in London during the examined period.

This investigation focused solely upon Great Ormond Street Hospital (GOSH) and its convalescent home Cromwell House (CH), as well as the Evelina Hospital (EH) (Figure 1). The Alexandra Hospital admitted no children with diagnoses of syphilis, whereas the Royal Hospital in Glasgow was outside of the geographic boundaries of this study.

GOSH was founded in 1852 by Dr Charles West and was the first devoted children's hospital to open in Britain (Tanner and Hawkins 2013). Its principal aims were to provide healthcare for the poor, encourage clinical paediatric research, and to provide training for paediatric nurses. It initially opened with only 10 beds and admitted local patients; it expanded over time, and by 1914 the hospital could admit over 200 inpatients and had an outpatient department treating over 20,000 children (Tanner and Hawkins 2013). GOSH was founded as a charity, with the option for donors and patrons to become Governors of the Hospital, entitling them to be able to recommend patients for admission, with the number of admissions per year being proportionate to their financial contribution.

GOSH's convalescent home, CH, was opened in 1869 to provide a care environment for the youngest convalescing patients, as well as those recovering from surgery or long-term illness (HHARP 2010). The home was opened in response to the governors of GOSH realising that many patients were being readmitted to the hospital's wards soon after being discharged because the circumstances at home mitigated their recovery.

EH was founded in 1869 by Baron Ferdinand de Rothschild with objectives mirroring those of GOSH (Tanner and Hawkins 2013). At the time of opening, EH was unique amongst London's children's hospitals because it was situated within a purpose-built building and was initially privately funded by the Baron, who did so for the first 20 years of its history. By 1900 the hospital had 100 beds, but only the funds to operate 66 of them. This led to the hospital focusing its efforts within its outpatients department, where over 73,000 visits occurred in 1904 (HHARP 2010).

Both hospitals had rules governing who could be admitted and these were based on age and health. The hospitals banned admission of any child with an infectious fever, whooping cough being an exception, and limited chronic or incurable conditions (HHARP 2010; Tanner and Hawkins 2013). Typically, children under two years of age were prohibited from entry. The purpose of this was to help ease the work of the nurses by ensuring that admitted children could walk and

partly feed and clothe themselves; the upper age limit was 10 to 12 years (HHARP 2010; Tanner and Hawkins 2013). Additionally, patients were theoretically meant to have a subscriber's letter to allow admittance. However, these rules were difficult to enforce, as often the medical need of the child won out (HHARP 2010; Tanner and Hawkins 2013).

Syphilis in brief

Syphilis is caused by the bacterium Treponema pallidum pallidum (*T. pallidum*) and has two distinct forms: acquired and congenital. Acquired syphilis is typically transmitted through sexual contact and the infection can be split into three stages. Primary syphilis occurs within, on average, a few weeks after exposure (Baker 2020). This manifests as one or several painless ulcers (chancres) at the site of infection, which spontaneously heal within several weeks. Secondary syphilis occurs after another couple of months and is characterised by flu-like symptoms and rashes which most frequently affect the palms and soles. Again, these symptoms will spontaneously heal after a couple of months. The disease then enters an asymptomatic latency period. After some years destructive lesions, known as gummas, will develop and the disease enters its tertiary stage (Dobson and Sánchez 2019). These gummas can affect multiple tissues, including the skin and bone. When bone is affected by acquired syphilis, it is typically bilateral and involves multiple sites, including most notably the tibia and cranium, of which the nasal structures and vault, are most affected (Roberts and Buikstra 2019). The gummatous lesions on the frontal bone are particularly distinctive and are known as *caries sicca* (Waldron 2009). Tertiary syphilis may also affect the cardiac and nervous systems.

The transplacental infection of syphilis from a mother to a foetus is the most common method for a child to contract congenital syphilis. During pregnancy, syphilitic infection can also lead to spontaneous abortion, still birth, or perinatal death (Baker 2020; Dobson and Sánchez 2019). Rarely, transmission can also occur at birth through contact with a syphilitic lesion. The likelihood of transmission ranges between 60% to 100% during primary and secondary syphilis, with decreasing rates of transmission occurring after the fourth year of infection (Woods 2005; Baker 2020). It is possible that a syphilitic infection may be passed on via breastfeeding, but this is due to the infant's exposure to a syphilitic sore upon the breast, rather than *T. pallidum* being present within breastmilk (Lewis 2007). Effective prenatal screening of mothers can eliminate mother-to-child transmission of the disease. However, transmission still occurs with Wijesooriya et al (2016) calculating that in 2012 there were 930,000 syphilitic pregnancies worldwide, of which 36.7% resulted in adverse outcomes, including stillbirth, neonatal death, preterm birth, and infection with congenital syphilis. Congenital syphilis can be split into two stages. Early congenital syphilis occurs within the first two years of life and late congenital syphilis occurs after this. Most children will not show signs of syphilitic infection immediately at birth; instead, symptoms can develop weeks or years later. Transplacental infection results in widespread presence of *T. pallidum* throughout the foetal tissues (Dobson and Sánchez 2019) leading to multiple organs manifesting symptoms, though not all will occur concurrently (Table 1).

Sexuality in England between 1850 and 1920

The study of sexuality and sexual health during the period examined here suits the historical model of the "long nineteenth century", often described as lasting from 1789 to 1914. Within this model historians refer to World War One rather than monarchical changes as the event which led to the greatest socio-economic and intellectual changes in Europe (Bevir 2001). The sociocultural attitudes that develop during the Victorian period (1837-1901) persisted into the Edwardian (1901-1914) and War (1914-1918) eras. Additionally, it was only at the turn of the twentieth century that medical science started to identify the causative pathogens of VD and develop tests and treatments for them. In the case of syphilis, *T. pallidum* was identified by Schaudinn and Hoffman in 1905, and in 1906 Wassermann introduced his eponymous blood test for the disease (Dobson and Sánchez 2019).

An arsenic based medicine called Arsphenamine, also known as Salvarsan, was then discovered in 1908 by Ehrlich.

TABLE 1. Some of the symptoms seen during early and late congenital syphilis (drawn from Baker (2020) and Dobson and Sánchez (2019)).

Early Congenital Syphilis		
Anatomical Element	**Symptom**	**Definition**
Liver & Spleen	Hepatosplenomegaly	Enlarged liver & spleen
Skeleton	Periostitis	Inflammation of the bone's outermost membrane
	Osteochondritis	Inflammation of the cartilage or bone within a joint
Skin	Maculopapular Rash	Small dark red-copper raised and flat lesions
	Mucocutaneous Lesion	Fissues and mucous patches around the lips, nostrils and anus
Blood	Anaemia	Iron deficiency within the blood
Central Nervous System	Meningitis	Infection of protective membranes around the brain and spinal cord
	Bulging Fontanelle	Firm outward curving soft-spots on the head caused by rising intra-cranial pressure
	Palsies	Types of paralysis frequently accompanied by weakness, loss of feeling and uncontrolled movement
	Seizures	Sudden uncontrolled electrical distrubance in the brain leading to changes in physical and mental wellbeing
	Hydrocephalus	Abnormal buildup of fluid within the brain
Respiratory System	Syphilitic Rhinitis (Snuffles)	White and often bloody nasal discharge
	Pneumonia	Infection of the alveoli in the lungs
Late Congenital Syphilis		
Anatomical Element	**Symptom**	**Definition**
Eyes	Interstitial Keratitis	Scarring of the cornea from chronic inflammation
Dentition	Hutchinson's Incisors	Notched appearance in the permanent upper central incisors
	Mulberry Molars	Maldevelopment of cusps on the first molar
Skin	Saddle-nose	Bridge of the nose collapse
	Hard Palette Perforation	
	Rhagades	Scarring resulting from mucocutaneous lesions
Skeleton	Sclerosing lesions	Abnormally thich and dense bone growth
	Saber Shin	Anterior bowing of the tibia
	Frontal Bossing	Enlargement of the frontal bone
	Higoumenakis Sign	Periostitis of the sternal end of the clavicle
	Clutton joints	Painless arthritis of joints, commonly the knees
Central Nervous System	Tabes dorsalis	Degeneration of spinal cord leading to additional symptoms such as dementia and paralysis
Eighth Cranial Nerve	Deafness	

This drug was called the "magic bullet" due to its highly effective nature and would be used in conjunction with the continuing use of potassium, mercury, and bismuth-based chemicals and silver nitrate until the introduction of Penicillin in the 1940s (Tampa et al 2014). However, these heavy metal-based drugs often produced side-effects that some recorded as being worse than the disease itself (Keen 1953; Dayan and Obi 2005).

From a sociological standpoint, whilst the Victorian period saw an increase in the study of gender, race and class, the ideas at the intersection of these subjects and sexuality were not new ones, but rather revisions upon well-established prejudices (Hall 2013). The moral standards for male and female sexuality during this period could be described as contrary and hypocritical: male sexual access to women was deemed to be a necessity, but chastity was the preeminent female virtue, and any fall from grace led to ostracization from respectable society (Cook 2004; Hall 2013). This double standard was well illustrated through the increased visibility of urban prostitution despite increasing social commentaries praising self-control and marital fidelity (Adams 2004). The consequences of this was an increased risk of exposure to VD for all, sex with prostitutes being the prime route by which syphilis could enter the middle classes (Cook 2004). By the 1880s, the blame for the spread of VD was primarily placed upon men, and this view was maintained into the early twentieth century, with the suffragette Christabel Pankhurst asserting in 1911 that 75% of men had contracted some form of VD prior to marriage (Savage 1990; Hall 2013). Indeed, Cook (2004) noted that of deaths linked to syphilis at the time, the highest rates were seen amongst men of the unskilled labouring classes and of the middle/professional classes.

Syphilis itself became somewhat of a national obsession in the 1880s due to it being seen as a threat to marriage, motherhood, and children (Townsend 2018). Socially, congenital syphilis was seen as a disease which negated childhood, with such children being described as old, exhausted with suffering, and the pallid victims of the vice of life (Townsend 2018). These Victorian beliefs along with the more general beliefs around sexuality persisted into the Edwardian and War eras with the sexual culture remaining relatively homogenous where respectability was considered to be of prime importance and members of all classes and age held negative attitudes towards sexuality (Cook 2004).

Materials and methods

The data present within HHARP includes the admissions data as transcribed from the admissions registers, as well as added standardised data. The information available can be viewed online or downloaded as an Excel file and it covers five main areas:

1. Personal details: The name, sex, age, and birth year of the individual and their date of admission.

2. Residence: The address, county, London district and subdistrict the address can be found in, or whether it was outside of London.

3. Admission and stay: The admitting institution and doctor, the length of stay, ward they stayed on, any remarks made by the doctor at admission.

4. Disease, outcome, and discharge: The disease the individual was admitted with and its ICD10 code, the disease group this belongs to, information about provided treatment, the outcome of the admission, post-mortem information, date of discharge and where the patient was discharged to.

5. Patient history: disease history, whether the patient was vaccinated for smallpox, and the parents' occupation.

A core of information is available for almost all admissions: the child's name, their age at admission, and their sex. The address of the admitted child is present in most cases. Also, frequently present is information regarding the diagnosis, dates of admission and discharge, and the result of the child's treatment during their admission. This final category is recorded as: a) Cured; b) Relieved; c) Not Relieved; or d) Died. Some areas of the data are only present in a single hospital's register. For example, only the Evelina Hospital provides post-mortem data for some of the admissions (Hawkins 2012).

The HHARP database was initially searched for all children admitted for VD using the "Venereal Disease"

category in the disease groups' options. Another search was made using the search terms "venereal" and "syphilis" in conjunction with the "Congenital Disorder" category. Hospitals outside of London and/or with no admissions for syphilis were excluded from the dataset. The remaining data was cleaned by removing duplicate records, which are multiple records listing the same individual entering the same institution on the same day. Then the names of the children in this cleaned dataset were used as their own search criteria to identify children who were admitted to hospital multiple times, regardless of diagnosis.

Data detailing refusals of admission into GOSH between the years 1881 and 1892 is available by request through HHARP. This data includes the names of the patient, the patient's address, a diagnosis, the date of and reason for refusal. This data was also searched for patients admitted with a diagnosis of syphilis.

Where an address was recorded and deemed by HHARP to be within London, a likely socioeconomic class for the child at the time of admission was identified using the Booth Poverty Maps (http://booth.lse.ac.uk). This is an open-source online resource available through the London School of Economics. The Maps synthesise the socioeconomic data collected between 1889 and 1903 by Charles Booth and covers a region running from Greenwich to Hammersmith on an East/West axis, and Hampstead to Clapham on a North/South axis, with the City of London omitted. Seven socioeconomic categories were used by Booth to categorise London: Lowest Class; Very Poor; Poor; Mixed; Fairly Comfortable; Middle Class; Upper-Middle and Upper Classes. If a street could not be found due to being outside the map borders, changes in street names or layout, or if a street exhibited multiple socioeconomic statuses, a socioeconomic status of "Unknown" was recorded. For addresses outside of London, Google maps was used to estimate a straight distance (rounded

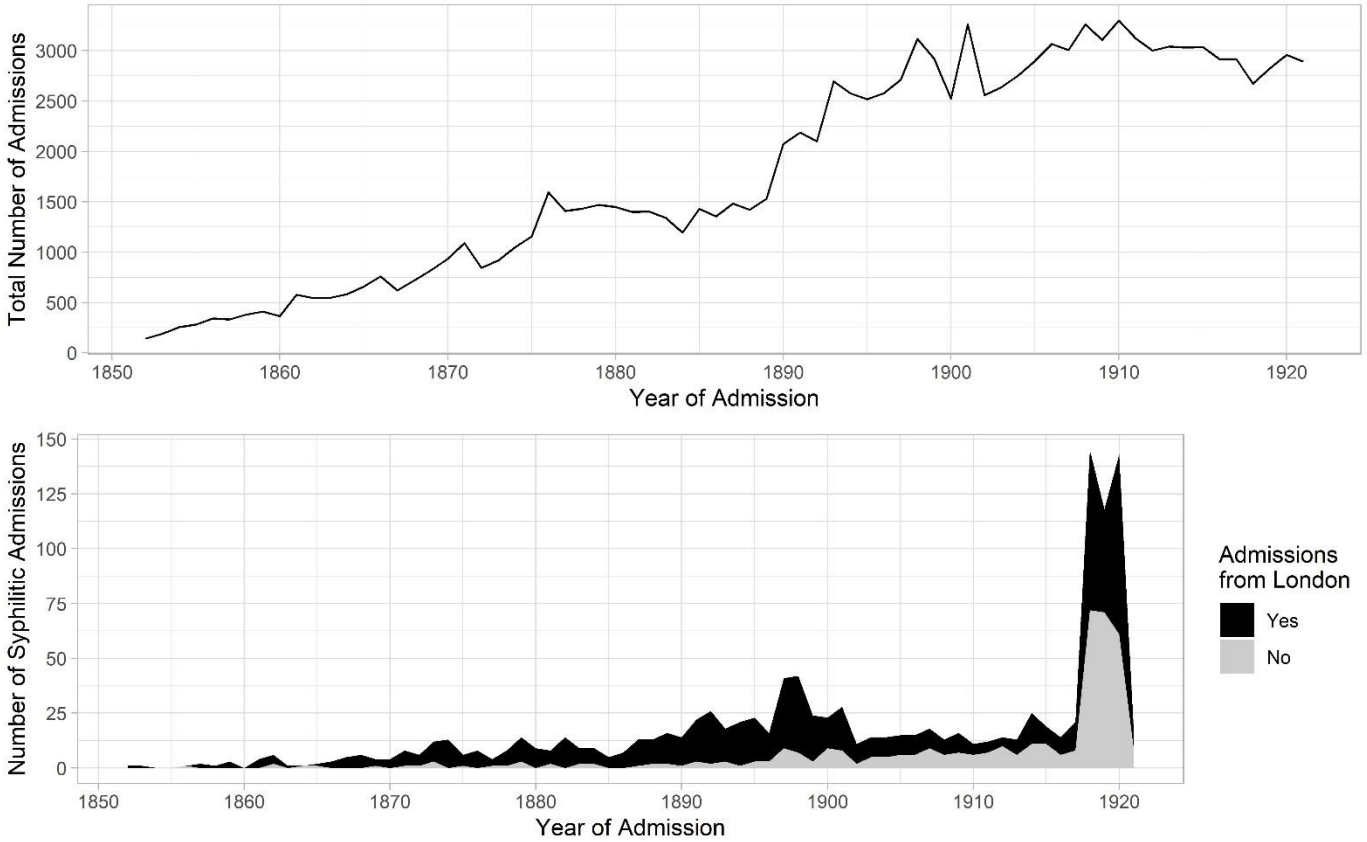

Figure 2: The total number of admissions and the number of syphilitic admissions recorded within the HHARP database from GOSH, CH and EH.

to whole kilometres) travelled by the child to reach their admitting institution.

Results

Admissions

Between 1852 and 1921, 1,194 children were admitted into GOSH, CH and EH with a diagnosis of syphilis (GOSH: 993; EH: 147; CH: 54) representing a total of 803 individuals, 391 males and 412 females. These represent 0.96% of the total admissions to the three institutions during this period, with between 0 and 145 admissions for syphilis occurring each year (Figure 2) with just over a third of these admissions (n=406, 34.00%) being admitted between 1918 and 1920.

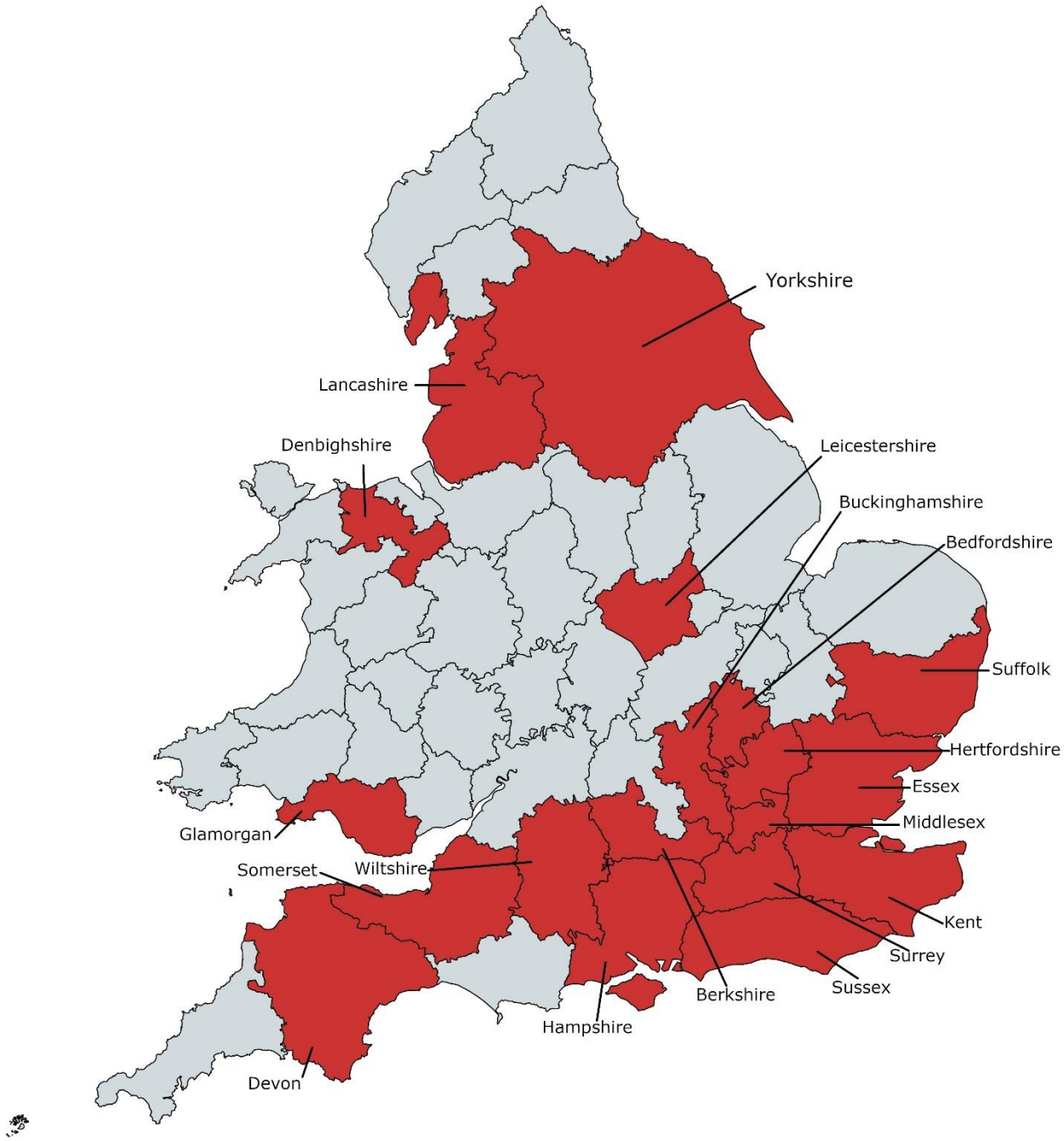

Figure 3: The historic counties of England and Wales, excluding Jersey. The highlighted and named counties are those from which children were admitted to the institutions in this study.

In addition to the diagnoses of syphilis, 217 children were admitted with additional diagnoses (n=234) representing 116 conditions. The two most common conditions present were marasmus (n=22), a severe form of malnutrition, and bronchopneumonia (n=15). There were also 26 types of conditions which would have affected bone. These occurred 44 times in the register and in 40 children. The most commonly recorded was periostitis (n=6), though periostitis of the femur and of the knee were also listed (both n=1). "Caries", "disease", "necrosis", and "tubercular" were descriptive terms used in the register for the conditions affecting specific bones or joints. This occurred 18 times, with the tibia (n=4), knee joint (n=2), mastoid (n=2), radius (n=2), ulna (n=2), spine (n=1), maxilla (n=1), mandible (n=1), fingers (n=1), and hips (n=1) all being recorded.

Children from within London (n=791) were admitted more commonly than those outside of London (n=403), with a mean admittance of 11 children from within London and six from outside of London per year. These values drop to nine and three, respectively, for the years outside of the 1918 to 1920 spike in admissions. Two-hundred-and-forty individuals make up the admissions outside London with 177 of these being within what would now be classed as the Greater London area. The shortest distance from the child's home address to the admitting institution was 5km from Finsbury Park, London. This area is just outside the northern edge of the Booth Maps. The mean distance travelled by the children was 28.52km. Only 42 children travelled distances greater than this mean value, and 27 of these were from within the counties surrounding London. Six children travelled over 200km with two children travelling from Wales, and one child each from Jersey, Yorkshire, Devon, and Lancashire with the greatest distance being 356km (Figure 3).

Age at admission

Age at admission data was present for all children except five. The age at admission ranged between 11 days old to 13 years and 11 months. Categorising the data into year groups showed that children under one year of age were the most represented age group (n=271; 22.70%) (Figure 4). A t-test of equal variance showed that there was no significant difference between the number of males and females admitted into the hospital, however males were slightly more

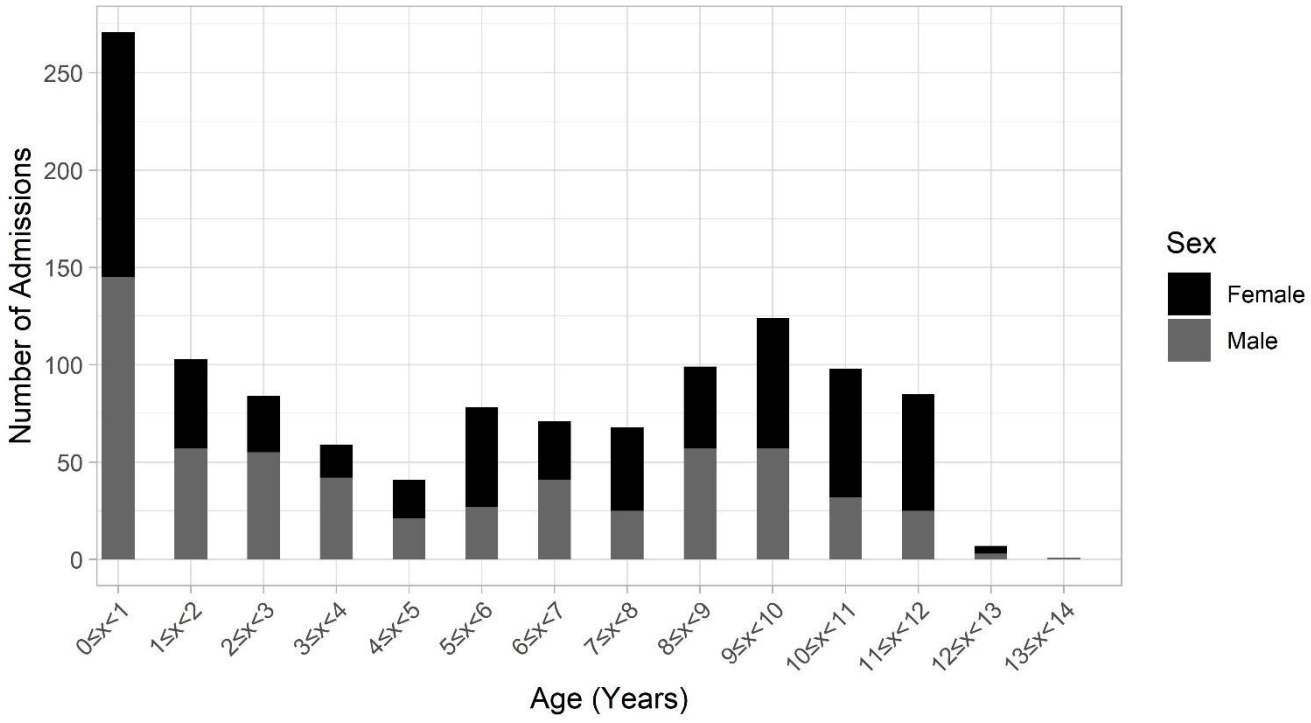

Figure 4: The number of syphilitic admissions to GOSH, CH and EH, split by age and sex.

represented in the younger third of the age groups (0 to 5 years old), whilst females were more represented in the oldest third of the age groups (10 to 14 years old).

Outcome

Outcomes were provided for 1,161 of the admissions (97.24%). “Relieved” (n=715) was the most common outcome recorded, accounting for 61.56% of the outcomes. An outcome of “cured” occurred 113 times (9.73% of outcomes). If “cured” and “relieved” are interpreted to mean symptoms absent by time of discharge, they account for over 70% of outcomes recorded. There were 139 (11.97% of outcomes) children who were “not relieved” of their symptoms during their admission, and 194 (16.25% of outcomes) children died after admission.

Socioeconomic status

Socioeconomic data was found for 648 (81.90%) of the addresses within London. Of these the most common socioeconomic statuses recorded were “mixed” (28.21%) and “fairly comfortable” (33.25%), representing the upper levels of the working classes. The poorest and richest socioeconomic groups were the least represented (Figure 5).

Repeated admissions

There were 212 children (26.40% of the admitted children) admitted multiple times into the hospitals with diagnoses of syphilis and other conditions. Most were only admitted twice (n=96), with 10 children being admitted 10 times or more: the maximum number of admissions for a single child was 13. Among the children admitted to GOSH, 65 were transferred to CH, with 53 of these being transferred just once. The remainders showed transfers between different wards at CH or being returned to GOSH.

There were 105 conditions other than syphilis present within the admissions records of the children who were repeatedly admitted. Periostitis of the tibia (n=14) and keratitis (n=10) were the most common. Where the diagnosis clearly indicated the element of the body

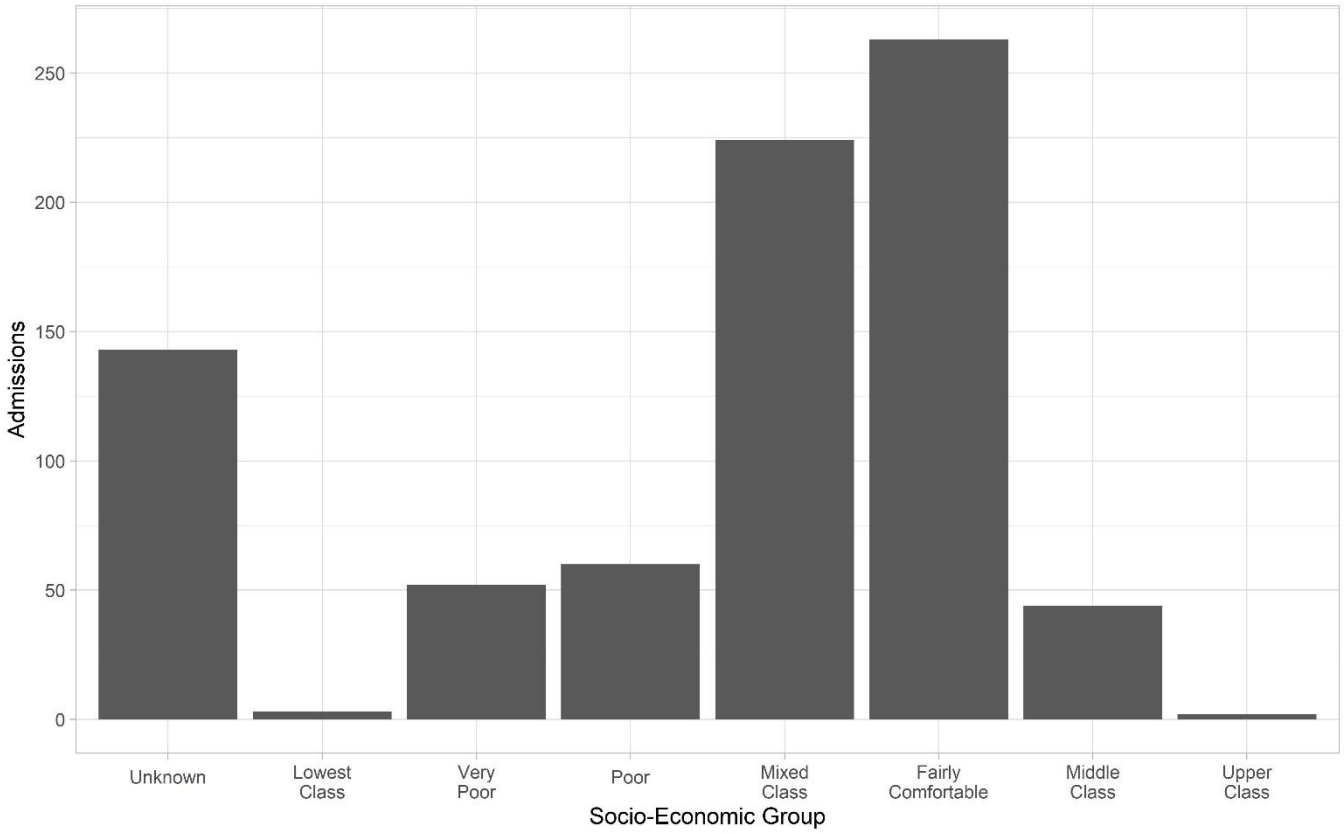

Figure 5: Likely socioeconomic statuses for the children admitted from within London.

affected by disease, the eye (n=19) and the knee and the tibia (both n=17) were the most affected elements.

Relatives

Four sets of likely relatives (defined by a shared surname and address) were present in the data, all admitted into GOSH. The Taylors, Victor (1 year old) and Eustace (3 months old), were admitted in October 1901 and March 1902 respectively, and both died after admission. The Clarks, William (3 years, 3 months old) and Emily (7 months old), were admitted in May and August 1918, respectively. Emily died after admission whilst William's symptoms were not relieved. The Heywood/Haywoods, Bertha (9 to 10 years old) and Percy (5 to 6 years old) were both admitted six times in the latter halves of 1918 and 1919 respectively, and were "relieved" of symptoms on all admissions. Finally, there were the Tavener/Taverners, Daisy, Edith and Emily who were collectively admitted a total of 22 times. Daisy (4 to 5 years old) was admitted 10 times between March 1918 and June 1919. Emily (5 to 8 years old) was admitted seven times between April and July 1919. Edith (10 years old) was admitted five times between July and September 1919. The sisters survived their admissions, but only Emily was recorded as having outcomes of "relieved" for every admission. The Haywood/Heywoods were from outside of London, whilst the socioeconomic statuses of the others are as follows: Clark and Tavener/Taverner: "Fairly Comfortable"; Taylor: "Unknown".

Deaths

A total of 194 (16.25%) children died after an admission for syphilis. More males than females died (106 versus 86 respectively), with 71.13% of deaths occurring before 1 year of age, and 90% before 3 years of age. The number of deaths per year ranged between 0 and 15, with a mean number of 2.74 deaths per year. When split into the socioeconomic groups, the only group with no deaths was the "Lowest Class" group, and the unknown addresses had 24 deaths (4.39%). In the "Very Poor" to "Middle Class" groups approximately 20% of admissions died. The "Upper Class" group had a 100% death rate. Of the children who died only 10 had any post-mortem information recorded in the admission records. Of these, none provided a cause of death, and they listed only the observed anatomical changes found during the post-mortem. Three causes of death were listed in the remarks section of the HHARP data, one being diphtheria, one congenital syphilis and the last rickets, congenital syphilis, and tuberculosis. There was no clear seasonal patterning to the deaths, with the least deaths occurring in May (n=12) and the most deaths in August (n=22). Spring months (March, April, May) showed the least deaths (n=43) whilst the summer months (June, July, August) showed the most (n=53). A mean of 16 deaths occurred per month, and a mean of 48 deaths occurred per season.

Treatment

Only 90 admissions, all from EH, contained information about the treatment a child received during their admission. The ages of the children treated ranged from possible neonates (age of 0 years and 0 months) to 13 years and 11 months. Shorthand is frequent so not all the treatments were clear. From what is legible, the most common treatment seen was the use of mercury (n=56), though potassium iodide (n=18) and silver nitrate (n=6) were also administered. These were administered to children of all ages, and 11 children were treated with both mercury and potassium iodide. There were also 23 listings of a surgical operation, most simply listed as that, but specifics include drainage of abscesses, a mastoidectomy, and an enucleation of an eye. Six of these also listed the use of chloroform, presumably as an anaesthesia. There is also a listing of a child being given "raw meat juice", possibly linked to the child's diagnosis of marasmus, a severe form of malnutrition.

Refusals

Between 1882 and 1891, 1,481 children were refused admission into GOSH. Only eight of these were diagnosed with syphilis. Three were female and two were male, and the remaining three lacked information indicative of sex. Three socioeconomic statuses could be identified: "poor", "mixed", and "fairly comfortable". The reasons for refusal included three children who were underage, one child who was deemed "unsuitable", and an occurrence of no available beds. Two children received treatment during their appointment, although there was no further

information regarding the treatment, and three children were made into outpatients

Discussion and Conclusion

Admissions

As seen in Figure 2, a spike in syphilitic admissions occurred between 1918 and 1920, with admissions exceeding 100 children in each of these years. The authors propose that this spike in children being admitted with syphilis was a by-product of WWI, as this spike immediately followed the conclusion of this conflict and the return of troops. During the war it was a generally held belief within society that sexual intercourse was a necessity for men and their health (Makepeace 2012). Some soldiers would frame their visits to the French brothels within the context of war as either providing reward for surviving or as a way of hiding from the spectre of death. Others may have frequented the brothels with the hope of acquiring a form of VD and therefore would have a legitimate reason to be removed from the front lines, at least for a time to seek treatment (Makepeace 2012). It is well documented that over 100,000 cases of acquired syphilis were treated among British troops during WWI (Hall 1993). Despite viable arsenic and mercury-based treatments being available, many were likely deterred by the treatment's side effects including jaundice and convulsions and there were no penalties if treatment was not sought after exposure (Beardsley 1976; Harrison 1995).

Initially, families were informed if a soldier was hospitalised with VD, including syphilis. However, this changed after the conscription of married men, and allegedly because of the reported suicide of an army major after his wife had been informed of his illness. For the remainder of the war, families were told simply that a diagnosis was yet to be made (Harrison 1995). The Cairo Purification Committee, a civil-military body appointed to examine how to reduce VD amongst the troops, continued to advocate that wives should be informed of their husbands' infection, to better protect themselves and any future children from infection. This advocacy was ignored, likely as army morale was considered of greater importance, and an infection with VD was one of the few available reasons that women could utilise to seek divorce (Makepeace 2012).

The taboos in publicly discussing VD likely resulted in many soldiers returning home and infecting their wives, who, if infected with syphilis, would then infect their unborn children. However, the risk and spread of congenital syphilis in connection to WWI was largely ignored by contemporary medical sources (Harrison 1954a; 1954b), and subsequently by military and medical historians studying sexual health during war (Beardsley 1976; Harrison 1995; Hall 1999; Frith 2012).

In 1921, the number of syphilitic admissions recorded in HHARP returned to pre-1918 levels. The admissions records for 1921 are seemingly complete as the total admissions for the year are comparable with the preceding years. It is logical that the decrease in admissions could reflect a fall in the number of syphilitic children needing admission. The Royal Commission on Venereal Disease (RCVD) (1913-1916), established by the government to investigate VD prevalence in the United Kingdom due to pressure from medical professionals, recommended that free treatment centres be established, with the first opening in 1917. The contemporaries of these centres testified to these being a success as the numbers of newly reported cases of syphilis would show a steady decline after the centre's opening (Evans 1992). This must be treated with a level of caution as these numbers do not necessarily represent the actual incidence of the disease, however, this does not negate the fact that there was a decline in deaths attributable to syphilis between 1917 and 1938 (Evans 1992). As such it is possible that parents of children diagnosed with congenital syphilis were themselves referred to these treatment centres, preventing future children from being infected. However, this theory could be better interrogated if admissions for the years after 1921 were available through HHARP.

Socioeconomic Status

The socioeconomic data present in the Booth Maps is representative of London over a 17-year period (1886-1903) within our 69-year study period (1852-1921). Although the socioeconomic status of these urban areas may have differed to that recorded during

Booth's data collection period, historical geographers have shown that once an initial socioeconomic pattern is established, the development history of an area is locked in place (Meen, Nygaard and Meen 2012). Indeed, it was only after the large-scale destruction of London by German air-raids during World War II (1938-1945) that large-scale urban changes would occur (Meen and Nygaard 2011). This is not to say there was no socioeconomic change on a geographic level during the late nineteenth and early twentieth centuries. While slum clearances did occur, these clearances and additions of new infrastructure would often merely compound the problem by reinforcing slums nearby as people moved from one to another (Dyos 1967; Yelling 1981; 1982). Due to the lack of any large-scale socio-geographic change occurring in London prior to WWII, the authors are confident that the Booth maps can still provide valid socioeconomic data for this study.

The lack of "upper class" admissions is likely because these individuals were not the intended demographic for the children's hospitals. These institutions were established to provide healthcare for those who could not normally afford it (Hawkins 2012). Indeed, the RCVD specifically noted that upper-class adults, and presumably their children, were able to receive treatment for syphilis from private practitioners (Hall 1999). However, the RCVD also noted that due to public taboo surrounding VD these individuals could still be misguided into seeking treatment for syphilis from unqualified sources (Royal Commission of Venereal Disease 1916). The low numbers of "middle class" admissions, may also be attributed to the same financial privilege of being able to pursue private treatment, rather than rely upon a charitable organisation. Considering the children from the upper class died during their admission, it may have been that children from more affluent families were sometimes admitted if they needed a level of care which exceeded that which could be provided within the home.

It is also possible that higher socioeconomic classes saw fewer cases of acquired, and later congenital syphilis, than the lower classes. During WWI the differences between army ranks, frequently correlated to socioeconomic status, was seemingly reflected in access to sex workers and contraception, as well as VD treatments. In the autobiography of Brigadier-General Frank Percy Crozier, it was noted that high-ranking officers who frequented "high-class" brothels would be provided with contraceptives; conversely these were not freely provided to lower ranking personnel who instead visited "lower-class" brothels or amateur prostitutes (Makepeace 2012). Also, whilst prophylactic packs were available to the soldiers, these frequently contained disinfectants rather than condoms (Hall 2013). Thus, whilst unwanted pregnancy was managed there was little protection against the spread of VD. Differences in treatment according to rank were also present, with higher ranking officers at Le Havre receiving 12 doses of arsphenamine whilst lower ranked soldiers received eight (Makepeace 2012). It cannot be shown that this was a universal treatment plan, but it may well have led to fewer members of the upper classes returning from the war with transmittable cases of syphilis. However, little is written focusing on Victorian and Edwardian upper-class sexuality, so there is an element of conjecture to much that is proposed here.

The lack of the lowest classes ("lowest class"; "very poor"; "poor") is unexpected as these were the classes the children's hospitals were ostensibly created to aid. It is possible that this lack of admissions is reflective of the views held about the poor by the higher classes during the examined period. The Victorians had a highly developed commitment to philanthropy, and considered it highly commendable to help the poor, though this was not always without conditions (Steinbach 2017). Whilst the children's hospitals had to maintain an appearance of care and competency for the patients and their relatives, the hospitals also had to show their financial backers that they were providing the moral education that lower-class families failed to provide (Tanner and Hawkins 2013). Charitable hospitals would therefore provide care to those deemed to be the "deserving poor" (Marland 1991). These individuals were those deemed to be deserving of help by those who provided aid, whether this be help from sickness or poverty (Grell and Cunningham 2017). Below the "deserving poor" were those deemed undeserving of aid because they were seen as being able to work but chose not too (Grell and Cunningham

2017), and the "criminal classes" who were deemed too degenerate to be lifted from their squalor (Dyos 1967).

The lack of consideration for those outside of the "deserving poor" can certainly be seen in the first epidemiological study of congenital syphilis in London. Fildes (1915) examined a one-mile radius around the Royal London Hospital, an area which, according to Simms et al's (2018) meta-analysis using the Booth Maps, included socioeconomic classes ranging from the lowest class to the middle class. However, Fildes only invited married couples from the "respectable" labouring classes to take part and ignored many of the most destitute areas as well as sex workers (Simms et al 2018). This is concerning, as it is these lowest class individuals who bore the brunt of congenital syphilis' impact. Harman (1916) found that syphilitic mothers would have 1.5 times more pregnancies than healthy mothers, whilst also being 3.5 times more likely to experience a pregnancy ending in miscarriage, stillbirth, infant death, or congenital syphilis. Thus, whilst the upper levels of the working class may have been the deserving poor that the medical establishment sought to help, it appears the lower levels of Booth's socioeconomic hierarchy were deemed to be outside of this designation.

It is also possible that the poorest members of society were refused admission or opted for their children to be treated as outpatients. Not enough syphilitic children are present in the refusals data for a case to be made for the former and it is not possible to test the latter as no outpatient data is available through HHARP. Though, with GOSH having 20,000 outpatients yearly at the end of the nineteenth century, compared to approximately 2,000 inpatients (Hawkins 2012) it is a plausible possibility.

The Possibility of Acquired Syphilis

During this investigation, the authors encountered an article (Anon 1880) which outlined three cases of tertiary syphilis among GOSH patients, none of whom were present in the HHARP admissions. Due to the lack of detailed symptom information in HHARP it was not possible to undertake a detailed analysis of whether a child experienced congenital or acquired syphilis.

The majority of the standardised diseases within the HHARP database were recorded as "congenital syphilis" (76.3%), and the remaining were recorded simply as "syphilis". Some of these are clearly due to transcription errors as several of the diseases as recorded in the admissions registers are "cong. Syphilis". However, amongst the admissions listed simply as syphilis there is one diagnosis of "syphilis (tertiary)" in the admissions register, and 41 mentions of gummas, the sores associated with tertiary syphilis. Of these, eight were recorded as being present alongside congenital syphilis. This is a possibility as gummas may occur in late congenital syphilis (Dobson and Sánchez 2019). Regardless, this leaves 33 children recorded as having gummas but not congenital syphilis, including gummas on the frontal bone (*caries sicca*) and around the groin and genitals.

If children in the present day were seen by a physician and presented with symptoms that could be attributed to acquired syphilis, and there was no satisfactory alternative explanation then it would be assumed that this was a sign of child abuse and reported as such (Dobson and Sánchez 2019; Baker 2020). Whilst not pleasant to dwell upon, this behaviour has happened throughout history. Bates (2016) examined almost 3,000 pre-trial statements from the Middlesex and the Gloucestershire, Somerset, and Devon court sessions from 1850 to 1914. In response to medical testimony outlining how a 10-year-old girl had acquired syphilis after an assault, a judge opined that the pollution of a child of tender years was a crime that no language could describe (Bates 2016). Beyond the trauma of the event itself, and the medical consequences of the syphilis, the abuse would have social implications for the child as well. Any child who had been sexually abused was seen as being corrupted with sexual knowledge, leading to segregation from their peers to prevent the spread of this corruption (Cook 2004).

Jackson (2000) tried to argue that due to the prevailing culture of the time, there was a reluctance amongst doctors to attribute syphilitic transmission in children to a sexual origin. However, Bates (2016) found only three doctors who raised the possibility of an "innocent transmission" due to poor hygiene, and none denied the possibility that transmission could corroborate

charges of sexual assault. Innocent transmission may certainly have occurred, as the survival rate of *T. pallidum* outside of the body, whilst only several hours, would be long enough to be passed on in conditions of poor hygiene. Indeed, one of the most common hypothetical situations presented for innocent transmission was that of a mother with a syphilitic sore around her mouth using the same spoon to feed herself and her child. However, such an explanation would not explain syphilitic symptoms upon the genitals (Taylor 1985) and within the HHARP data there were several occurrences of syphilitic gummas around the groin. Whilst this study raises the possibility of these children suffering from acquired syphilis rather than congenital, it is impossible for researchers to know the true extent of this within the past because of its social taboo both past and present.

Limitations of HHARP

With any archival data researchers are limited to the information that is present in the archive, and in this case that which has been digitised from the physical archive itself. In the HHARP data there was no additional information regarding symptoms beyond the diagnosed disease, and there was limited post-mortem information available. As such, no comment could be made regarding the prevalence of the different symptoms possible within cases of congenital syphilis, and it was not possible to examine whether congenital syphilis or a concurrent condition was more likely to cause the death of a child after admission. Additionally, despite the volunteers who transcribed the hospital admissions being provided with training and reference guides of health terms and geographic areas of London, we cannot exclude the potential for human error leading to information being missed or inaccurately transcribed. However, the project did include proofreading and data validation procedures, so effects should be minimal.

Conclusion

This investigation provided a glimpse into the occurrence of syphilis within London's children's hospitals through the mid-nineteenth and early twentieth centuries. Some children were able to be taken to the hospitals from within the London area and further afield to receive care both as outpatients and inpatients. However, though these hospitals were established to help the poor, the poorest children of London society were not clearly visible within those admitted, though the reason for this remains obscured. We also saw that those in positions of power, to a certain degree, preferred to prioritise the sexual needs of men, during both peace and war, in such a way as to promote damage, both physically and mentally, to women and their children due to syphilitic exposure. This was deadly to children, and women (regardless of whether they were mothers) when combined with the growing culture of taboo when discussing sexuality and more specifically sexual health during the period this paper examined. This paper also highlighted that, although untasteful, it is important to raise the possibility of acquired syphilis when looking at archival data surrounding childhood syphilis. Though the presence of acquired versus congenital cannot be proven with certainty, this was a possible reality for some children in the past and it must be considered during discussions of this disease.

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Reconstructing the childhood diet of the individuals from the Middle/Late Bronze Age Bezdanjača Cave, Croatia (ca. 1430 - 1290 BCE) using stable C and N isotope analysis of dentin collagen

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Abstract

This paper investigates the childhood diet of 16 individuals from the Middle/Late Bronze Age (1430-1290 BCE) Bezdanjača Cave (Lika region, Croatia) using stable isotope analysis of dentin collagen from permanent first molars. Results from the analysis reveal that the individuals from Bezdanjača consumed notable quantities of C_4 plants during their childhood. The most common C_4 plant is millet, whose spread throughout Southern Europe was recently dated to the second half of the 2nd millennium BCE, which agrees with the results obtained in this research. Comparisons between the data collected for the individuals from Bezdanjača and other Middle and Late Bronze Age sites in Croatia suggest that only the individuals from the site of Veliki Vital (Middle Bronze Age, inland Croatia) exhibit similar isotopic values to those from Bezdanjača. Human isotopic values from coastal sites, however, reveal that during the Middle and Late Bronze Age people from the coast had diet that still predominantly contained C_3 plant-based foods, which appears to suggest that the dispersion of this crop in Croatia during the Bronze Age followed an east-west trajectory, appearing earlier (Middle and Late Bronze Age) in inland settlements such as Veliki Vital and Bezdanjača and only later (Late Bronze Age and mostly Iron Age) in coastal sites.

Introduction

The Bronze Age can be considered a pivotal time for the prehistory of Europe, as it saw the proliferation of new architectures as well as a change in the social structure of communities with a progressive hierarchization of the population and the birth of social elites. The production of bronze goods, the quest for raw materials (e.g., tin) and other luxury goods (e.g., amber, textiles, spices etc.), greatly boosted trades by sea and land. Food commerce is especially significant during the Bronze Age as far as millet is concerned because its diffusion across Eurasia represents the first example of "*food globalization*" (Filipović *et al.,* 2020: 2). Broomcorn millet (*Panicum miliaceum*) was first domesticated and cultivated in northeast China around 6000 BCE (Early Neolithic). As recently proved by Filipović and colleagues (2020), the earliest millet findings in Europe date back to sixteenth-century BCE southwestern Ukraine and, one century later, the crop spread throughout the Middle Danube Region, most likely in Romania, Hungary, and probably Croatia and

northern Italy. By the thirteenth century BCE, millet was also present in central Europe, Greece, the whole Balkan region, reaching Germany and Poland only around the twelfth century BCE (*ibid*). Archaeobotanical data from coastal Croatia, in particular Istria and Dalmatia (Becker, 2001; Chapman *et al.,* 1996), confirm the presence of two different varieties of millet (broomcorn and foxtail [*Panicum italicum*]) in these regions throughout the Late Bronze Age and the Iron Age. Furthermore, archaeobotanical studies conducted by Reed (2012; 2016), also suggest that broomcorn millet was present in Croatia only starting from the Late Bronze Age. These data have been corroborated by Filipović and colleagues (2020) who have shown that increased trade networks across the Mediterranean during the Bronze Age allegedly promoted the commerce of millet towards Southern Europe, more specifically Italy and the Balkans (*ibid*).

Since millet is a drought-tolerant, fast-growing, and highly nutritional crop that survives well even on poor soils and adapts to various environments and climates and has a rather narrow growth span (Lightfoot *et al*., 2014), the crop is considered to have been amongst the preferred cultivated plants of the Lika region (Western Croatia) dwellers from the Bronze Age onwards (Zavodny *et al.,* 2017). As a matter of fact, a study conducted by Zavodny and colleagues (2019) suggests that during the Middle and Late Bronze Age the Lika region was densely covered by forests with some clear areas for pasture. This heavy vegetation coverage most likely prevented the diffusion of light and oxygen on the forest floor, causing the area to suffer from the so-called "canopy effect" (Van der Merwe & Medina, 1991), which made the whole area rather unsuitable for intensive farming, and this might be one of the reasons why we can observe a rapid increase in the population of the region only from the beginning of the Late Bronze Age (1200-800 BCE), which corresponds with the occupation of the area by Iapodian cultural groups. Although the information regarding the Iapodians' social, political, and economic structures as well as their material culture during the Late Bronze Age and Early Iron Age is still rather scarce for this area, recent studies (Bakarić, 2010; Zavodny *et al.,* 2017) suggest that they employed a mixed farming strategy that also resorted to breeding. Evidence of dietary habits in this regard is primarily derived from small faunal assemblages excavated from house contexts. Stable isotope analysis were carried out by Zavodny and colleagues (2017) on both domesticated (cattle, sheep, goat, pig, dog, horse) and wild species (roe deer, red deer, chamois and hare) from the Middle Bronze Age sites of Jozgina Pećina (Ličko Valley), Ličko Lešće and Veliki Vital (Gacka Valley), as well as the Late Bronze Age settlements of Cvituša, Pipica and Miljača (Ličko Valley) and Hrvatsko Polje (Gacka Valley), all located in the Lika region[1]. Conversely, little is known about agricultural practices in the Lika region because few paleobotanical remains have survived. According to Greek historian Strabo, however, the Iapodians were dependent on millet and spelt because of the poor agro-ecology of the land (*ibid*). This has recently been proven by stable isotope analysis carried out on seven adult individuals from the Bronze and Iron Age sites of Bezdanjača[2], Gospić-Lipe and Veliki Vital (*ibid*). Here, millet appears to have formed an important portion of diet, comprising about 20% of the overall intake, with Bezdanjača being chronologically the first site to present this dietary trend. Interestingly, the consumption of millet by the Lika region communities seems to increase up to 40% of the overall diet at the beginning of the Iron Age.

Dietary profiles for Bronze Age coastal Croatia have been reconstructed by Lightfoot and colleagues (2014). The individuals from the coastal sites of Koprivno, Radošić-Biluška Griža, Vučevica, Konjsko Polje, Matkovici, Veliki Vanik and Zavojane Ravča seem to have consumed little or no millet and to have relied on a pure C_3 plant-based diet instead. However, similarly to what has been observed for the Lika region, this trend changed, very gradually and slowly, at the beginning of the Iron Age, when isotopic signal from C_4 plants starts being detectable in individuals from the same sites. Based on the analysis presented by Lightfoot *et al.* (2014), it appears that millet was not

[1] The results from this study have been used to determine the faunal baseline of our research.

[2] In this case stable isotope analysis used bone collagen collected from four individuals.

available throughout coastal Croatia during the Middle and at least the beginning of the Late Bronze Age, but rather, it only started being significantly important to human diets during the Iron Age.

These works provide an important overview of the differences and similarities in both space and time of diet changes observed in different regions of Croatia during prehistory but focus mainly on adult diet. The aim of this study was therefore to investigate childhood diet in protohistoric Croatia using stable carbon and nitrogen isotope analysis of dentin collagen. In this paper the term "childhood" is used to refer to the age span that goes from birth to the onset of adolescence (0-15 years). The "infancy" period, which in bioarchaeology usually indicates the period between birth and the end of the first year (Scheuer & Black, 2000a,b; Lewis, 2007), has been arbitrarily incorporated in the "childhood" age category by the authors for convenience. We compared the results of our study with those available from other coastal and inland contemporary sites in Croatia in order to identify similarities and/or differences in isotopic dietary data, with a special focus on the consumption of millet.

Figure 1 Geographical location of Bezdanjača Cave (from Boljunčić, 1997)

Materials and methods

Bezdanjača Cave (**Figure 1**) is located on the Vatinovac hill, near Vrhovine in the Lika region in Croatia (**Figure 2**) (Malez & Nikolić, 1975). The cave was first recognized as a prehistoric site in October 1964 and the archaeological excavations began in July 1965 (Malez, 1979-80). The cave has been explored in all its branches for a total of 1176 meters, of which only the first 190 meters were of archaeological interest. The entrance to the cave is south of Zalužnica, above Brakusova Draga in the Stružnice region and is located 740 meters above sea level. The upper part of the entrance is funnel-shaped, and at the end of it there is a steep chasm which terminates in a stack of irregularly deposited material. The cave is naturally hidden and difficult to access (Malinar, 1998), which suggests that no one entered it or disturbed the material it contained after it ceased being used by the prehistoric communities. The overall length of the channels is estimated to be 1176 meters, while the difference in height between the highest and the lowest point of the cave is around 200 meters. At its base, the entrance, which today is inaccessible due to the danger of mines left from the 1991-1995 wars in Croatia, bifurcates in two main branches, namely the western channel and the eastern channel. The western channel of the cave is short and broad. Here, archaeologists could only open four excavation units (blocks 1-4), since the whole area was covered with several scattered wooden blocks and fallen rocks (most of which had collapsed near the channel may have been used as a burial space as well (Drechsler-Bižić 1979-80). The eastern channel is

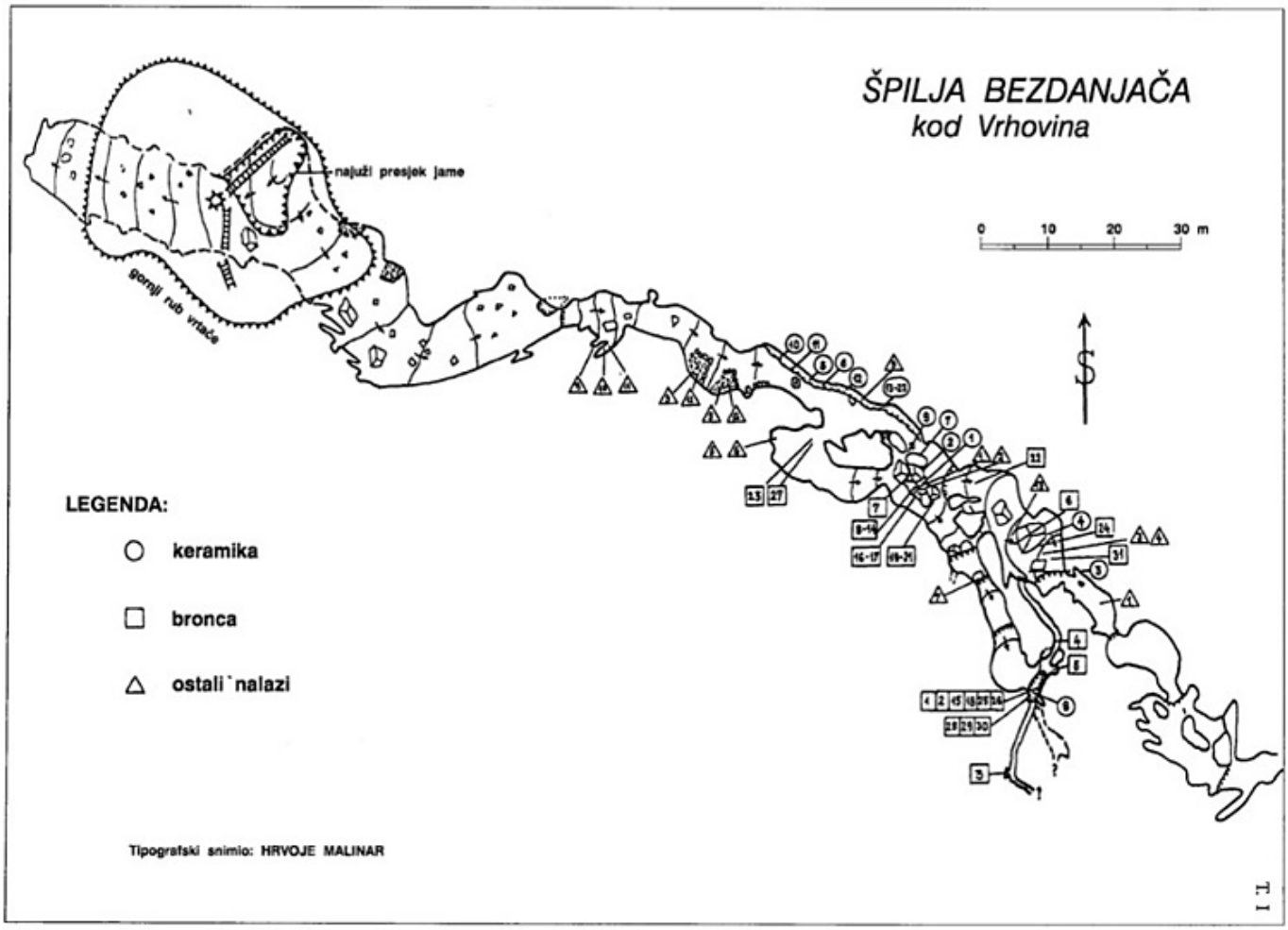

Figure 2 General topography of Bezdanjača Cave (from Malinar, 1998)

positioned at a 40° angle from entrance). Some fragments of animal bones and pottery were found among the rocks, suggesting that this the vertical entrance of the cave. It is much longer and morphologically different from the western channel, as it contains numerous side branches and levels. Seven excavation units were opened right at the entrance of this channel (blocks 5-11), where four disarticulated skeletons were found. Just over 70 meters further from the entrance of the eastern channel, archaeologists were able to open the greatest number of archaeological units (blocks 12-39), that revealed the presence of several well-preserved human skeletons. From block 27 departs a shorter and narrower channel, at the end of which more skeletal remains were found (Drechsler-Bižić 1979-80). In the eastern channel, archaeologists found architectural remains including numerous drywall and wooden structures (Malinar, 1998). Supposedly, these structures could have served to facilitate the entrance to the cave or as plateaus that may have functioned as working surfaces or beds. Traces of hearths, pottery, bronze artifacts, and remains of bracken and hay were found on the stone structures and the floor of the channel and were used in some cases to assess the chronology of the site.

In Benac's opinion (1993-94), based on the materials found in the cave, two cultural horizons can be distinguished at Bezdanjača: an older one, dating to the Middle Bronze Age (BrC/D, 1500-1200 BCE), and a more recent one, dating to the Late Bronze Age (BrD/HaA, 1200-1000 BCE). Drechsler-Bižić (1979-80) assigns both horizons to the Proto- Illyric period, which roughly corresponds to the turn of the second to the first millennia BCE.

This hypothesis agrees with that of Benac (1993-94), who suggests that the development of the Illyric tribal

communities settled in the southern part of the Sava river can be divided into four main phases, the second of which being the one called Proto-Illyric, which was to some extent influenced by the Danube area, the Carpathians, and the eastern Balkans. According to Benac (1993-94), Bezdanjača Cave, with regards to its cultural manifestations and rituals, perfectly fits this phase. Radiocarbon analysis of several wood samples from the site resulted in dates between 1350 and 1100 BCE (Sliepčević & Srdoč, 1979-80). Zavodny and colleagues (2017) provided radiocarbon dates for two individuals found in Bezdanjača Cave. New ^{14}C dates for two individuals from Bezdanjača have been recently carried out at the University of California, Santa Barbara as well (M. Novak, personal communication), and these agree with the previous radiocarbon dates from the same site.

Stable isotope analysis

A total of 49 *crania* from Bezdanjača have been considered for this research. The *crania* had been collected during the 1960s and stored at the Institute for Quaternary Paleontology and Geology of the Croatian Academy of Sciences and Arts. The analysis and the sampling were conducted in the Centre for Applied Bioanthropology, Institute for Anthropological Research, Zagreb. In this research we used permanent first molars to reconstruct the diet during the early life of the individuals from Bezdanjača. The permanent first molar is the first of the permanent teeth to emerge. It begins to form and calcify at birth and completes its formation at approximately 9-10 years of age when the root is fully developed. For this reason, they are the best means to investigate diet during the early years of an individual's life. Since teeth form incrementally, they can be sampled in bulk to investigate the changes both in diet and environment that happened during their formation period (Miller *et al*., 2018). Only 16 out of 49 individuals from Bezdanjača were used for stable isotope analysis as their dentition presented permanent first molars with a wear ≤3 (Smith, 1984). A low rate of wear likely indicates little (or no) loss of primary dentin due to dental attrition and/or abrasion, as well as limited development of secondary dentin, which might interfere in the analysis blurring diet signal during childhood.

Dentin collagen was extracted following a modified version of the Leipzig protocol (Sealy *et al.,* 2014). All teeth were mechanically abraded using a Dremel sandpaper burr. This was done to remove superficial enamel to fasten the subsequent demineralization process. Intra-tooth sampling was performed using a diamond-coated circular blade. Only one half of each tooth was weighted out and used for the analysis, while the other half was stored for future analyses. The chosen tooth halves were then demineralized in 0.5 M aq. HCl at 4°C until demineralized. Samples were rinsed with de-ionized water and then gelatinized in acidic solution (pH 3) at 70°C for 48 hours. The liquid solution containing the gelatinized protein was frozen for 24 hours and then freeze-dried for 48 hours to obtain the final collagen product. The collagen from each tooth was weighed out and the samples were then shipped to the Iso-Analytical laboratory (Crewe, Cheshire, UK) where they were loaded into an auto-sampler on a Europa Scientific elemental analyzer for the mass-spectrometry analysis of δ^{13}C and δ^{15}N.

The carbon stable isotope ratio (δ^{13}C) helps distinguish between diets based on C_3 plants from those based on C_4 plants, since atmospheric plants use different photosynthetic pathways that differently discriminate between ^{13}C and ^{12}C during CO_2 fixation. C_3 plants such as rice, various kind of grasses, all root crops, legumes, vegetables and fruits usually display variable δ^{13}C values that can range between -22/-24 to -36‰ (Burt & Amin, 2014; Dupras & Tocheri, 2007; Katzenberg & Saunders, 2008; Lee-Thorp, 2008), whereas C_4 plants (e.g. sorghum, millets, maize, sugarcane and tropical pasture grasses) show carbon values that range between -16 to -9‰ (Dupras & Tocheri, 2007; Katzenberg & Saunders, 2008). The δ^{13}C isotopic values of plants fixate into the consumer's tissues with an increase of circa +3-5‰ in large herbivores (Al-Bashaireh *et al*., 2010) and of circa +1-2‰ in subsequent trophic levels (carnivores and omnivores including humans). It follows that the δ^{13}C values for humans are usually around -19‰ for diets based on C_3 plants and around -8‰ for diets based exclusively on C_4 plants (Dupras & Tocheri, 2007). The nitrogen found in bone and dentin collagen provides information about

the consumption of terrestrial and marine plant and animal proteins by an individual. Generally, $\delta^{15}N$ values increase by approximately +2/3‰ every step up in the food chain. In humans the nitrogen fractionation is variable and can be up to +6‰, although it is still unclear how and when nitrogen isotopic fractionation occurs in the body (Ambrose, 2000; Gannes *et al*., 1997; Sealy *et al*., 1987).

Osteological and paleopathological analysis

The determination of age at death on the adults' skulls of Bezdanjača was assessed using the method of ectocranial suture closure (Meindl & Lovejoy, 1985) and the observation of dental wear (Smith, 1984), whereas age at death of the subadults was carried out on the basis Ubelaker's dentition chart (1999). Determination of sex for the individuals from Bezdanjača was conducted exclusively on adult individuals using the morphological/observational method of skull traits since we lacked the postcranial portion of the skeletons. Paleopathological observation on the skulls were limited to the pathologies that interest the cranium and the teeth. Specifically, we looked for and/or observed: porotic hyperostosis, *cribra orbitalia*, scurvy, osteoma, caries, abscesses, calculus, alveolar resorption, dental enamel hypoplasia. Osteological and paleopathological data are presented only for the 16 individuals used for stable isotope analysis.

Results

Stable carbon and nitrogen isotope values, as well as osteological and paleopathological data, for the 16 individuals from Bezdanjača are presented in **Table 1**.

The overall sample consists of two adult females (12.5%), seven adult males (43.7%), and seven subadults (43.7%). With regard to pathologies, six individuals presented signs of active *cribra orbitalia* (37.5%). Of these, five individuals showed lesions on both orbits (BzV 18a, BzV 18b, BzV 21c, BzV33h, BzV 30c), and one only on the left orbit (BzV X). Porotic hyperostosis has been detected on a total of four individuals (25%): one subadult (BzV 21b), one adult female (BzV 30a) and two adult males (BzV 30c and BzV X). All of these individuals, with the exception of BzV 30a (adult female), also presented *cribra orbitalia*. An indication of the only probable case of scurvy was the diffuse porosity observed on BzV Y's palatine bones.

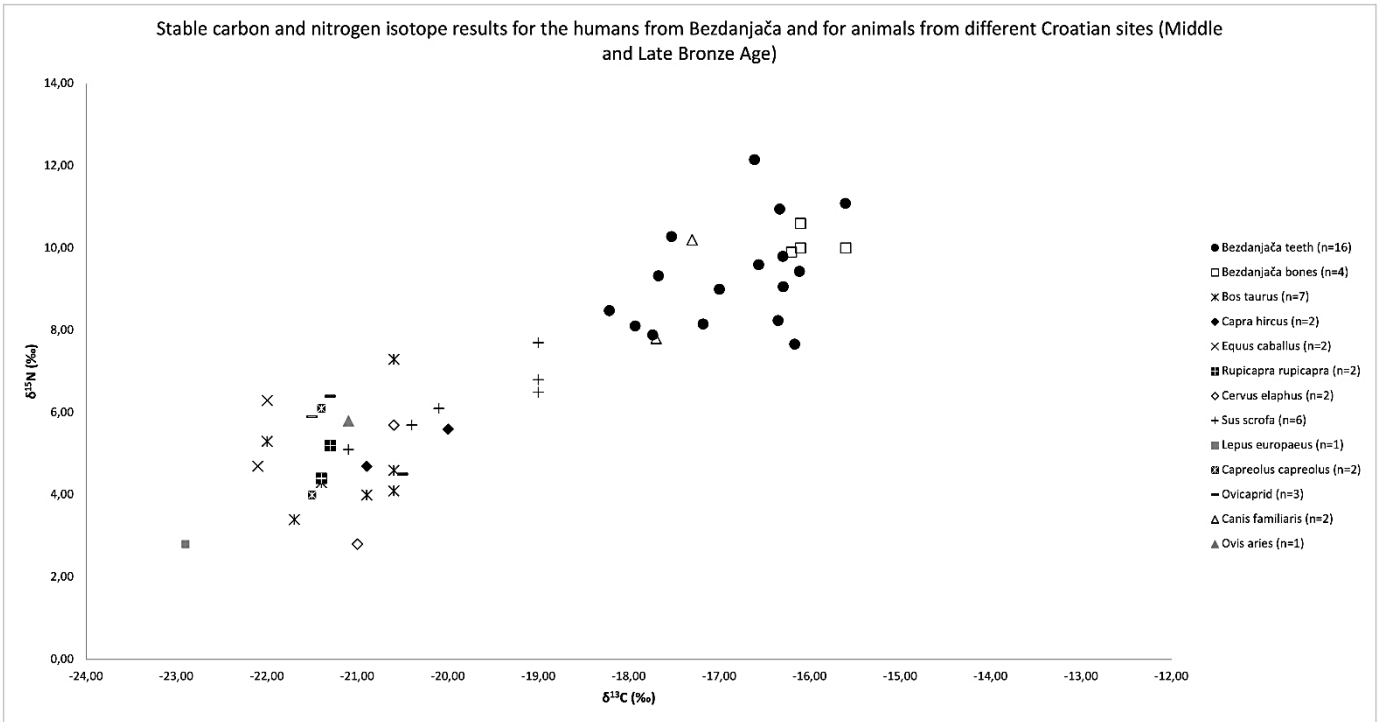

Figure 3 Stable $\delta^{13}C$ and $\delta^{15}N$ isotope values for the individuals from Bezdanjača compared with the faunal baseline's isotopic values

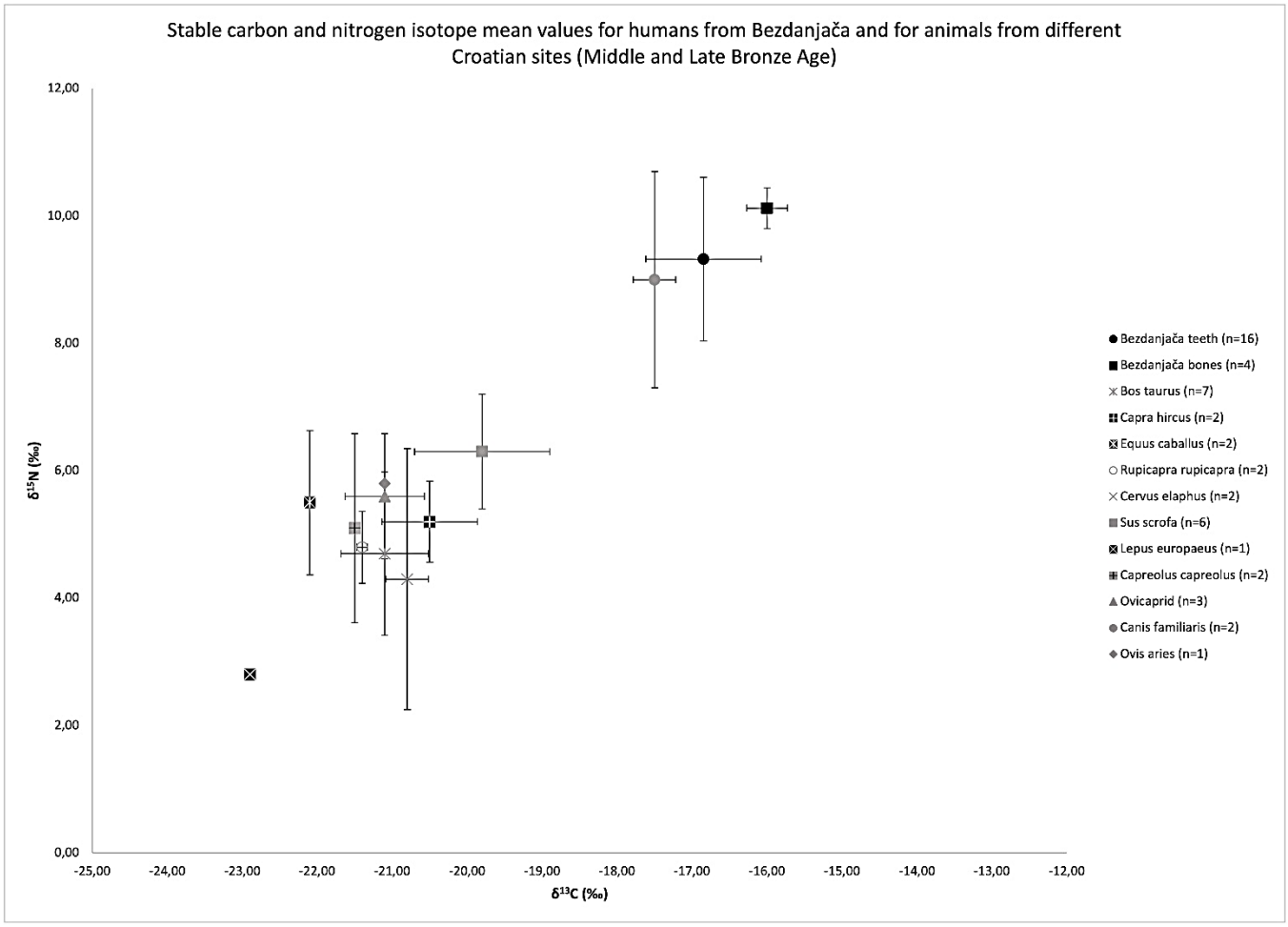

Figure 4 Stable $\delta^{13}C$ and $\delta^{15}N$ isotope mean values for the individuals from Bezdanjača compared with the faunal baseline's isotopic mean values

However, lacking the postcranium, this diagnosis could not be confirmed.

There were no major dental pathologies associated with the 16 individuals considered for this study. Four adult individuals (25%) presented enamel hypoplasia either on the upper canines (BzV 18a, BzV 33b, BzV X) or on the upper second incisor (BzV Y). Only BzV 33f-2, an adult male, showed slight signs of caries on the buccal side of the left M_2.

Carbon and nitrogen isotopic values for the 16 individuals from Bezdanjača are shown in **Figure 3**. Isotopic data show rather high $\delta^{13}C$ values that range from -18.2 (BzV 30c) to -15.6‰ (BzV 30d), and high $\delta^{15}N$ values that vary between 7.7 (BzV 18a) and 12.1‰ (BzV 21c), whose nitrogen values represent the only outlier in the overall sample. The mean isotopic values for the 16 individuals are -16.8‰ for $\delta^{13}C$ and 9.3‰ for $\delta^{15}N$ (**Figure 4**).

TABLE 1 Results of $\delta^{13}C$ and $\delta^{15}N$ for the individuals from Bezdanjača with osteological and paleopatholgical determinations.

Sample name	Sex	Age at death	Pathologies	$\delta^{13}C$ (‰)	$\delta^{15}N$ (‰)	Mean $\delta^{13}C$ (‰)	Mean $\delta^{15}N$ (‰)	C:N	s.d. $\delta^{13}C$	s.d. $\delta^{15}N$
BzV 18a	F	20-30 y	*Cribra* (L+R); osteoma on the occipital bone	-16.2	7.7			3.2		
BzV 18b	n.d.	8±2 y	*Cribra* (L+R)	-16.3	11.0			3.2		
BzV 21b	n.d.	11±2.5 y	Light porotic hyperostosis on the posterior part of the left parietal and some light porosity on the left side of the occipital	-16.1	9.4			3.2		
BzV 21c	n.d.	9±3 y	*Cribra* (L+R)	-16.6	12.1			3.2		
BzV 21d	M	30-40 y		-17.5	10.3			3.2		
BzV 27b	M?	30-40 y		-17.7	7.9			3.2		
BzV 30a	F	20-30 y	Diffuse light porotic hyperostosis on the posterior part of both temporals and on the occipital	-16.3	8.2			3.2		
BzV 30c	M	15-18 y	*Cribra* (L+R); porotic hyper. on both parietals and the occipital	-18.2	8.5	-16.8	9.3	3.2	0.77	1.28
BzV 30d	n.d.	10-12 y		-15.6	11.1			3.2		
BzV 33b	M	20-30 y		-17.9	8.1			3.1		
BzV 33e	n.d.	10±2,5 y		-16.3	9.1			3.1		
BzV 33f-2	M	25-35 y		-16.3	9.8			3.2		
BzV 33h	n.d.	9±3 y	*Cribra* (L+R)	-17.7	9.3			3.2		
BzV X	M	18-22 y	*Cribra* (L); Porotic hyperostosis on the frontal bone	-16.6	9.6			3.2		
BzV Y	M	18-25 y	Porosity on the palatine bones	-17.2	8.2			3.1		
BzV ?	n.d.	15±3 y		-17.0	9.0			3.2		

Discussion and Conclusion

The isotopic results from Bezdanjača seem to confirm Filipović's (2020) data by clearly showing that humans from this site consumed good amounts of C_4 resources during their childhood, given that all the individuals show $\delta^{13}C$ values >-18‰. (Filipović *et al*., 2020). These enriched $\delta^{13}C$ values, however, likely suggest an early diet based on the inclusion of C_4 plants such as millet rather than marine foods. This argument is based on two main indicators. Firstly, Bezdanjača Cave is located far from the coast, and no fishbone and or shells have been found either at the site - except from two sea snail shells used as beads for a necklace (Malinar, 1998) - or at the other sites considered for this study, suggesting consumption of marine food by these communities during the Middle and Late Bronze Age. Secondly, at the study site, the $\delta^{15}N$ values do not seem to indicate an intake of marine proteins in the individuals' diet when compared to the $\delta^{13}C$ ones (Ambrose *et al.*, 1997). On the other hand, stable isotopic values related to faunal remains, although limited, suggest that the major part that the high $\delta^{13}C$ values are not a consequence of of the livestock did not consume enough C_4 plants so that their presence in the animals' diet could be reflected by their isotopic values, and it is therefore likely that millet was consumed exclusively by humans (Lightfoot *et al.,* 2014).

Previous research on paleodiet in Middle and Late Bronze Age inland Croatia (Zavodny *et al*., 2017), shows both similar and different trends in subsistence strategies when compared to the individuals from Bezdanjača (**Figures 5 and 6**). Two individuals from the hillfort settlement of Veliki Vital, dated to the Middle Bronze Age, show similar isotopic values to those from Bezdanjača, with $\delta^{13}C$ values ≥-18‰, which suggests an intake of C_4 plants in their diets during adulthood. The single adult individual sampled from the Late Bronze/Early Iron Age necropolis of Gospić-Lipe, on the other hand, shows isotopic values that are consistent with a C_3-predominant diet in which a possible consumption of C_4 plants would have been limited after childhood. Although the number of samples from other inland settlements was smaller than from Bezdanjača, comparisons between different sites of inland Croatia during the Middle and Late Bronze Age seem to suggest that the spread of millet, which reached Croatia in the second half of the second millennium BCE, was more consistent in some sites than in others. It must however be noted that both Bezdanjača and Veliki Vital are

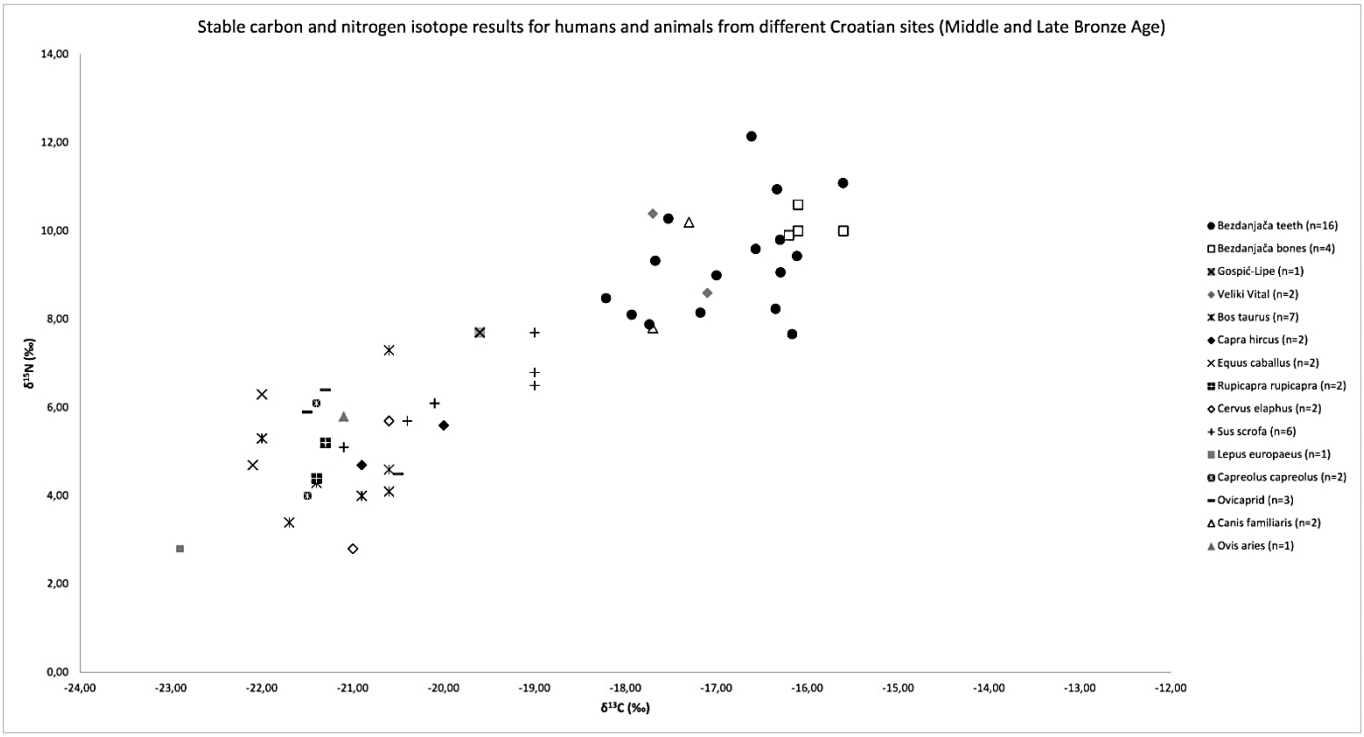

Figure 5 Stable $\delta^{13}C$ and $\delta^{15}N$ isotope values for the individuals from Bezdanjača compared with other inland sites and with the faunal baseline's isotopic values.

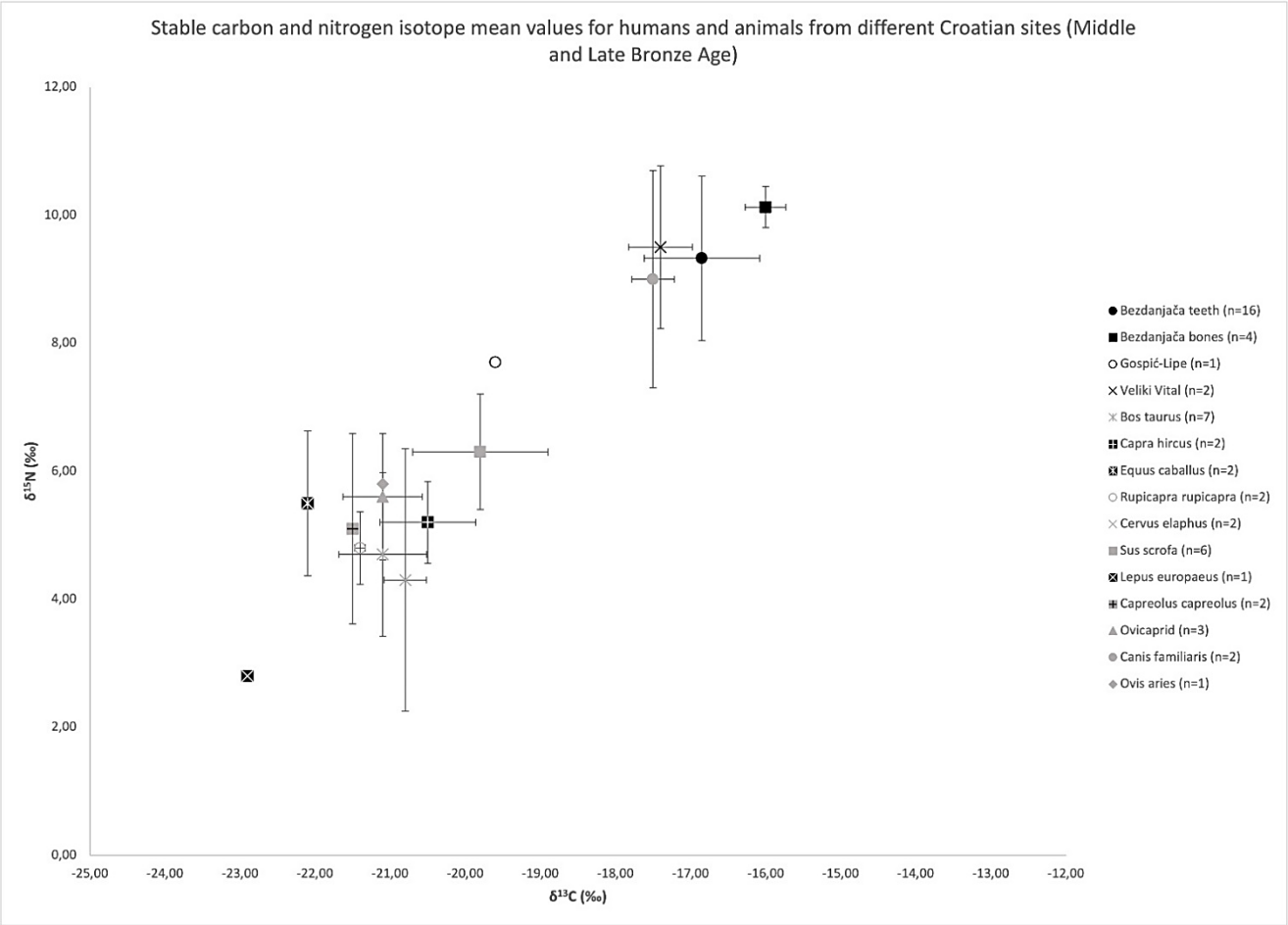

Figure 6 Stable $\delta^{13}C$ and $\delta^{15}N$ isotope mean values for the individuals from Bezdanjača compared with the individuals from other inland sites and with the faunal baseline's isotopic mean values.

geographically close to each other, and this may be the reason why the individuals from these sites show similar dietary stable isotope values. Gospić-Lipe, on the other hand, although positioned in inland Croatia, is located south, towards the coast. Isotopic values for the only individual recovered from this site are, in fact, closer to the diet of the individuals from coastal sites of Croatia in the same period, who also show a C_3 plant-based diet, with little or no consumption of millet (**Figure 7**). The research carried out by Zavodny *et al*. (2017) also indicates that the consumption of millet grew steadily in inland settlements particularly from the Early Iron Age onwards, with a clear switch from a C_3-based diet to a consistently mixed C_3/C_4 diet in this period.

Lightfoot and colleagues (2014) also draw the same conclusion about coastal Iron Age sites, but neither the isotopic values nor the information recently provided us by Filipović (2020) actually support that hypothesis. As a matter of fact, the $\delta^{13}C$ values for individuals from the Iron Age Croatian coast are all <-18‰ and therefore point towards a diet with a seemingly exclusive intake of C_3 plants. Additionally, as stated by Filipović and colleagues (2020), some dietary stable isotope studies of humans from Iron Age Coastal Croatia seem to indicate how some communities from this area did not consume millet, unlike their neighbors. It is therefore possible to assume, in accordance with Filipović's (2020) data, that the spread of millet in Croatia from the Middle Bronze Age onwards most likely followed an east-west axis over land, was first introduced to individuals from northwestern inland Croatia and later to southeastern coastal sites.

Some differences can be seen in $\delta^{15}N$ values between both inland and coastal sites of Croatia during the Middle and Late Bronze Age, but some authors (Lightfoot *et al.,* 2014) have been reluctant in ascribing

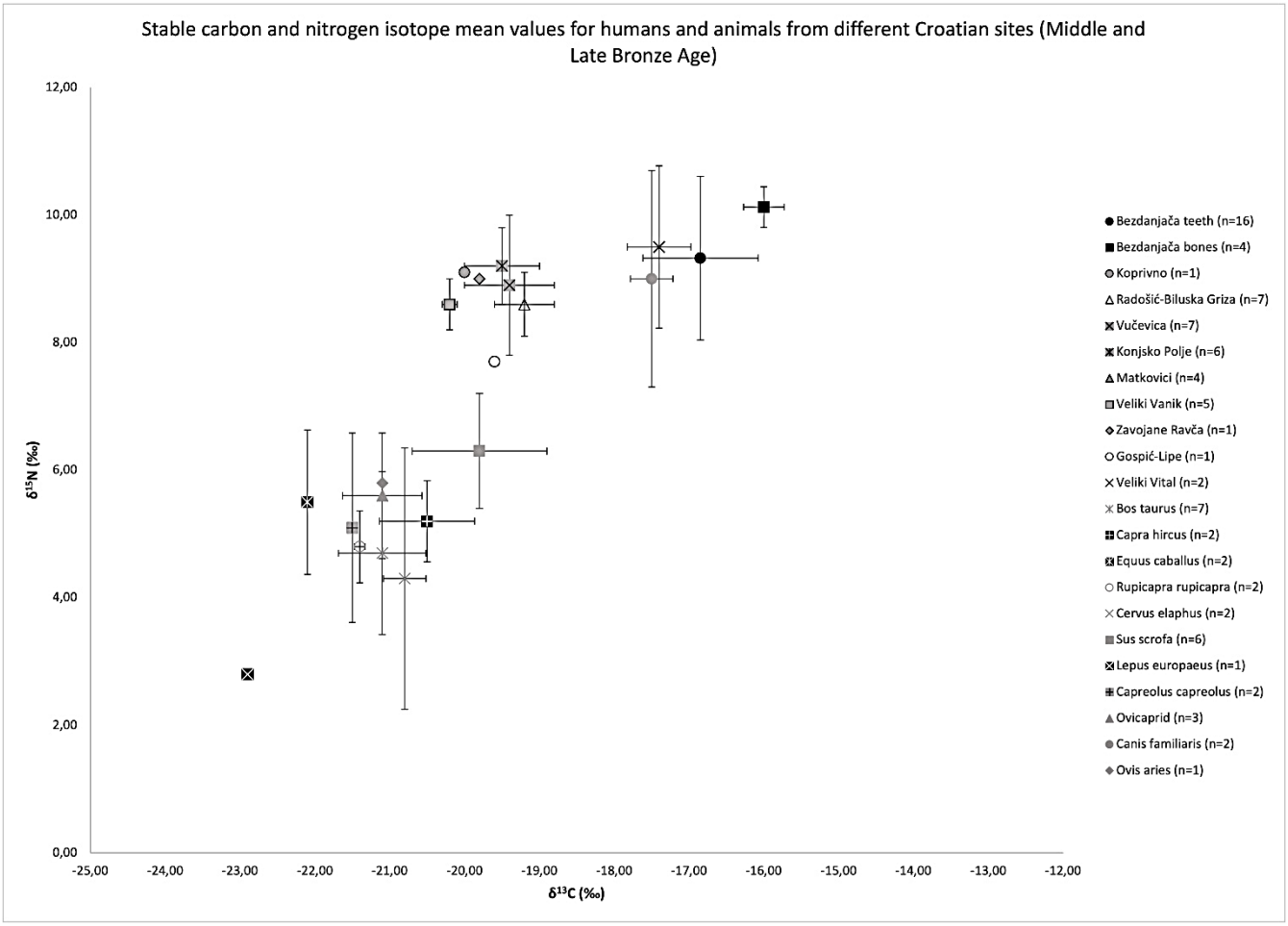

Figure 7 Stable $\delta^{13}C$ and $\delta^{15}N$ isotope mean values for the individuals from Bezdanjača compared with other Croatian sites and with the faunal baseline's isotopic mean values

these changes to dietary differences exclusively, considering also possible changes in the environmental baselines. The nitrogen values for the individuals from Bezdanjača is generally slightly higher compared to those of the individuals from other contemporary sites and that can be ascribed to a reverberation of the signal from the weaning period given that we are considering childhood diet. As a matter of fact, it is known that during the breastfeeding period the consumption of maternal milk places an infant on one trophic level above that of its mother in the food chain (Beaumont *et al.*, 2015). This means that if a child was still being breastfed when it died, its isotopic values will show an enrichment in $\delta^{15}N$ of approximately +2.5‰ and in $\delta^{13}C$ of ~1‰ (Ventresca Miller *et al.,* 2016; Laffranchi *et al.,* 2018). Infant $\delta^{15}N$ values decrease during the weaning period through progressive substitution of breast milk with supplementary foodstuffs. When the breastfeeding has fully ceased and the infant is fully weaned, the reduction to maternal levels is allegedly more rapid for $\delta^{13}C$ values than for $\delta^{15}N$ values, which lower more slowly over time (Howcroft *et al.,* 2012). Nonetheless, among the 16 samples from Bezdanjača, sample BzV 21c, belonging to a 9-11-year-old individual, exhibits unusually high $\delta^{15}N$ values (12.1‰) for Bronze Age communities in Croatia (**Figure 8**). Such a value places individual BzV 21c even above the normal values for animals that have a strictly carnivore diet and whose $\delta^{15}N$ values are usually between 8-12‰ (Codron *et al.,* 2007; 2016). Paleopathological observations on the skull of this individual revealed the presence of active *cribra orbitalia* on both the right and the left orbits. Moreover, it must be noted that the dentin sampled from BzV 21c was the first to complete the demineralization process in the hydrochloric acid, which means that the hydroxyapatite of the tooth was likely very frail or almost absent. Considering that: **1)** we sampled BzV 21c's permanent first molar, whose

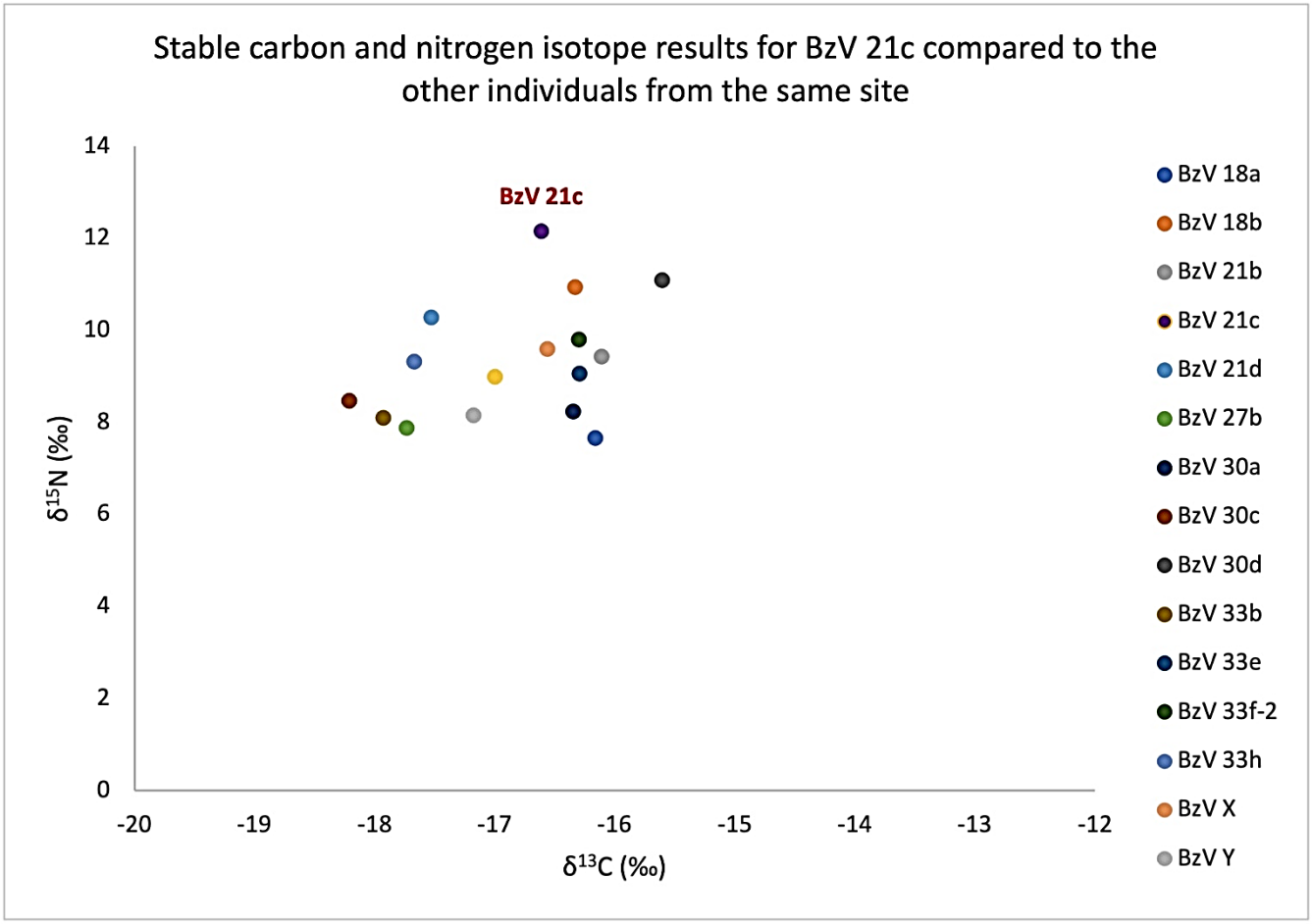

Figure 8 Stable carbon and nitrogen isotope results for BzV 21c compared to the other individuals from the same site

mineralization occurs between birth and 3 years of age; **2)** the age at death of BzV 21c was around 9-11 years; and **3)** Bzv 21c's dentin did not undergo a tissue turnover because secondary dentin is usually not observable in individuals <28 years of age (Gustafson, 1950), it can be assumed that the high nitrogen levels exhibited by individual BzV 21c are a consequence of the preservation of the isotopic signal related to its breastfeeding and weaning. However, if we look at the overall trend in the nitrogen values for the individuals from Bezdanjača we can see how they do not differ much - or at all - from those of the individuals from other contemporary sites, most of whom are adults, meaning that in their case, the slightly high nitrogen values cannot be linked to a resonance of nursing signals.

Given the presence of *cribra orbitalia* and the quick demineralization of its dentin it seems more plausible that individual BzV 21c suffered from bad health, was most likely severely malnourished and was probably affected by other pathologies that, however, were not observable on the skull. Therefore, it is not implausible to think that BzV 21c's high δ^{15}N values could be a consequence of a cellular process occurring when lysosomes degrade intracellular components and known as *autophagy* (Cuervo & Macian, 2012). Autophagy is not only indispensable for cell physiology but is also a common conservative and protective process in our body, since it can affect the immune response against viruses, bacteria, and some forms of cancerous cells. Additionally, the breakdown products of autophagy are usually recycled for important cell functions, particularly during periods of stress or starvation (He *et al.*, 2018). From an isotopic point of view, it is likely that the process of "autoconsumption" of the body's own proteins and tissues could cause the nitrogen levels to rise. Cells can adapt to face nutrient deficiencies through various nutritional sensors or regulators (*ibid*). When amino acids (which affect the growth and survival of cells) are deficient in the cell

milieu, "*cellular protein synthesis and mitosis will cease immediately. More importantly, with a shortage in amino acids, the autophagic signaling pathway will be activated to release amino acids by degrading proteins in order to maintain the availability of amino acids pool for vital protein synthesis*" (He *et al.*, 2018: 498). There are two different types of amino acids that regulate the nitrogen ratio in our bodies. Particularly, non-essential amino acids are those amino acids that are not absorbed by the organism through the consumption of food but are produced by the body itself. These AA usually have a nitrogen isotope ratio which differs greatly from that of dietary proteins. Autophagy, with the subsequent production of new amino acids by the body itself to face starvation or malnutrition and degradation of the enamel, could therefore be an explanation for BzV 21c's unusually high levels of nitrogen.

Conclusion

The earliest archaeobotanical remains of millet were found in China and date back to the Early Neolithic (6000 BCE), whereas the first isotopic evidence for the consumption of millet in Europe was found from sixteenth-century BCE southwestern Ukraine (Filipović *et al.,* 2020). From here, millet spread through Europe following most likely an east-southwest axis over land. In Croatia millet appeared from the fifteenth/fourteenth century BCE. The data presented in this study suggest that the spread of this crop in Croatia during the Bronze Age also followed an east-west trajectory, appearing earlier (Middle and Late Bronze Age) in inland settlements such as Veliki Vital and Bezdanjača and only later (Late Bronze Age and mostly Iron Age) in the sites located along the coast, thus corroborating Filipović and colleagues' (2020) data. Nonetheless, there are some notable dietary differences amongst prehistoric Croatian populations with regards to millet consumption. Data suggest that the individuals from Bezdanjača had a mixed C_3/C_4 diet during their childhood and therefore their intake of millet was higher than it was for the individuals from the nearby contemporary settlement of Veliki Vital whose diet, although still slightly mixed in adult years, did not make much use of millet. In contrast, isotopic values for the Bronze Age individuals recovered from coastal sites reveal an adult mixed diet with more negative values than those that could be observed for inland sites. This suggests that during the Middle and Late Bronze Age millet either had not voluntarily been adopted as a crop or had not yet reached coastal Croatia. These hypotheses may be confirmed by further isotopic analysis conducted on Iron Age individuals from other coastal sites (Lightfoot *et al.,* 2014) which show a clear shift from a mixed diet with a predominant intake of C_3 plants to a mixed diet with a higher intake of C_4-based foods, but further research is needed to corroborate this.

Although the number of samples gathered and studied from both inland and coastal Croatian settlements is much smaller than the number of individuals from Bezdanjača, and although they take into consideration values referred to adulthood diet, which makes the comparison between these settlements not fully representative and definitive, so far it can be concluded that: **1)** the individuals from Bezdanjača not only started consuming C_4-based foods already from childhood, but they also consumed higher quantities of C_4 plants than other contemporary sites in Croatia; **2)** the isotopic data for the reconstruction of the diet for individuals from both inland and coastal Croatia seem to corroborate Filipović and colleagues' work (2020) regarding the timing and the routes of the spread of millet trough Europe via land following an east-west axis; **3)** the millet was welcomed differently in different parts of Croatia. Supposedly, it was first used by inland settlements located east (such as Bezdanjača) beginning from the Middle-Late Bronze Age and only later (LBA and especially EIA) started being consumed by people from the coast (west and southwest).

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A possible case of Gigantism and/or Acromegaly in a 15th-17th century woman from Đurine ćelije, Serbia

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Abstract

Endocrine disorders during growth and development that occur due to the secretion of excessive growth hormones are very rare in archaeological and modern populations. The human skeletal remains analyzed in this paper belong to an unusually tall woman, approximately 35-40 years of age, buried at the Đurine ćelije site (15th-17th century) in Serbia, who may have suffered from overgrowth syndrome. Individuals with this condition have an unusually tall stature and accompanying pathological changes related to organ systems and joint diseases. The aim of this paper is to show how the aforementioned disorder affected the health status of an individual (grave No. 7a) and the performance of daily activities, but also the attitude of the community towards deformities during life and after death. Differential diagnosis was performed since other diseases tend to lead to similar skeletal changes. During the analysis, changes in growth were noticed, and her stature was determined to be 186.42 cm. Compared to the documented stature of post-medieval population from this period, the skeletal remains show a significant deviation from the average, especially when it comes to female individuals. Other pathological changes observed in this woman are osteoarthritis, spondyloarthropathy, and periosteal new bone formation.

Introduction

The human skeletal remains analysed in this paper belong to an unusually tall individual buried at the Đurine ćelije site (15th-17th century) (Figure 1a, b), who may have suffered from overgrowth syndrome. The most common etiology of this syndrome is related to pituitary dysfunction that produces excessive amounts of somatropin or growth hormone. In most cases, growth disorders occur due to pituitary adenoma (benign tumor) or pituitary tissue hyperplasia (Aufderheide and Rodríguez-Martín, 1998; Ђурић-Срејић, 1995; Ortner and Putschar, 1981). Excessive secretion of this hormone leads to excessively tall stature and is a serious obstacle to the normal physical development of the individual. If this disorder occurs before the fusion of the growth plate, then the condition is called gigantism, if growth is complete before the tumor develops, then it is known as acromegaly (Atanacković, 1990; Roberts and Manchester, 2010). However, when excessive secretion of growth hormone occurs in childhood and continues through adulthood, the result is the simultaneous development of both disorders related to acromegaly and gigantism (Ortner, 2003). Such disorders are rare in ancient people, as well as in modern populations, with the higher occurrence of acromegaly in modern society. Today's statistics show that acromegaly occurs in 3: 1,000,000 cases annually worldwide, with a higher incidence in women than in men (Extabe, et al. 1993), while gigantism is less common, around 100 cases have been documented in the literature so far, although this certainly does not correspond to the real data and this number is probably underestimated (Sotos, 1996).

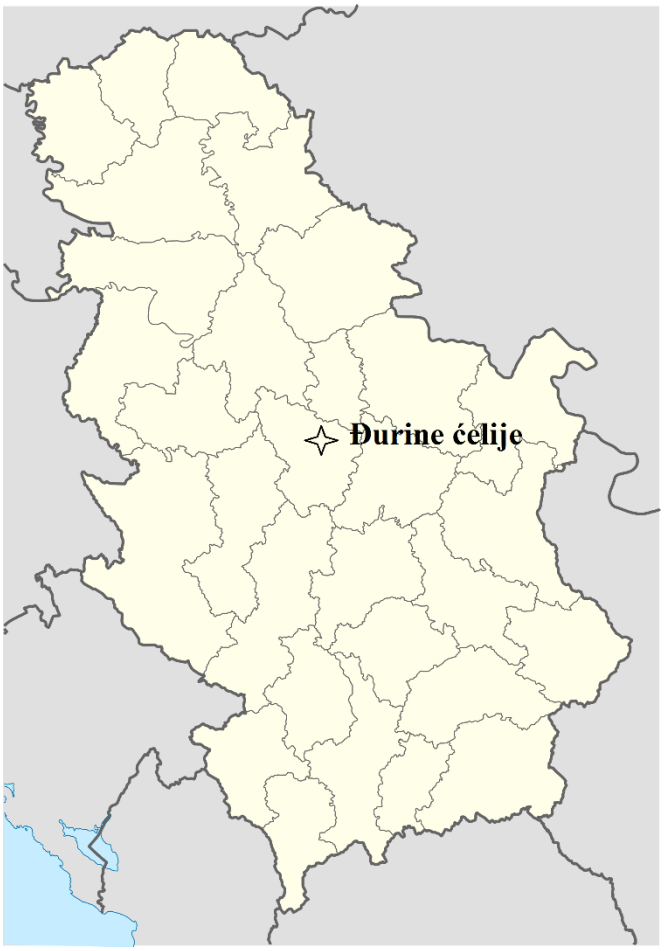

Figure 1a: Map of the Republic of Serbia showing the geographical location of the Đurine ćelije site

Excessive secretion of growth hormone in people younger than 10 years, suffering from gigantism, leads to accelerated linear growth. Body proportions are normal if the balance of linear growth is established by uniform fusion of the epiphyseal plate, however, uneven fusion can also occur, resulting in asymmetric body proportions (Aufderheide and Rodríguez-Martín 1998). In this condition, additionally to the excessively tall stature, the length and diameter of long bones are also increased (Ortner and Putschar 1981). If the main cause of this condition was a tumor then the sella turcica is enlarged (Weisberg et al. 1976). In acromegaly, the most noticeable changes are visible on the facial bones leading to a general enlargement, as well as an enlargement of the paranasal sinus, and the bones of the skull vault are thickened. The lower jaw is elongated and prognathism and dental malocclusion occur. In the bones of the skull vault, changes leading to a robust appearance are evident, the superciliary

Figure 1b: Geographical position of the Republic of Serbia in a map of Europe

arches are prominent on the frontal bone, and the external occipital protuberance of the occipital bone is pronounced (Ortner and Putschar, 1981; Ortner, 2003). On the postcranial skeleton, the bones of the hand and foot as well as the vertebrae are enlarged and the ribs are broad (Aufderheide and Rodríguez-Martín, 1998; Waldron 2009). The pathological changes that accompany these endocrine disorders are related to organ systems and joint diseases. In ancient and modern skeletons, in addition to degenerative changes, spondyloarthropathies lead to difficulties of breathing and moving, and signs of infectious diseases are often detected. Altogether, along with other pathologies, this will shorten the life of the individual (Ortner and Putschar, 1981; Chanson and Salenave, 2008).

According to the paleopathological literature, a modest number of certain and potential cases of gigantism and acromegaly in ancient people have been documented (Table 1). The commonality linking all these individuals is primarily extremely tall stature, long bones of the upper and lower extremities, robust and thickened skull, large and protruding lower jaw, enlarged sella turcica, numerous pathologies that accompany this condition and a short lifespan that rarely exceeds 30 years of age.

Table 1 Certain and probable cases of gigantism and acromegaly in ancient people that have been documented

Site	Sex and age	Stature (cm)	Endocrine disorder	Pathology	Source
Pržine, Gacko (14th-15th century), Bosnia and Herzegovina	M, 30	173	Acromegaly	Mandible shaped like "antique lamp", hyperplasia and hypertrophy cranial, extensions of paranasal cavities, longitudinal growth of femurs	Hošovski, 1991
Monte Bibele (4th-2nd century BC), Italy	M, 18-20	-	Possible gigantism with acromegalic features	Bones are hypertrophic, especially the facial bones and the clavicle, mandible and the skull are thickened, the epiphyses are very broadened.	Brasili et al., 1997
Ostrow Lednicki (12th-13th century) Poland	F, 23-30	215.5	Gigantism and acromegaly	Excessive body height, enlargement of bones, disproportionately large mandible, enlarged *sella turcica*	Gladykowska-Rzeczycka et al., 1998
Giza (5th dynasty; 2494–2345 BC), Egypt	M, 20-30	192.4	Possible gigantism	Tall and proportional stature, delayed epiphyseal union, enlarged *sella turcica*, biparietal thining	Mulhern, 2005
Bonn Square (11th-19th century), England	M, Adult	-	Possible acromegaly	Disproportionately large mandible	Webb and Norton, 2009
Eleutherna (7th century), Greece	?, 25-40	-	Acromegaly	Thickened skull, bone reliefs were robust, enlarged *sella turcica*	Charlier and Tsiganoki, 2011
Torre Serpentana (3rd century), Italy	M, 18-20	202	Gigantism	Very tall stature and long bones, possible enlargement of the *sella turcica*, nonuniformity or delayed epiphyseal closure	Minozzi et al. 2012; Minozzi et al. 2013
Blossom Mound (4350-3000 BP), Central California	M, 30-40	-	Possible acromegaly	Pronounced bone reliefs of the skull, crowding and malocclusion of the anterior dentition, enlargement of *sella turcica*	Bartelink et al., 2013
Ronda Sur (8th-9th century), Spain	M, 22.22–33.74	-	Possible gigantism/acromegaly	Large and thick neurocranium and pronounced bone reliefs, large and massive mandible, enlargement of the vertebral bodies, thickened ribs, slight increased length of the diaphysis with an increased cortical bone thickness of lower limbs	Viciano et al., 2015
Tasmasor (post-medieval period), Turkey	Young adult	188.9	Gigantism and acromegaly	Excessive bone growth in length and width, enlarged *sella turcica*, biparietal thinning, prognathism, facial robustness, elongated and enlarged ribs, widened metatarsals and metacarpals	Özdemir et al., 2017

Therefore, the aim of this paper is to show how the aforementioned disorders affected the health status of an individual found at Đurine ćelije site (grave No. 7a) and the performance of daily activities, but also the attitude of the community towards deformities in the life of the person and after death. Also, based on the detected pathological changes on the cranial and postcranial skeleton, which may indicate the presence of other diseases, differential diagnosis was performed here.

Materials and methods

The skeletal remains analyzed in this paper come from the post-medieval site of Đurine ćelije in the area of Rudnik, Serbia (Figure 2). Continuous archaeological excavations of this site took place between 2013-2016 (Радичевић и Миливојевић, 2013; Радичевић и др., 2015; Гордић и Ћирковић, 2018). During that time, the remains of a monastery complex with a necropolis were discovered.

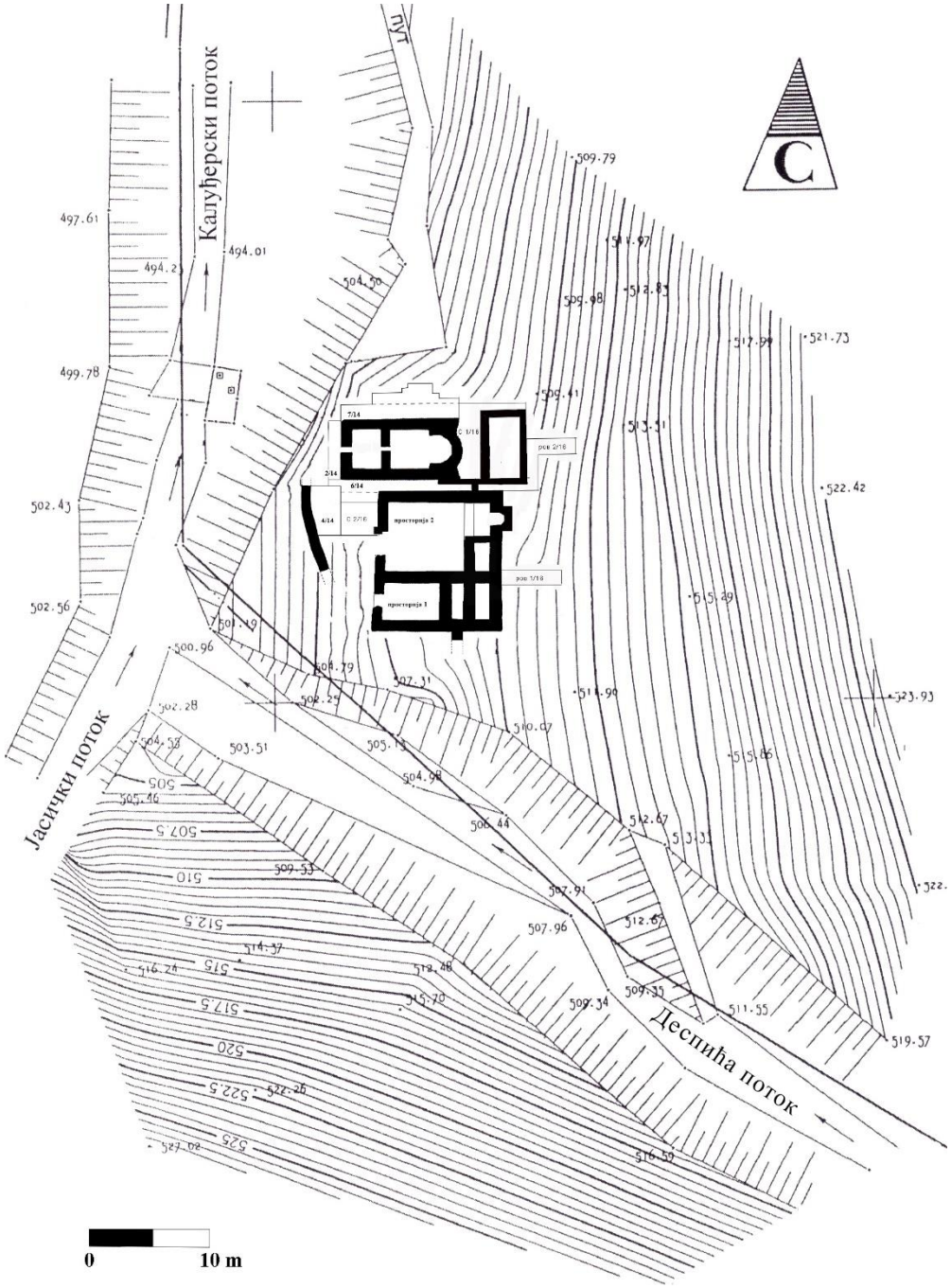

Figure 2: Site plan of Đurine ćelije site (from Радичевић и др. 2016)

The deceased were buried in the immediate vicinity of the monastery church. Several horizons of the use of the necropolis have been recorded, dated to the period from the 15th to the 17th century on the basis of archaeological findings. According to the tombstone inscription of grave No. 6 which testifies to the burial of Jovan Sipahi[1], archaeological finds from the same grave and a coin found in grave No. 8, it was possible to date

[1] The Sipahis were horsemen in the Ottoman army and could own a timar (land). They had a high social status among Serbs during the Ottoman Empire (Радичевић и Миливојевић, 2016).

only the youngest burials from the 17th century. Archaeological excavations have revealed 25 graves (Радичевић и Миливојевић, 2013; Радичевић и др., 2015; Гордић и Ћирковић, 2018). The deceased were buried in an extended position on their backs, usually with their hands on their chests or stomachs, orientation west-east (Радичевић и др., 2015). There were some deviations and the orientationthe orientation of some burials was northwest-southeast (Гордић и Ћирковић 2018). North of the church, burials were located under the tombstones (Figure 3) and they are dated to the 17th century (Радичевић и др., 2015). Below one of the tombstones, marked as grave No. 7 there were two buried individuals. The first buried deceased (7b) was in the primary position, while the skeletal remains of the second buried individual (7a) were disturbed, i.e. in the secondary position (Figure 4). According to the researchers of this site, the grave was disturbed before archaeological excavations took place.[2]

The state of preservation of skeletal remains was observed according to the categories proposed by Mikić (Mikić 1978). Determination of the sex was based on the morphological characteristics of the pelvic bones, as well as the morphological characteristics of the skull (Workshop of European Anthropologists, 1980; Buikstra and Ubelaker, 1994). The auricular surface of the ilium (Lovejoy et al., 1985b) and the degree of closure of the cranial sutures were observed to determine age at the time of death (Workshop of European Anthropologists, 1980). The standard tooth numbering system was used in the analysis of dentition (Federation Dentaire

Figure 3: Tombstones north of the monastery church (from Радичевић и др. 2016)

[2] Đurine ćelije-report 2015, December 15th 2015.

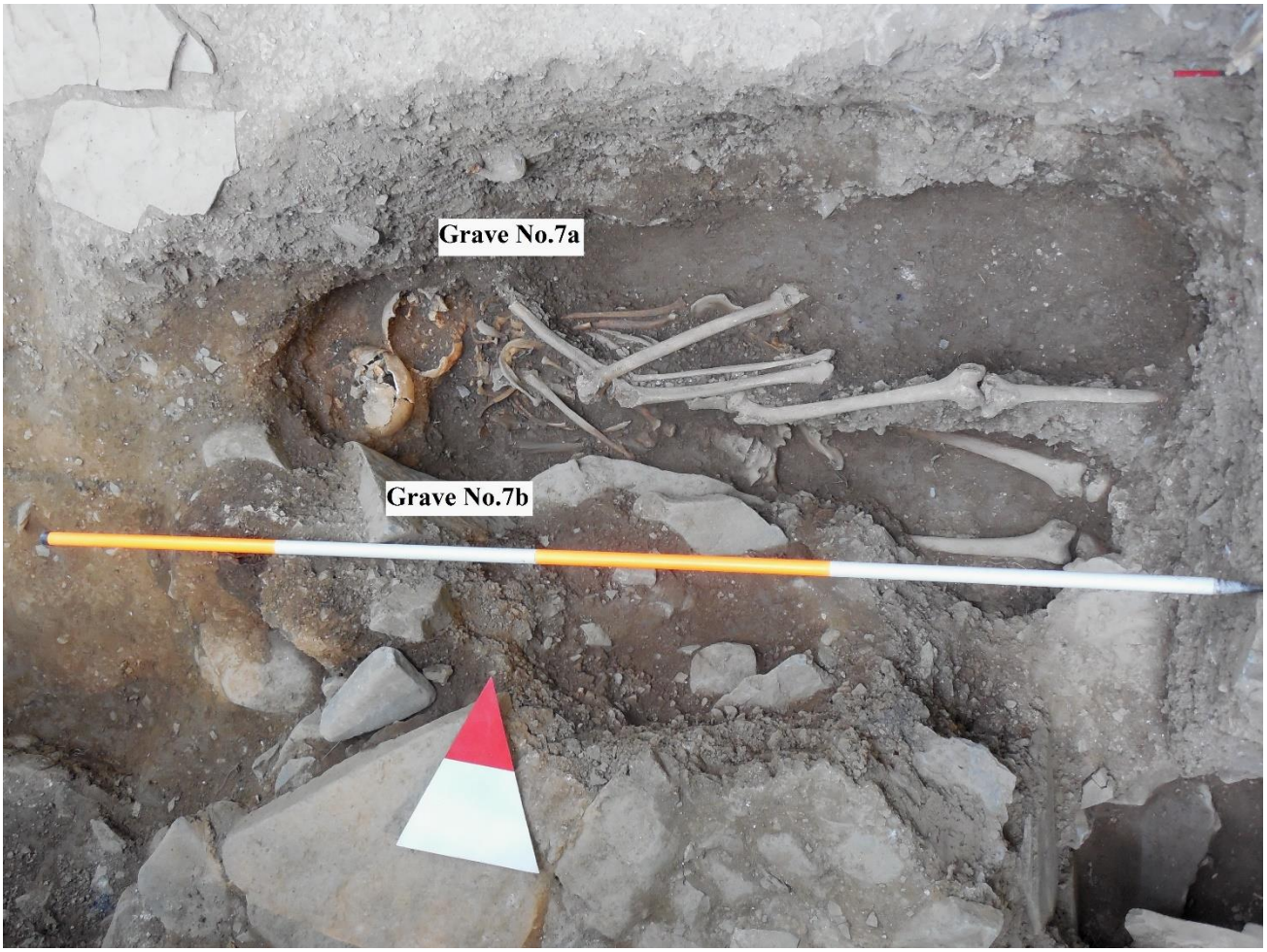

Figure 4: Grave No. 7 with two buried individuals (photo credit: V. Milivojević)

Internationale, 1971). Metric analyzes were applied in this paper to obtain data on stature based on maximum length of long bones, according to the formulae of Trotter and Gleser (1958) and body weight was calculated based on the maximum diameter of the femoral head, according to the formula of Ruff et al. (1991). Existing standards (Ortner and Putschar, 1981; Aufderheide and Rodríguez-Martín, 1998; Ortner, 2003) were used to identify and diagnose pathological changes. In this paper, the analysis of macroscopic examination of musculoskeletal stress markers was also performed (Mariotti et al., 2017).

Results

The analyzed human skeletal remains in this paper belong to the category of well – preserved, incomplete skeletal remains. In Figure 5 the state of preservation of skeletal remains is presented. Table 2 provides the skeletal measurements buried in grave No. 7a. Morphological characteristics of the skull (*os frontale, arcus superciliaris, tuber frontale et parietale, planum nuchale*, total aspect of the mandible, *mentum, angulus mandible*) and postcranial skeleton (*incisura ischiadica major*) showed that the skeletal remains belong to a female individual. Her age at the time of death, based on morphological changes of the auricular surface of the ilium, was 35-39 years (stage IV), and based on the degree of closure of the cranial sutures from 35-40

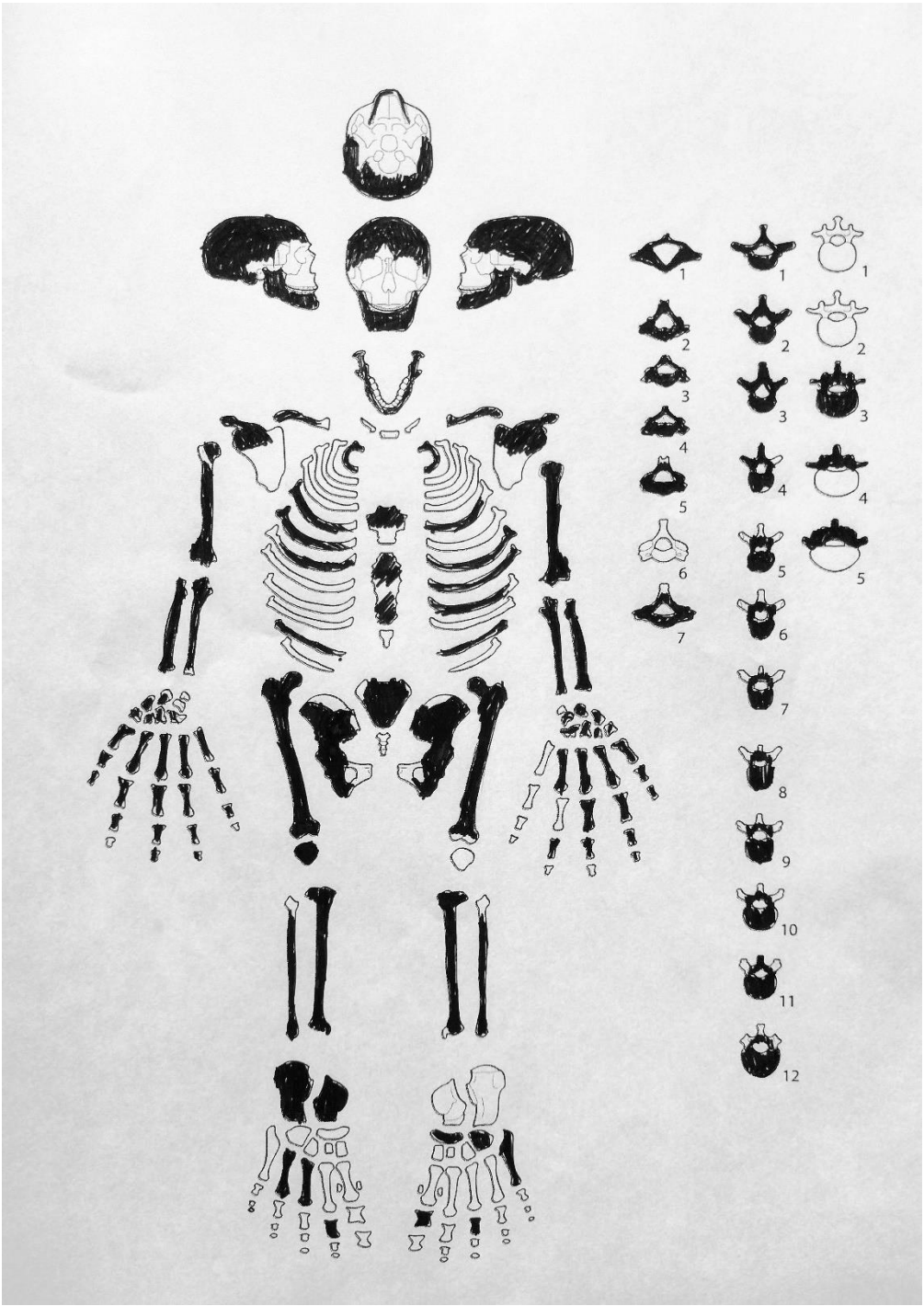

Figure 5: Inventory of burial No. 7a. Bones shaded in black are present.

years of age.[3] According to the method of Trotter and Gleser (1958), the maximum lengths of long bones were measured and her body height was calculated (Table 3). Stature values ranged from 189.93 cm for the right tibia and 182.92 cm for the right femur, with an average value of 186.42 cm. According to the formula of Ruff et al. (1991) her body weight was 80.9 kg.

[3] Although cranial suture closure is used for decades as an indicator of age it is an unreliable method. Diseases or genetic disorders can lead to faster or slower suture closure.

Table 2 Measurements of the cranial and postcranial skeleton

Grave No. 7a			
Cranial osteometric data (cm)		a-p diameter at midshaft	1 1
Mandible		m-l diameter at midshaft	1.3 1.4
Height of the mandibular body	2.4	**Ulna (cm)***	
Breadth of the mandibular body	1.1	Maximum length	30.9 -
Bigonial width (go-go)	8.7	a-p diameter	1 1.2
Bicondylar breadth (cdl-cdl)	10.9	m-l diameter	1.2 1.3
Minimum ramus breadth	3.5	Physiological length	27.5
Maximum ramus breadth	4.2	Minimum circumference	2.9
Maximum ramus height	7.5	**Femur (cm)***	
Mandibular length	8.2	Maximum length	- 50.6
Postcranial osteometric data		a-p subtrochanteric midshaft	2.3 2.4
Humerus (cm)*		m-l diameter subtrochanteric midshaft	2.1 2.2
Maximum length	35 -	Maximum head diameter	- 4.8
Maximum diameter at midshaft	2.4 2.5	Midshaft circumference	9.2 9.4
Minimum diameter middle	2 2,1	**Tibia (cm)***	
Epicondylar breadth	6.5 6.7	Length	44.3 -
Clavicule (cm)*		Maximum diameter at the nutrient foramen	2.7 2.5
Maximum length	15.5 -	m-l diameter at the nutrient foramen	2.1 2
Sagittal diameter at the midshaft	4.2 4.1	Circumference at the nutrient foramen	9.7 9.4
Radius (cm)*		**Fibula (cm)***	
Maximum length	28,5 28.6	Maximum diameter at the midshaft	2.2 2

Bones marked with * have two measurements, the upper is for the left, and the lower is for the right side of the body

Table 3 Measurements of the long bones and estimated stature (grave No. 7a)

Long bones	Maximum length (cm) Left	Maximum length (cm) Right	Stature (cm) Left	Stature (cm) Right
Humerus	35	-	179. 25 ± 4	-
Ulna	30.9	-	188. 95 ± 4	-
Radius	28.5	28.6	187. 43 ± 4	187. 81 ± 4
Femur	-	50.6	182. 92 ± 4	-
Tibia	-	44.3	189. 93 ± 4	-

Table 4 presents an overview of estimated stature of medieval populations on the territory of Serbia during the late Middle Ages. The range of estimated stature for men ranged from 153-181 cm, and for women from 146-172 cm (Живановић, 1985; Живановић, 1987; Ђурић-Срејић, 1997; Миладиновић-Радмиловић, 2007; Вуловић и Бизјак, 2019). At the Đurine ćelije site, the average stature for males was 179.19 cm, and for

Table 4 Estimated stature for late Medieval population from Serbian sites. ([a]M-9, F-2; [b]M-25, F-10; [c]M-9, F-13; [d]M-32, F-24; [e]M-4, F-0; [f]M-5; F-0).

Site	Stature (cm)			
	Male-average value	Range	Female-average value	Range
Đurine ćelije (15th-17th century) [a, 1]	179, 19	165, 04-192, 25	165, 32	165, 17-165, 46
Deževo (14th-15th century) [b, 2]	168, 36	158, 39-175, 69	162, 60	152, 59-172, 38
Valjevska Gračanica (15th-19th century) [c, 2]	169, 3	161-172	159, 2	158, 8-164
Crkva 4 (Trgovište) (15th-17th century) [d, 2]	166, 97	153, 75-181, 07	155, 67	146, 51-163, 09
Manastir Resava (15th century) [e, 1]	174, 5	168-178	-	-
Madžarsko brdo (late middle ages) [f, 1]	175	170-181	-	-

[a-f] Number of male (M) and female (F) individuals
[1] Authors used formula of Trotter and Gleser (1952)
[2] Authors used formula of Pearson (1899)

females 165.32 cm[4]. In individual No. 7a estimated stature was 20 cm higher than the average height of females. This is most evident in this case, abnormal height and proportional growth, significantly long bones of the upper and lower extremities (Figure 6) and pathological changes in the cranial and postcranial skeleton. Robust characteristics were noticed on the skull, a pronounced external occipital protuberance and large mastoid process. Prognathism-protrusion and obtuse angle are noticeable on the mandible (Figure 7a) and a significant number of teeth lost antemortem[5] (Figure 7b).

Anatomical variation such as bilateral perforatio fossa olecrani, also known as septal aperture, was detected on both humeri (Figure 8). The pathological changes

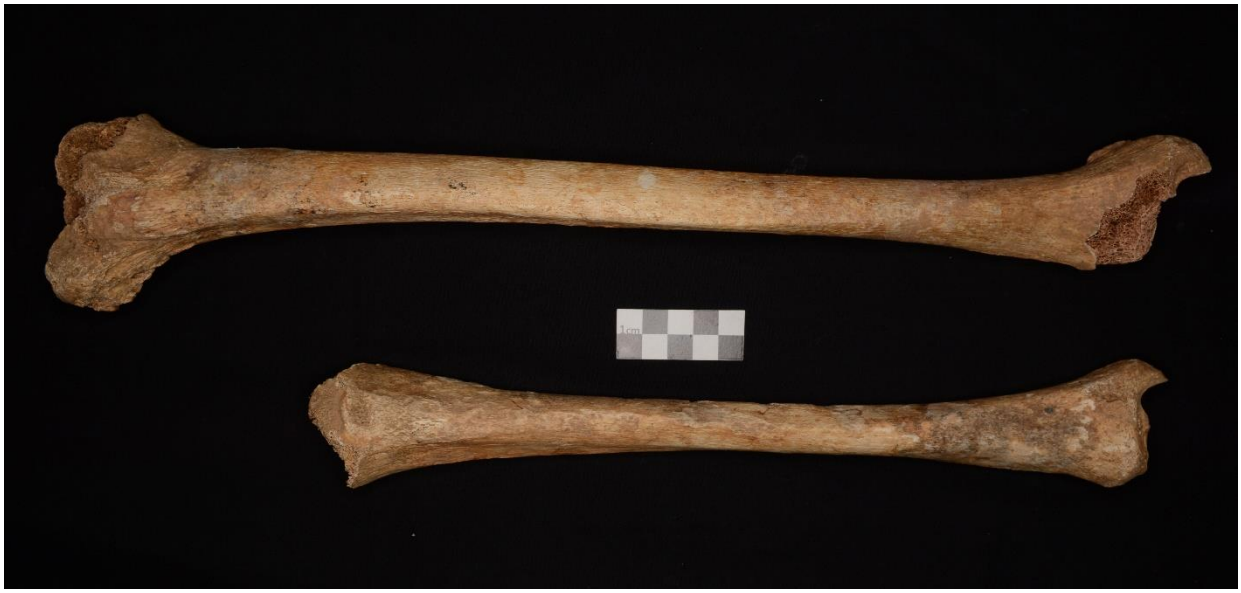

Figure 6: Comparison of the long bones of the lower limbs between 7a and normal body height of the female individual (grave No. 6) (photo credit: author)

[4] It was possible to calculate stature only for three women. However, the individual from grave No 7a was excluded from this analysis due to growth disorder (Miljević, 2018).

[5] FDI numbering system for the permanent teeth: Teeth lost antemortem: 37, 38, 44, 46-48.

Figure 7a: Protrusion and obtuse angle on the mandible (photo: author)

Figure 7b: Teeth lost antemortem (photo: author)

observed in this individual are: osteoarthritis, spondyloarthropathy, and periostitis. Osteoarthritis has been observed in almost every joint, most often in the form of osteophytes and eburnation. The new bone formation or osteophytes were found on the proximal ends of the left and right humerus, radius, femur, tibia and preserved distal ends of fibulae, on the distal ends of clavicles, metatarsal, and tarsal bones. On the right clavicle and acromion of the right scapula, in addition to osteophytes, eburnation also occurs (Figure 9). Fusion of the right rib with the vertebra was observed on one thoracic vertebra (T4) (Figure 10). Traces of fusion are also noticeable in other thoracic vertebrae, but during the excavation it was separated. Fusion also occurs in the area of the spinous process, i.e. in the articular surfaces of the lumbar vertebrae (from L3 to L5) and thoracic vertebrae (from T9 to T12) with the intervertebral space between the bodies of the thoracic vertebrae (Figure 11). Significant curvature and sacralization with L5 was observed in the sacrum. The missing sacroiliac joint probably existed and was lost

Figure 8: Bilateral epigenetic variation perforatio fossa olecrani on the distal ends of both humerus (photo credit: author)

Figure 9: Osteoarthritic changes (eburnation) on the acromion of right scapula (photo credit: author)

Figure 10: Costovertebral joint on the thoracic vertebrae (T4) (photo credit: author)

during or after excavation. Excessive bone growth on the remaining parts of the left pelvic and sacral bone parts indicate an ossification, probably an ankylosing spondylitis. Periosteal reactions occur on almost all long bones of the upper and lower extremities (humerus, femur, tibia, fibula). These are healed periosteal reactions, none of which were active at the time of death. In the left femur, due to this disorder, there was never an adhesion of the proximal end (femoral head) with the diaphysis (Figure 12), although ossification on all bones showed that the growth was complete.

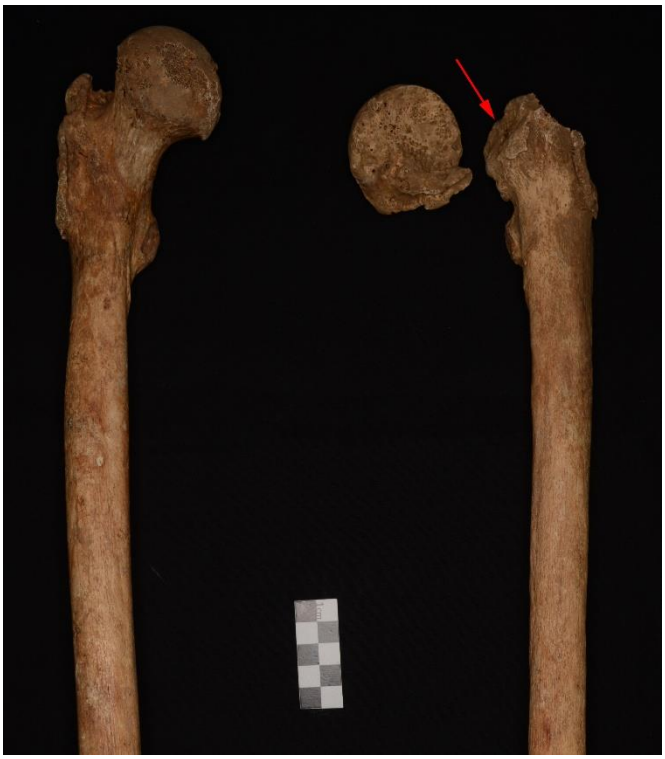

Figure 12: Nonunion of the proximal epiphysis with diaphysis of the left femur (photo credit: author)

Bilateral indentations on the lateral sides of both proximal femurs were observed (Figure 13), as well as narrowing of the iliac bone on the left preserved pelvic

Figure 11: Fusion of articular surface of thoracic and lumbar vertebrae (photo credit: author)

Figure 13: Bilateral indentations on the lateral sides of both proximal femurs (photo credit: author)

bone. Musculoskeletal stress markers were observed on the postcranial skeleton, and the most pronounced muscle attachments were present on the right side of the skeleton (Table 5).

Table 5 Degree of musculoskeletal stress markers on the upper and lower limb bones (grave No. 7a)

	Muscle attachments
Humerus	*m. deltoideus*
Right	2
Left	1c
Humerus	*m.brachioradialis*
Right	3
Left	2
Radius	*m. biceps brachii*
Right	2
Left	1c
Ulna	*m .brachialis*
Right	3
Left	2
Femur	*m.gluteus maximus*
Right	2
Left	2
Patella	*quadriceps tendon*
Right	3
Tibia	*m.soleus*
Right	3
Left	2
Tibia	*quadriceps tendon*
Right	2
Left	2

Discussion and Conclusion

Discussion

Growth and development disorders that lead to tall stature rarely occur in archaeological and modern populations, and they are especially difficult to diagnose on osteological material. However, if abnormal stature is not associated only with excessive secretion of growth hormone from the pituitary gland, these changes can also occur due to other similar disorders. Diseases that lead to similar development and growth disorders are Marfan's syndrome (Petitt and Adamec, 2005; Aufderheide and Rodríguez-Martín, 1998), Sotos syndrome (Parker and Parker, 2007), Weaver syndrome (Bansal and Bansal, 2009) and Beckwith-Wiedemann syndrome (DeBaun and Horst, 2011). Marfan's syndrome is a genetic disorder that affects the cardiovascular, ocular and skeletal systems (Petitt and Adamec, 2005). The skeletal changes that dominate due to Marfan's syndrome are excessively long upper and lower extremities, especially the upper ones. In addition, dental anomalies and malocclusion occur, scoliosis, kyphosis or pectus carinatum (pigeon breast) are common in the area of the chest and spine (Aufderheide and Rodríguez-Martín, 1998). Sotos syndrome is another disorder that affects the skeletal system and where growth is accelerated. Affected babies and children tend to grow faster and they are taller than children of the same age. However, their

adult height is quite normal. An abnormal curvature of the spine (scoliosis) can also be the sign of Sotos syndrome (Parker and Parker, 2007). Weaver syndrome is a disorder that usually starts with rapid growth before birth of the baby and continues through childhood. It is characterized by accelerated bone maturation, craniofacial, skeletal and neurological abnormalities. The mandibule can be smaller than normal. Fingers of people affected with this syndrome are usually broad (Bansal and Bansal, 2009). Beckwith-Wiedemann syndrome is an overgrowth syndrome of the prenatal period and it is characterized by congenital malformations, and predisposition to cancer. Children with this syndrome can have asymmetry of the limbs or face, as well as joint laxity, scoliosis, and thoracic cage abnormalities (DeBaun and Horst, 2011).

Despite the differential diagnosis, where none of the above examples completely fit into the presented pathological picture, and the insufficient preservation of skeletal remains (especially facial bones and sella turcica), which would facilitate and confirm the diagnosis that this is an overgrowth syndrome due to pituitary adenoma, we can only assume that the observed changes in the osteological material may have been due to excessive secretion of this hormone. The results of the anthropological analysis which may indicate that the individual from grave No. 7a was suffering from gigantism and / or acromegaly are as follows:

1. The appearance of the skull which has robust characteristics, as indicated by the prominent external occipital protuberance, large mastoid processus. Protrusion-prognathism and obtuse angle of the mandible were observed on the mandible.

2. On the postcranial skeleton, increased longitudinal growth of the upper and lower extremities, nonunion of the proximal epiphysis with the diaphysis of the left, abnormal stature for period and sex and accompanying pathologies (degenerative joint diseases, spondyloarthropathy of the spine, periosteal changes on the long bones) were detected.

Although the skull has robust characteristics, morphological changes of the pelvis indicate a female individual. Mandibular prognathism occurs in these disorders leading to remodeling of bites, malocclusions, and large numbers of teeth lost antemortem (Aufderheide and Rodríguez-Martín, 1998; Ortner, 2003). Incomplete fusion of the proximal end with the diaphysis occurs in younger individuals who have been diagnosed with gigantism, because this disease leads to growth disorder (Waldron, 2009). However, in this individual (grave No. 7a) the growth on all the bones was complete, so we cannot speak of a younger person. It is obvious that the excessive secretion of growth hormone that developed in youth continued in adulthood, which could have resulted in both gigantism and acromegaly. This is also indicated by her tall stature (186.42 cm), which stopped at one point. If the increased secretion of hormones continued in youth (before the complete fusion of the pineal gland), this individual would certainly have a height of over 200 cm (Aufderheide and Rodriguez-Martin 1998). Pathologies observed in No. 7a belong to the group of pathologies that are standardly associated with constant excessive growth disorder (Aufderheide and Rodriguez-Martin, 1998; Hošovski, 1991; Mulhern, 2005; Ozdemir et al., 2017). Patients with gigantism rarely or never live longer than 30 years, because of the progression of other diseases (Minozzi et al., 2012), while in patients diagnosed with acromegaly life expectancy exceeds 50 years of age (de Herder, 2008; de Herder, 2014). Possible ankylosing spondylitis in No. 7a was detected in the form of fusion which affected the lumbar and thoracic vertebrae in the area of the spinous process and joint surfaces, as well as the costovertebral joints on the thoracic vertebrae. The sacroiliac joint also existed, but during or after the excavation, this joint was damaged and separated. According to Olivieri et al. (2009), Waldron (2009) and Ortner and Putschar (1981) the disease usually begins in the lumbar vertebrae and sacroiliac joint and progressively affects the thoracic vertebrae and their costovertebral joints. Also, for a full list of diagnostic criteria follow up Šlaus et al. (2012). Perforatio fossa olecrani, which is observed on the distal ends of the humeri, may be related to this disorder. It has been observed that this epigenetic anomaly occurs with a higher frequency in the female population (Mays, 2008). The hypothesis is that weaker muscles can lead to increased joint looseness, which results in hypermobility and the appearance of

perforatio fossa olecrani, and that it occurs in a higher percentage in older individuals. There have been attempts to compare the incidence of osteoarthritis with this anomaly (Myszka and Trzcinski, 2015; Myszka, 2015), but it has been concluded that it develops in youth and not as osteoarthritis in old age. The question of the cause of this anomaly remains open. In addition to the observed pathological changes, changes in the form of indentations on the lateral sides of both femurs were recorded, as well as narrowing of the iliac bone of the left pelvic wing. It was not possible to observe the right one because it was fragmented.

This case showed that, despite the aggravated pathological picture and indisputably different physical appearance and development, she was not separated and isolated from other graves, but received the same treatment in funeral practice as all the deceased, including burial below the tombstone. Although this is not an isolated example, it is known from previous research that the caring attitude of the society towards deformities and weaknesses of people with gigantism and acromegaly did not always extend to posthumous customs (Gladykowska-Rzeczycka et al., 1998). The analysis of the skeletal remains of a giant woman from the Ostrow Lednicki site showed that, once or probably several times, she received medical care throughout her life during the repair of the limb fracture. However, during the mortuary treatment, she was not buried in the same necropolis as the others, but in another former necropolis that ceased to be used, but was previously reserved for the burial of the elite. Also, she was not buried in the same position. Her body was placed in an unusual position and out of order. Her skeleton was lying on the left side, with her left hand close to her head. The right upper limb was bent at the elbow, the left lower limb was bent at the knee, and apparently without care. This does not mean that the woman from Ostrow Lednicki was completely rejected, but in the contrast to the case presented in this paper from Đurine ćelije, she was probaly not a full member of the community (Gladykowska-Rzeczycka et al., 1998; Matczak and Kozlowski, 2017).

Conclusion

Abnormally enlarged long bones of the upper and lower extremities, robust skull, mandibular prognathism, numerous pathologies and tall stature above the average for the post-medieval population and sex were recorded in a female individual (grave No. 7a) from the Đurine ćelije site. These changes observed on skeletal remains may indicate the presence of gigantism and acromegaly at the same time. However, although the pathological picture indicates a difficult life for the infected person, this disorder did not prevent her from performing physical activities during her lifetime, since there is a noticeable absence of muscle atrophy and pronounced enthesis on the upper and lower extremities. It is difficult or almost impossible to find out to what extent this woman suffered from pain at all, but it seems very likely that she went through some periods of pain or discomfort during her life. The results of the anthropological analysis indicate that during her life, and after her death, she was treated equally by her contemporaries, despite obvious differences in physical appearance and needs for a functional life.

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The case of hip dysplasia of an adult from the Roman Period site of Velebit (Serbia)

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Abstract

Objective: This study is designed to reveal the diagnosis of a rare hip condition with an estimation of the possible cause of death.
Materials: Archaeological site of Velebit dated between the 3rd and 4th century AD is located in northern Serbia. Grave No 24 differs from others in the unusual position of the skeletal remains in situ.
Methods: The bioanthropological analyses included an estimation of skeletal preservation, cranial and postcranial skeletal measurements, estimation of sex and age at the moment of death, dental analysis and a paleopathological examination. This skeleton was analysed for signs of bone disease, using diagnostic paleopathological procedures comprising gross examination and CT scanning.
Results: The results revealed that the analysed male individual was 40 to 55 years of age. The bioanthropological analyses showed two deformities of the pelvic bones, each on the outer surface, located posteriorly and superiorly of the acetabular area. The observed lesions were characterised as type 4 of developmental dysplasia of the hip. In addition, a sharp lesion was observed in the right posterior region of squama of the occipital bone.
Conclusions: Our results clearly suggest that this individual had been suffering from hip dysplasia. The possible cause of death could be the observed head lesion. In addition, there is no skeletal conformation of unfavourable living conditions related to physiological stress and diet.

Introduction

Hip dysplasia is defined as a modelling failure of the acetabulum and, subsequently, the femoral head. People who suffer from hip dysplasia are born with the condition. In neonates, the condition is connected to a variety of anatomic abnormalities, from dysplastic to severe morphological findings that occur in rare idiopathic teratologic dislocations, usually in association with neurological diseases (Morrissy and Weinstein, 2006). Initially, this condition is commonly presented with delayed ossification of the lateral epiphysis of the acetabulum, which could lead to secondary dislocation during the first few months of life (Hefti et al., 2007). This occurs as the possible consequence of a subtle lack of coverage of the femoral head by the acetabulum i.e. a noncongruent femoral head and acetabulum (Manaster et al., 2016). The hip

joint can become partially or completely dislocated. Subluxated hips are more susceptible to the onset of symptoms than completely dislocated hips (Morrissy and Weinstein, 2006). Usually, pain is not present during childhood, but most commonly presents as a symptom during adolescence and adulthood (Hefti et al., 2007; Manaster et al., 2016; https://hipdysplasia.org/developmental-dysplasia-of-the-hip/infant-signs-and-symptomshipdysplasia.org).

Geographical variation in the incidence of this disease has been noted, and both genetic and environmental elements are recognised as main background factors (Roberts and Manchester, 2007; Hefti et al., 2007; Mitchell and Redfern, 2007; Morrissy and Weinstein, 2006). In the contemporary population, this condition has an incidence of 1:1000, with a slight female predominance (1:5-8). Furthermore, a bilateral occurrence is recorded in 20% of cases (Manaster et al., 2016). In archaeological populations, hip dysplasia also tends to be more common in females than males, and occurs most frequently on the left side (Anderson, 2000). Analysing a series of 572 adults from the Medieval period in London, Mitchell and Redfern (2011) noted that the prevalence of developmental dysplasia of the hip (DDH) such as (acetabular dysplasia, subluxation, or dislocation) amounted to 1.7% of the investigated population (Mitchell and Redfern, 2011).

In bioanthropological literature, just a few systematic papers that included numerous cases of this pathological condition have been published thus far (Mitchell and Redfern, 2007; 2011). However, the importance of the case studies of this pathological condition should not be underestimated. Its importance lies not only in the rarity of the condition but also in the significant impact on a person's everyday life.

The aim of this case study is to present the hip dysplasia of an adult from the Roman Period site of Velebit (Serbia). We will discuss the differential diagnosis of the observed pathological conditions, outlining the development of hip dysplasia during this individual's life. Additionally, we will also evaluate the circumstances in which the perimortem cranial trauma found on the skull of the investigated individual occurred, as well as the potential outcomes.

Materials and methods

The archaeological site of Velebit is situated near the city of Senta (northern Serbia). According to unpublished archaeological records, the necropolis of Velebit is a multilayered site dated between the 2nd and 3rd century AD. Among the excavated graves, grave no. 24 differs from the others in the unusual position of the skeletal remains in situ. The shallow grave pit was situated in humus soil and the well preserved skeleton in situ was in an extended supine position. However, the position of the lower extremities was unusual in that both legs were bent at the knees, with the right leg bent more than the left and resting over the left. The orientation of this individual was SW-NE, with a deviation of 15 degrees towards the north. There were no grave goods present.

The bioanthropological analyses included an estimation of skeletal preservation, cranial and post-cranial skeletal measurements, an estimation of sex and age at the moment of death, a reconstruction of body height, dental analysis and a paleopathological examination. The degree of preservation was evaluated according to a modified Mikić scheme, which takes into account the quantity of bones present as well as bone fragmentation (Mikić, 1978). Measurements were taken following standard osteological procedures (Buikstra and Ubelaker, 1994). The age assessment was based on the morphological appearance of the pubic symphysis, in accordance with the recommendations of Suchey-Brooks (Brooks and Suchey, 1990). The final estimation also included Iscan's methods (Iscan et al., 1984, 1985), based on the appearance of the sternal end of the ribs, the cranial suture closures (Meindl and Lovejoy, 1985), dental wear (Gustafson, 1950) and the degenerative changes of the skeletons. Since hip bones present the most reliable indicators of sex in the human skeleton (Djuric et al., 2007), in this case study sex determination was primarily based on the dimorphic features of the os coxae (Buikstra and Ubelaker, 1994). An additional method for sex assessment was based on cranial morphology, and this was followed using standard bioanthropological criteria (Buikstra and

Ubelaker, 1994). The reconstruction of body height was based on the length of the long bones (Trotter and Gleser, 1958). This skeleton was analysed for signs of bone disease, using diagnostic paleopathological procedures, comprising gross examination and CT scanning. The gross examination was based on a macroscopic observation of each bone including a detailed written and photographic description following the recommendation of Buikstra (2019), while CT scanning was conducted using a Siemens SOMATOM Sensation 16 with study reading in Carestream Vue PACS Power Viewer (ver. 12.0.0.5756).

Results

The skeletal remains of this individual were in a relatively good state of preservation (Fig 1).

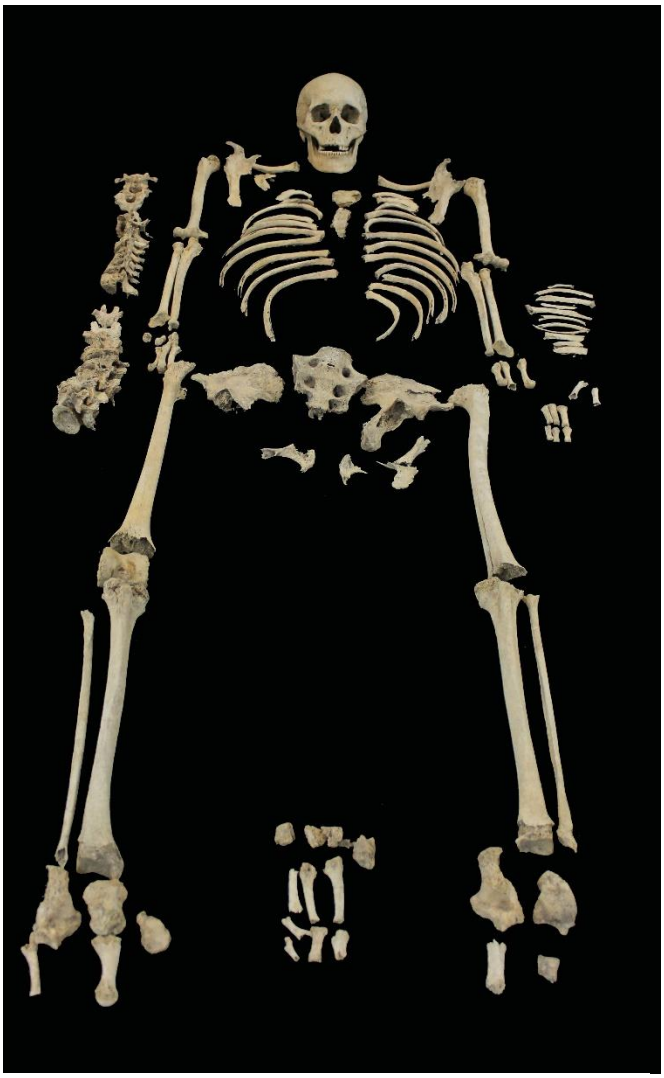

Figure 1: Skeletal remains from grave no. 24 (Photo and modification by Tamara Pavlović).

Based on the maximum length of the humerus and ulna, the body height has been reconstructed and estimated to be approximately 169 cm. Bioanthropological analyses revealed that the male individual buried in this grave was 40 to 55 years of age at the moment of death. During the bioanthropological analyses, two deformities of the pelvic bones were noted, each on the outer surface, located posteriorly and superiorly of the acetabular area (Fig 2).

Figure 2: Deformities of pelvic bones (Photo and modification by Tamara Pavlović).

The surface bone was changed in comparison to the surrounding area, in the form of an oval bone impression, moderately deep with partially obtuse margins. A subtle new bone formation could be observed in the caudal half of the lesion periphery. The observed changes represented a false acetabulum. The condition was characterised as a type 4 developmental dysplasia of the hip, represented with a completely dislocated hip, and an inversion and highly possible hypotrophy of the labrum during life (Resnick and Kransdorf, 2005). On the left pelvic bone, in the expected area of true acetabulum, a triangular, narrow cavity with an uneven surface could be observed. This feature was partially preserved and represented an undeveloped true acetabulum. Unfortunately, on the right pelvic bone the expected area of the true acetabulum was not preserved.

A sharp lesion was observed in the right posterior region of the squama of the occipital bone (Figs 3 and 4). The find was described as a linear fracture with diastatic, dominantly sharp margins followed inferiorly by a tangential defect in the outer lamina, a possible repercussion of a loose fragment. Signs of discrete

Figure 3: Occipital lesion (macroscopic oblique view) (Photo and modification by Tamara Pavlović).

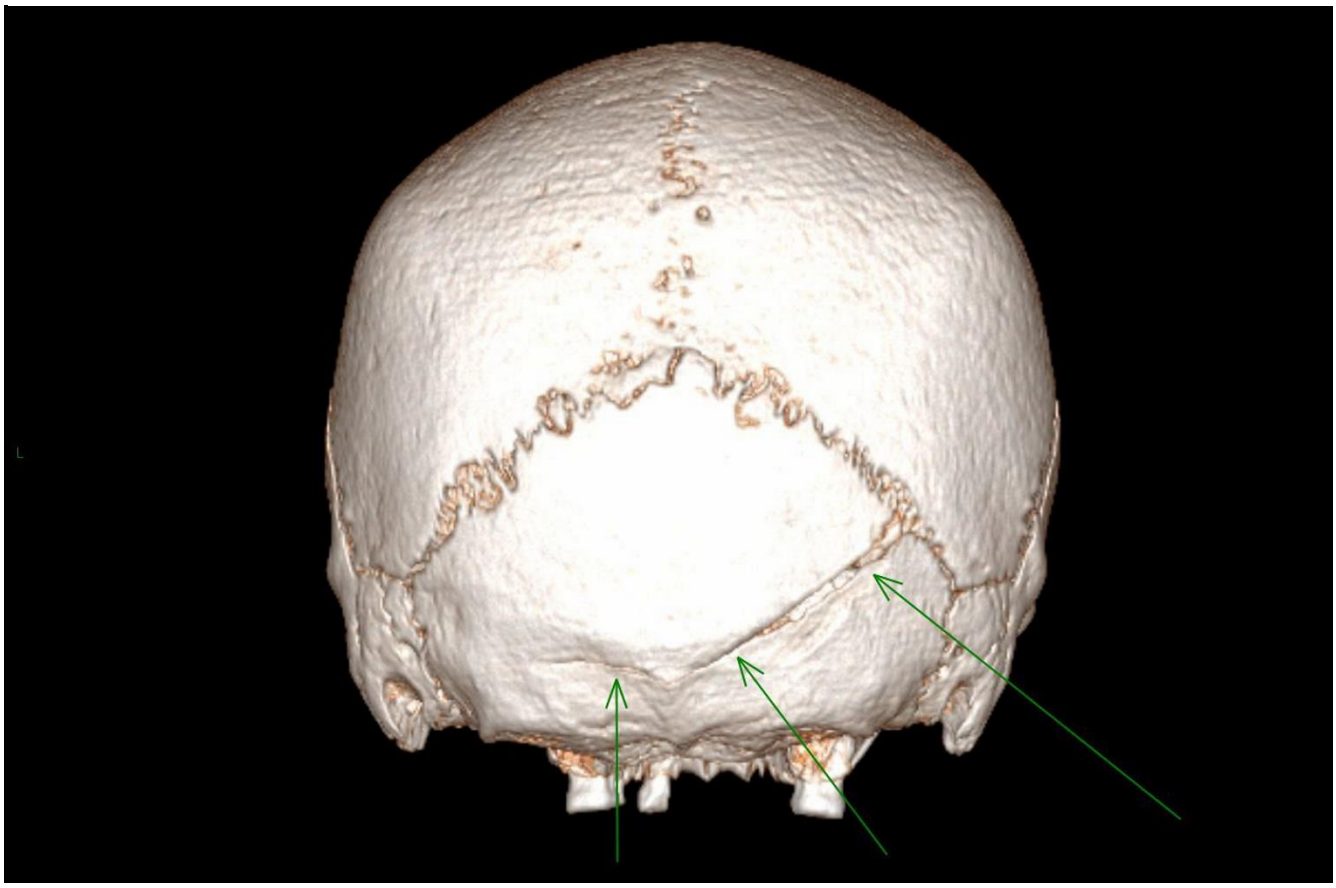

Figure 4: Occipital lesion (MDCT Volume Rendering, posterior view) (Photo and modification by Petar Milenković).

callus formations were observed during radiological analyses, with the most pronounced records in the caudal third of the lesion, especially on the right side (Fig 5). At the same level on the left side, only the outer tabula were involved (Fig 6), while in the cranial and middle third, destruction affected both tabulas as well as the diploe.

In addition, malnutrition traces such as enamel hypoplasia, cribra orbitalia, subperiosteal inflammation, specific infectious diseases or metabolic diseases have not been noticed.

Discussion and Conclusion

Discussion

The normal development of the acetabulum occurs not only through growth of adjacent hip bones and the proximal femur, but is also highly influenced by vascularisation, muscle tone and forces transmitted through muscle attachments, as well as across the hip joint (Morrissy and Weinstein, 2006). The disturbance of physiological balance in these factors induce numerous health issues. Some of them are mild, such as asymmetry in the skin folds of the gluteal, thigh or labial region, while others are of more importance like limb length discrepancy, limited range of motion, waddling gait, and hyperlordosis of the lumbar spine (Morrissy and Weinstein, 2006). The most common disability is represented in a limitation of abduction as a consequence of adductor shortening due to hip subluxation or dislocation (Morrissy and Weinstein, 2006). Hip dysplasia can damage the cartilage lining the joint, leading to the early onset of osteoarthritis. This is the reason why, in cases with an early occurrence of osteoarthritis, attention should be focused on the possible underlying development of hip dysplasia (Manaster et al 2016). Although rare, a complication of untreated hip dislocation could be avascular necrosis of the femoral head, causing morphological alterations of the proximal femur that further leads to limb shortening, rotation and, finally, movement constriction. Even with complete dislocation, the

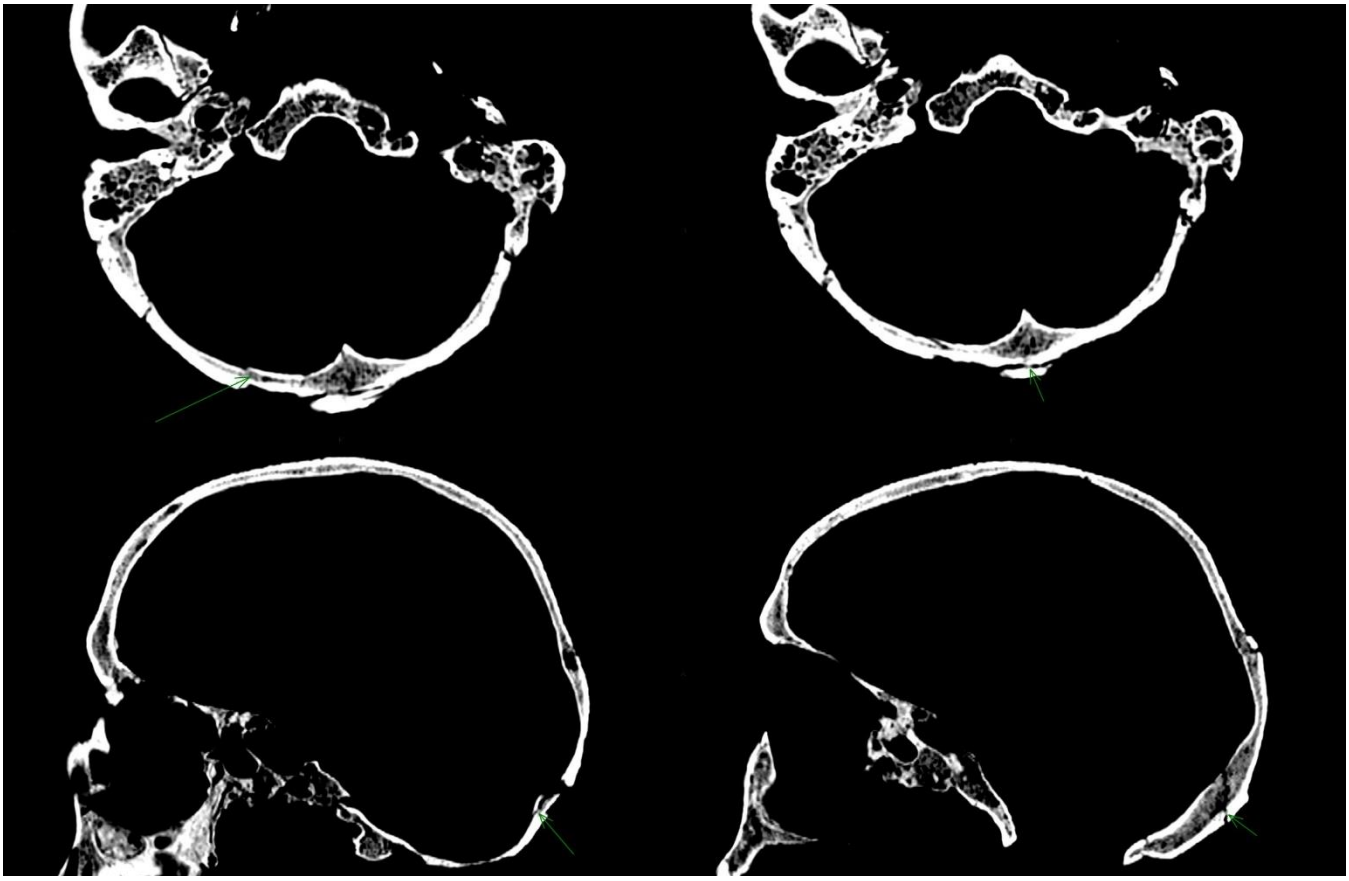

Figure 5: Calus formations (MDCT MPR Reconstructions) (Photo and modification by Petar Milenković).

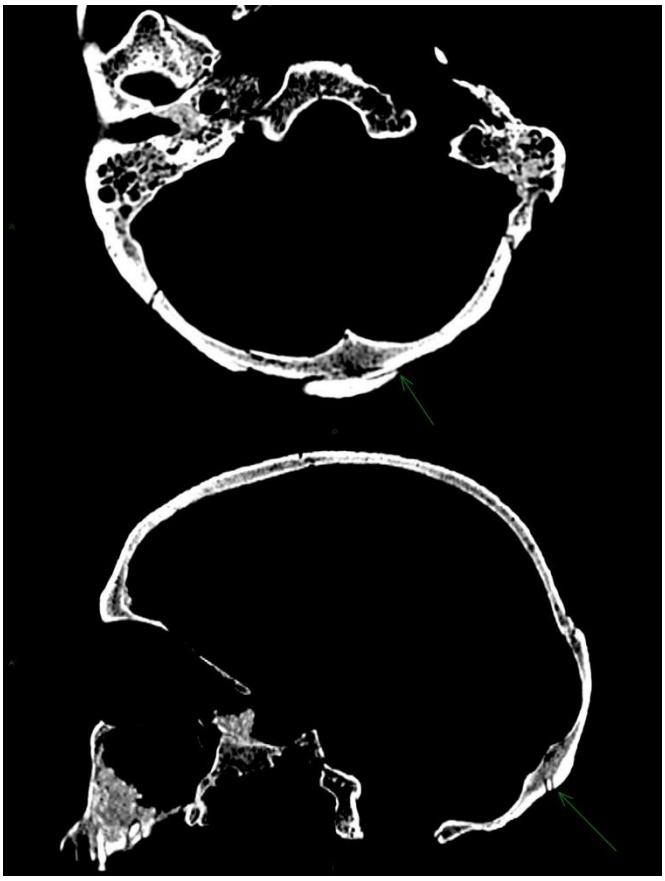

Figure 6: Predominant involvement of external tabula (MDCT MPR Reconstructions) (Photo and modification by Petar Milenković).

affected person may be with little or no functional disability. The level of disability is mainly affected by bilaterality and the state of development of the false acetabulum (Morrissy and Weinstein, 2006).

In hip dislocation there is a lack of physiological stimulus for acetabular development provided by the femoral head (Morrissy and Weinstein, 2006). The true acetabulum would be misshaped and filled with fibrofatty material (Resnick and Kransdorf, 2005). This results in the most severe form of the disease characterised by an absence of a formed acetabulum, with the femoral head articulating with the iliac bone, creating a pseudoacetubulum i.e. a false acetabulum (Manaster et al 2016). The absence of a false acetabulum allows a good range of motion and little functional disability, while a well-developed false actetabulum leads to degenerative joint diseases (Morrissy and Weinstein, 2006).

In the present case, the anatomical features of the true acetabulum indicated an early abruption of physiological development, which resulted in an irregular shape, size and surface. Based on the aforementioned, the presence of a false acetabulum undoubtedly leads to a diagnosis of hip dysplasia. Due to the morphological characteristics, the affected person probably suffered from the so-called swaying gait.

Abnormal gait, incapacitating pain, and the occurrence of severe arthritis certainly would be limiting factors in the performance of any daily activity that includes the action of the lower limbs. Therefore, an active role in activities such as hunting, agriculture or even warfare, which in many ancient societies represented the basis of economic development, must have been restricted or even not possible (Roberts and Manchester, 2007). Moreover, the health situation in which these people found themselves also demanded some form of care that had to be constant and daily. In the presented case, based on the results of bioantrhoplogical analysis, traces of some malnutrition conditions, such as enamel hypoplasia, cribra orbitalia, subperiosteal inflammation, specific infectious diseases or metabolic diseases, were not noticed. Although very generally, this could suggest that this person had a satisfactory diet and living conditions throughout their life, despite the potential limitations that may have arisen as a result of the presented hip disease.

Taking into account that in ancient societies this condition became visible in the period when a child started walking, it seems that the application of any treatment would be too late and with poor results (Roberts and Manchester, 2007). The fact that the developmental hip dysplasia would not resolve spontaneously in the absence of treatment (Mitchell and Redfern, 2007) further outlines the importance of early detection, even today. Even from the standpoint of modern medicine, it is not possible to predict the outcome of developmental hip dysplasia in neonates, therefore, all cases with clinically detectable hip instability should be treated (Morrissy and Weinstein, 2006). According to contemporary medical practice, secondary adaptive changes in the hip joint take place even after six months of life, making simple treatment

options ineffective and leaving techniques of closed and open reduction as the only possible options (Morrissy and Weinstein, 2006). Until the age of three, closed reduction is recommended, while open reduction is applied only in unsuccessful cases. Later in the course of life, i.e. after the age of five, operative treatment is only recommended in unilateral dislocations, while bilateral dislocations are treated with open reduction only if a false acetabulum has already been formed (Hefti et al., 2007). The possibility of normal acetabular development is less likely with an increased age of detection (Morrissy and Weinstein, 2006). It is obvious that modern diagnostic techniques were not possible in that time and that any applied treatment would have been too late, leaving the possibility of visible marks on dry bones. To our knowledge, there is no evidence of any effective treatment of this condition during the Roman Period, although some simple techniques would have been possible. Thus, any traces of pathological conditions in the region of the spine, hips, or feet should be precisely recorded and carefully investigated. If there is the possibility, analyses of factors such as cultural practices, attitude towards health or available obstetric care should not be neglected.

The previously described blow to the head would cause laceration of the occipital brain tissue, due to the direct effect of the blade and bone fragment displacement intracranially. Usually, this is followed by the development of hemorrhagic contusion sites, traumatic subarachnoid hemorrhage, the formation of a subdural or epidural hematoma with a compression effect, and pneumocephalus. The formation of "bridging" bone tissue between fragments suggests that this individual did not subdue to the primary effects of head trauma, but later, due to secondary effects, most possibly an infection of the soft tissue (meningitis, encephalitis) (Osborne 2018). The partial obtuse margins of the skull lesion showed diminished signs of healing, suggesting perimortal trauma delivered by a long, sharp weapon. The observed head lesion should be considered as a possible cause of death.

Conclusion

The results of our analyses clearly suggest that this individual had been living with a health problem for decades, suffering from hip dysplasia during life. The condition was progressive and led to an abnormal development of the hips, with the presence of a false acetabulum. The position in the grave suggested the presence of lower limb contractures, which could develop in untreated cases of developmental hip dysplasia. The observed features could have evolved throughout life, incapacitating normal function, making even simple everyday activities challenging and painful. This led us to the conclusion that any previously applied treatment in this case would have been unsuccessful. Unfortunately, the poor preservation of the proximal end of both femurs as well as vertebrae limited more detailed analyses of this condition. The possible cause of death could be the observed head lesion. However, signs of healing signal that this person did not succumb to the injury on the spot, but most likely sometime after, probably due to an infection of the brain tissue.

In addition, there is no confirmation of unfavourable living conditions related to diet. It is important, however, to note that, in this particular grave, archaeologists found no grave goods, so the social status of this individual cannot be discussed.

A detailed examination and reconstruction of health problems that were incurable and that prevented an individual performing day-to-day activities would allow us to better understand the overall attitude of the community towards disabled persons and health in general.

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A case of bipartite patella and vastus notch from Kneževići hillfort - Malo Libinje, Croatia

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Abstract

Here we present six adult patellae with superolateral concave defects observed amongst the remains of at least 28 individuals retrieved from four Late Iron Age burials from Kneževići hillfort - Malo Libinje, Croatia. The right patella of an adult individual displays a rough-edged concave defect on superolateral side of the bone called bipartite patella. Other five patellae show concave defects with smooth edges also located on superolateral side; a defect known as vastus notch. Though physically similar, the two conditions are etiologically distinct. A large amount of observed cases of vastus notch in this assemblage may indicate that these individuals frequently performed activities involving kneeling and/or squatting. This is the first documented case of joint occurrence of bipartite patella and vastus notch in a Croatian skeletal assemblage, but also the largest amount of patellae with vastus notch in an archaeological population from Croatia recorded so far.

Introduction

Bipartite patella is a congenital condition caused by incomplete ossification of the bone. The condition usually remains asymptomatic and is most commonly diagnosed as an accidental finding (Okuno et al., 2004). First reported case of bipartite patella, discovered during an autopsy, was noted by Gruber (1883). Since then, more cases have been described in clinical as well as bioarchaeological literature (Wright, 1903; Adams & Leonard, 1925; Paal, 1932; Blumensaat, 1933; George, 1935; Stuke, 1950; Shulman, 1955; Resnick & Niwayama, 1981; Tachdjian, 1990; Silverman & Kuhn, 1993; Duthie & Bentley, 1996). In 1921, Saupe provided the first classification of bipartite patella, dividing it in three types according to the location of the secondary ossification center (Saupe, 1921). Type I involves the inferior pole of the bone with relative prevalence of 5%; type II (20%) involves the lateral side and has longitudinal expression; type III (75%) involves superolateral portion (Mesina & Sineo, 2007). Most recently, a new classification of bipartite patella was proposed by Oohashi and colleagues (2010), based on both location and number of fragments. They excluded inferior pole from the classification and included two more subtypes based on more than two fragments (the so-called 'tripartite patella'). In general, the condition is nine times more common in males than in females (Rich et al., 2005); however, different studies recorded different male/female ratios ranging from 2.1:1 to 4.3:1 (Weaver, 1977; Ogata, 1994; Kavanaugh et al., 2005; Oohashi et al., 2010; O'Brien et al., 2011). Bipartite patella occurs bilaterally in about 43% of cases (Green, 1975).

Bipartite patella is profoundly similar and thus frequently confused with a defect called vastus notch. Continued contraction associated with the flexion of

the knee induces impression on the superolateral side of the patella, referred to as a vastus notch (Messeri, 1961). Two conditions are macroscopically similar yet occur by a different cause. A presence of a depression in the upper portion on the outer margin of the ancient Egyptian's patella was first mentioned by Kempson (1902) who stated that this was a common variation of the patella. Oetteking (1922) also examined a patella (no. 697 from Chihuahua, Mexico) with a deep superolateral notch, which he compared to Kempson's finding. Messeri (1961) recorded high frequency of this marker in Neolithic populations from northern Italy, and suggested that this was due to continuous tension of the vastus lateralis muscle associated with squatting and/or kneeling. Since then, the condition is known as the vastus notch. Afterwards, vastus notch was mentioned and described by several authors (e.g. Mann & Murphy, 1999; Anderson, 2002; Inskip, 2013; Molleson, 2016; Bedić, 2017). There is a lack of evidence of the most probable cause of bipartite patella and vastus notch, especially if the conditions have a genetic component, but future studies may elucidate this matter further.

Bipartite patella and vastus notch are not common findings in archaeological populations (Baudounin, 1935; Wells, 1981; Zammit, 1983). A few cases with a

Figure 1. Map of Croatia with Kneževići hillfort - Malo Libinje site.

small prevalence of the conditions have been reported (e.g. Anderson, 1963; Finnegan, 1978; Mullen & Hoppa, 1992; Anderson, 2002; Kjellstrom, 2004; Messina & Sineo, 2007; L'Abbé et al., 2008; Stephan & Gill, 2016; Rios et al., 2018), without further examination through radiographs. Bilateral knee radiographs were acquired only on modern population to investigate the prevalence of two conditions, symptoms and treatments, if possible (Kose et al., 2015; Sim et al., 2016).

Among the skeletal remains, six adult patellae with superolateral concave defect were unearthed during the excavations of Kneževići hillfort - Malo Libinje site in 2020; a highly uncommon occurrence in terms of prevalence in such a small sample. The aim of this study is a detailed presentation of cases recorded in Malo Libinje and comparison with similar ones from both archaeological and clinical contexts. In addition, the differential diagnosis will try to identify if these conditions indeed represent bipartite patella and vastus notch or some other pathological lesions, and what the potential causes of these conditions are.

Materials and methods

An Iron Age settlement surrounded by a rampart and a necropolis chronologically ascribed to the 6th century BCE (Glavičić, 1984) on the south slope, Kneževići hillfort is located next to Malo Libinje field in South Velebit Mountain in Zadar County, Croatia (Figure 1). At the beginning of the 20th century, a single grave was excavated at the bottom of the hillfort. Further excavations were not conducted until the 1980s, when another grave was unearthed near the first. Archaeologists also discovered a few tumuli nearby the hillfort, as well as on the field nearby on the East, Gornje polje (Glavičić, 1982, 1982a, 1984). Systematic research began in 2018 and was conducted by the Archaeological Museum in Zadar. The osteological finds were found in four burials; in the revision excavations of two burials (G1 and G2) and in newfound graves (G3 and T1G1). Three graves were unearthed in the necropolis

Figure 2. The grave in the tumulus; a burial in a rectangular stone chest.

underneath the hillfort and one in the newfound tumulus on the East side near the hillfort. Grave 1 (G1) was a burial in a rectangular stone chest, while Graves 2 and 3 (G2 and G3) were constructed out of amorphous stone. The grave in the tumulus (T1G1) was also a burial in a rectangular stone chest (Figure 2). All burials except G2 contained the remains of several individuals. The remains in the graves were randomly assembled, overlying one another. The archaeological context suggests that burials in G1, G3 and tumulus grave could represent family tombs.

The skeletal remains presented in this paper were analyzed at the Laboratory for Evolutionary Anthropology and Bioarchaeology of the Institute for Anthropological Research in Zagreb. Since the human remains from Malo Libinje were commingled and highly fragmented, it was not possible to analyze individual skeletons. Therefore, a minimum number of individuals (MNI) was established by using the methodology described in the volume edited by Osterholtz and colleagues (2014).

In this study, sex estimation was conducted using the discriminant analysis of patella measurements due to heavy fragmentation of skeletal remains, with approximately 60-80% accuracy (Indra et al., 2021). Following the protocol of Dayal and Bidmos (2005), six variables from the patella were recorded using a standard sliding caliper. The patellae measurements from the Malo Libinje individuals were also compared with other, morphologically most similar populations: contemporary Spanish population (Peckmann et al., 2016), Southern Italians (Introna Jr. et al., 1998), and Medieval Germans (Kemkes - Grottenthaler, 2005).

Age-at-death was possible to establish only for subadults based on the development and formation of deciduous and permanent teeth and the degree of bone ossification (Fazekas & Kósa, 1978; Scheuer & Black, 2000). Subadult individuals were categorized into three groups: newborns, infants, and small children (0-5 years); older children (6-11 years) and adolescents (12-18 years). Due to heavy fragmentation and weathering the precise age-at-death for the adults could not be established. Therefore, all adults were pooled into one group. All bones were comprehensively examined for pathological conditions, according to Ortner's (2003) and Aufderheide & Rodriguez-Martin's (1998) identification of pathologies.

Results

The MNI in the Kneževići - Malo Libinje assemblage is 28 (19 adults and nine subadults). G1 contained the remains of at least eight adults and four subadults. G2 contained the remains of a very fragmented and poorly preserved skeleton of an adult individual. In G3, the remains of at least five adults and one subadult were interred. And finally, the MNI in the grave from the tumulus was concluded to be nine. The discriminant

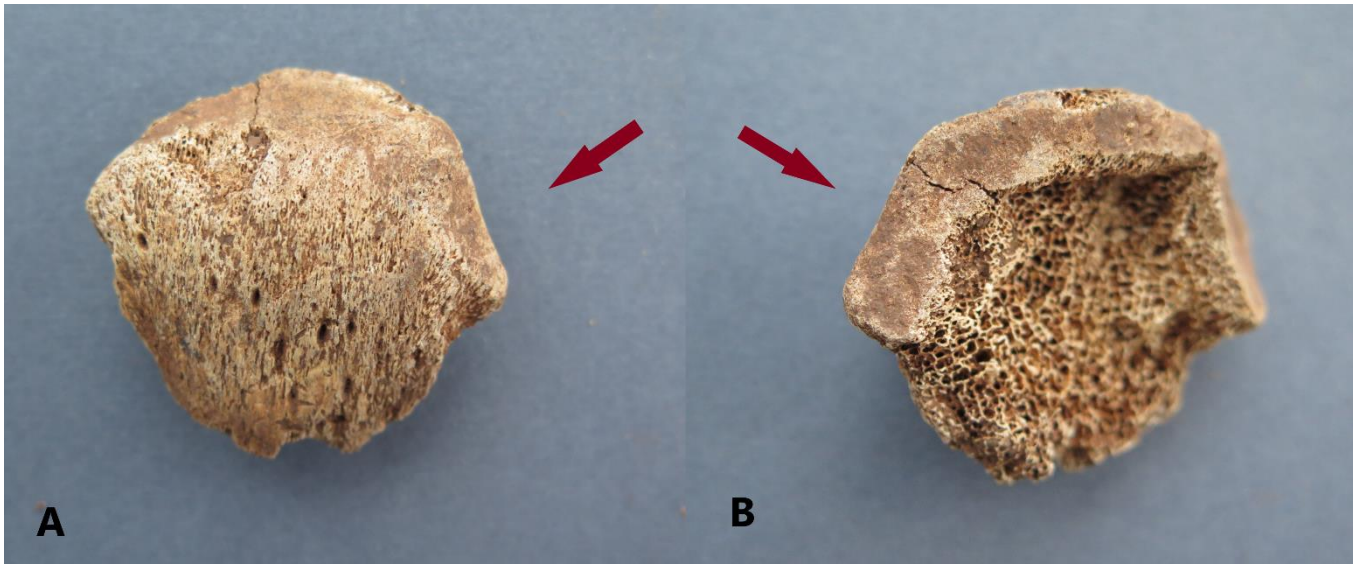

Figure 3. Patella A with vastus notch, anterior (A) and posterior view (B).

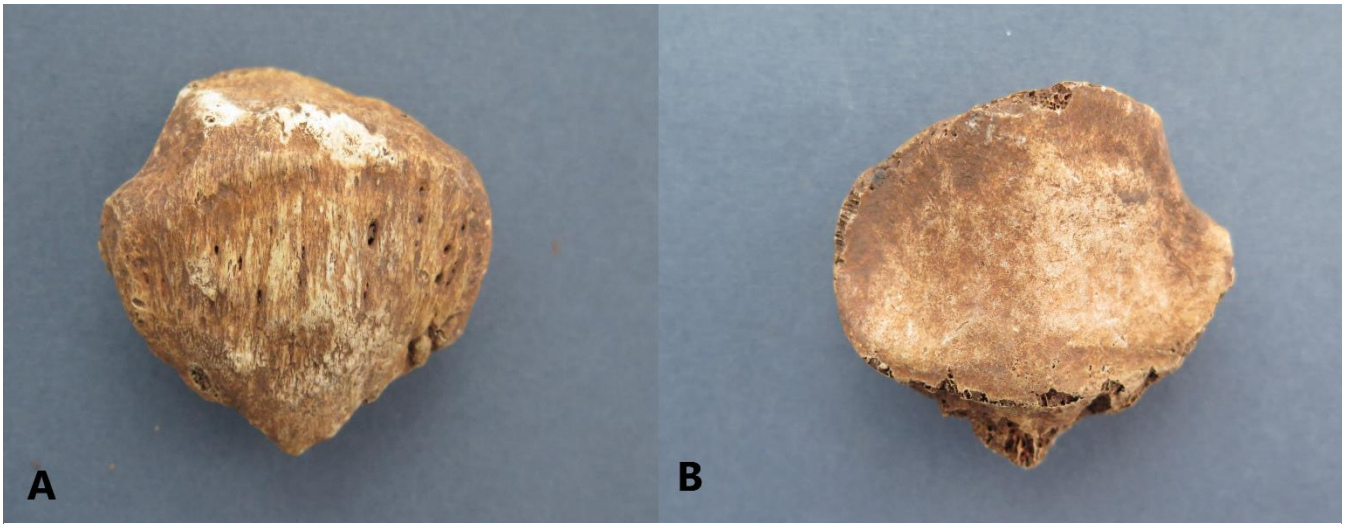

Figure 4. Patella B with vastus notch, anterior (A) and posterior view (B).

analysis of patella measurements from Malo Libinje indicates that three most probably belonged to females (patellae A, C, and D) and three to males (patellae B, E, and F).

As far as pathological conditions are concerned, the following were observed: porotic hyperostosis, cribra orbitalia, osteomas, blunt and sharp force traumas, abscesses, caries, Schmorl's nodes, degenerative osteoarthritis, vastus notch, and bipartite patella. However, these conditions, apart from vastus notch and bipartite patella, will be described and comprehensively discussed in a separate study.

Six out of nine patellae available for the analysis displayed an incomplete ossification on the superolateral side of the bone. In G1, there were two patellae belonging to two adult individuals; one smaller, left patella (Patella A), very fragmented on the posterior side of the bone, and one larger, right patella (Patella B), which was well preserved. Patella A shows mild tendon ossification on the anterior surface - a feature

Figure 5. The pair of patellae; patella C with vastus notch and bipartite patella D.

Figure 6. Bipartite patella D, anterior (A) and posterior view (B).

typically recorded as an activity marker - while its superolateral side shows indications of a concave defect with smooth edges (Figure 3). Patella B shows more severe tendon ossification than Patella A (Figure 4). The concave defect on superolateral side is also more accentuated, especially on the posterior end, but the edges retain their smoothness.

In G3, there were four patellae with concave defects, two left and two right, belonging to three adults. Two patellae from the group (Patellae C and D) seem to be a pair since they are identical and slightly smaller in size than the other two (Patellae E and F). The left patella from the pair (Patella C) shows moderate concave defect on the superolateral side with smooth edges (Figure 5). The right patella (Patella D) shows substantial concave defect on the superolateral side - the borders of the defect are porous and thick, different from the other patellae from Malo Libinje (Figure 6). Both patellae are well preserved and show mild tendon

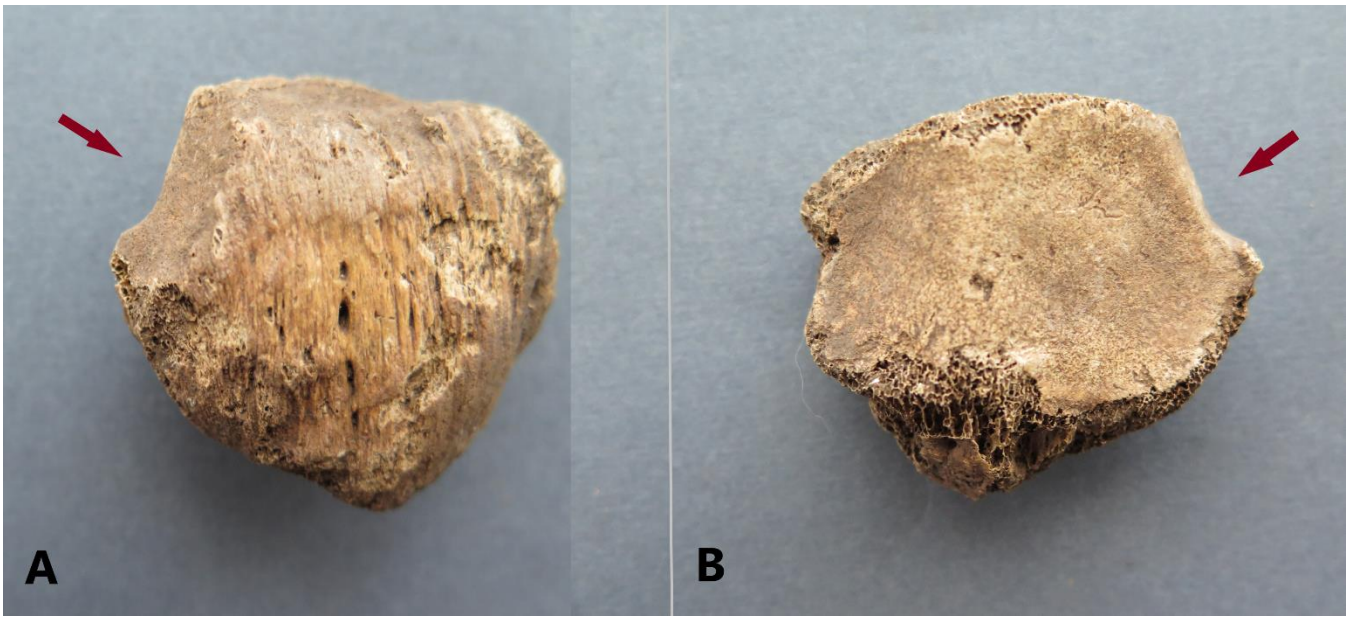

Figure 7. Patella E with vastus notch, anterior (A) and posterior view (B).

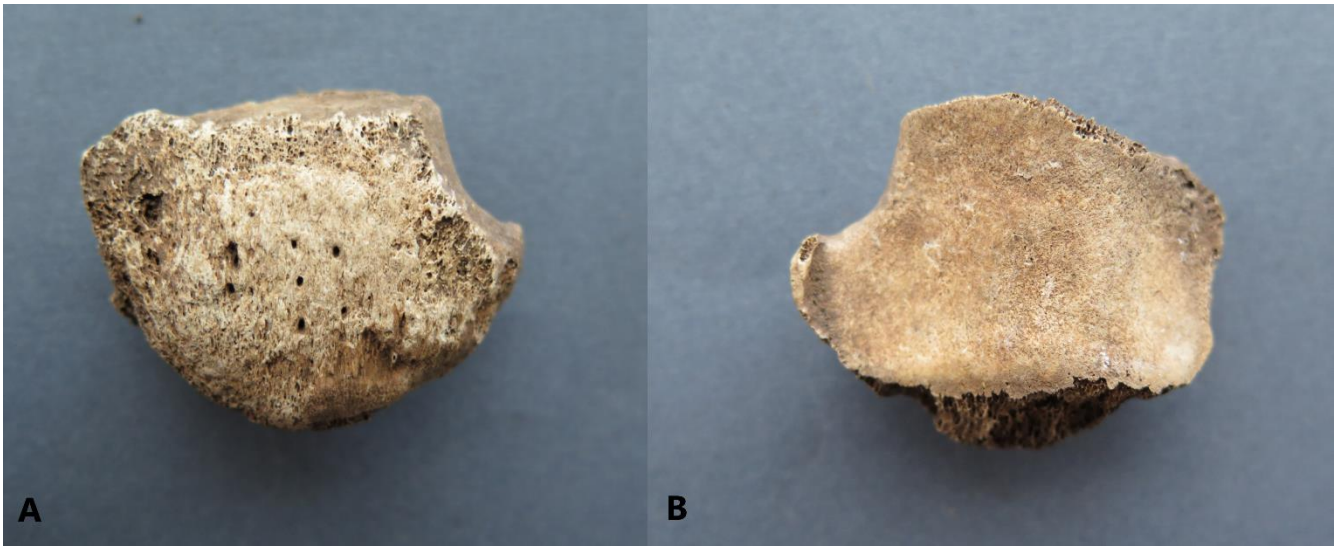

Figure 8. Patella F with vastus notch, anterior (A) and posterior view (B).

ossification on the anterior surface. The other, larger, right patella (Patella E), is well preserved with slight porosity on the superior and inferior sides and moderate tendon ossification on the anterior surface - the concave defect is located on the superolateral side; the edges are smooth with porous, accentuated tip on the posterior end (Figure 7). The cortex of the last, left patella (Patella F) is badly preserved and there is visible tendon ossification on the anterior surface (Figure 8). On the superolateral side, the concave defect is accentuated, with pronounced osteophytosis on the posterior end.

Discussion and Conclusion

Discussion

In this study, two physically similar but etiologically distinct conditions were recognized. Six patellae from Malo Libinje display superolateral concave defects, a relatively rare finding in archaeological populations (Messina & Sineo, 2007). These defects were diagnosed as bipartite patella and vastus notch.

Patella D has a porous, roughed-edged lesion known as bipartite patella. It is a condition where patella is composed of two separate bones. Based on the location of the secondary ossification center, it is possible to diagnose Patella D as bipartite patella type III (Saupe, 1921). Secondary ossification centers of the patella appear around twelve years of age (Ogden, 1984), and if they later fail to merge, a bipartite patella develops. Separate ossicle may stay detached or can fuse incompletely (Green, 1975). In Patella D's case from Malo Libinje, the ossicle is detached and is not present, as it often occurs in skeletal assemblages. Some authors suggest mechanical stress (Oetteking, 1922) or repeated microtrauma (Todd & McCally, 1921; Green, 1975) as possible causes. Usually, bipartite patella is considered asymptomatic (Atesok et al., 2008). In some cases, it is a source of persistent pain and can even cause complete disability in the knee (Messina & Sineo, 2007). In treatment of painful patella, the most common surgical approach is excision of distressing fragment (Weckström et al., 2008).

The oldest known example of bipartite patella dates back to 49,000 years ago to the Neandertals from El Sidrón cave (Spain) where a small, probably left tripartite patella with separate ossification center located inferiorly was recovered (Rios et al., 2019). Since bipartite patella with separate ossification center located superolaterally is the most common morphological variant, such a condition is even rarer. Another example of bipartite patella from archaeological context was recorded at the Palaeochristian necropolis of San Giovanni in Marsala, Sicily (Messina & Sineo, 2007). This left patella shows lack of ossification on the lateral side, which can be diagnosed as bipartite patella type II (Saupe, 1921). Furthermore, a bipartite patella was discovered in a skeleton of a 13-15 years old juvenile from the

cemetery associated with Franciscan friary at St. Faith's Lane in Norwich, England dated between the 13th and 16th century CE (Anderson, 2002). In this case the fracture line is clearly visible on the right patella and the resultant ossicle is fused incompletely (Anderson, 2002). The bipartition of the patellae of two skeletons from Pilanesberg National Park, South Africa dated to the Late Iron Age (ca 1300 to 1820/1830 CE) show that this condition can also occur bilaterally (L'Abbé et al., 2008). And finally, Anderson (1963) recorded very high prevalence (8%) of bipartite patella in a Canadian Iroquois ossuary dating back to 1400 CE.

In modern populations, bipartite patella is usually discovered through knee radiographs. One of the studies involved analysis of the radiographs in Turkish patients in order to determine the prevalence of bipartite patella and analyze the differences between sex and laterality (Kose et al., 2015) concluded that there is a prevalence of around 1% of the condition being more frequently found in males, and mostly on the superolateral side. A similar study was conducted using magnetic resonance imaging (MRI) to determine the prevalence of bipartite patella and perform analysis of this rare condition (Akdag et al., 2019). This study confirmed that the condition occurs mainly in males and more frequently on the superolateral side, and that the overall prevalence is found to be 0.8% (Akdag et al., 2019). However, true prevalence of bipartite patella is still uncertain. Different authors reported different data: Green (1975) states that the prevalence of the condition is 0.2-6.0% while others say it may affect 1-3% of a population (Todd & McCally, 1921; Adams & Leonard, 1925; Tachdjian, 1990; Aufderheide & Rodriguez-Martin, 1998). There is a wide variation in prevalence in different ethnic groups, and sometimes high percentage can be the result of close kinship (Kose et al., 2015). Since the condition is mostly asymptomatic and a rare find in archaeological excavations, it is no surprise that a true prevalence can be difficult to determine.

Five other patellae from Malo Libinje show a condition called the vastus notch. This anatomical variant occurs due to continuous contraction of the vastus lateralis muscle of the femoral quadriceps (Capasso et al., 1999). It is associated with chronic knee flexion, i.e. squatting. Vastus notch appears as a slight or a deep concavity, frequently with the processus spinosus located at the inferior margin of the notch which marks the lower limit of the tendon (Oetteking, 1922). It is commonly mistaken for bipartite patella because it also occurs on superolateral side of the bone. The two conditions can be distinguished due to fact that vastus notch is smooth-edged (Mann & Murphy, 1990) as opposed to the porous surface with visible trabecular bone on bipartite patella. A separate ossicle can only occur if the patella is bipartite, detached or incompletely fused, and never associated with vastus notch. The pair of patellae (C and D) from G3 are especially interesting since the left one exhibits a vastus notch while the right one is bipartite.

According to the available bioarchaeological literature, vastus notch occurs a bit more frequent than bipartite patella. In Croatia it was recorded at several sites: the earliest example was observed on the right patella of an adult male from the Late Bronze Age cremation cemetery of Poljana Križevačka 2, dated to the 13th century BCE (Premužić, 2016); the second case was recorded again on the right patella of an adult male, this time in Glagoljaška Street in Zadar, dated to the Late Roman Period (Bedić, 2017). Another case was registered at the Sokol fortress in Konavle, dated to the Late Antiquity (6th century CE) (Topić et al., 2019). And finally, two cases were observed on the left patella of an adult male and the right patella of an adult female from Pakoštane - Maksanova gomila site, dated between the Late Middle Ages and the Early Modern Period (15th-16th century CE) (Šućur et al., 2020).

Opposite to bipartite patella, vastus notch occurs mostly due to repetitive activity. It is associated with chronic and consistent kneeling and squatting (Capasso et al., 1999). There are but few studies focusing on this lesion occurring in archaeological populations. For example, in a study of human skeletal remains from the early Neolithic settlement (10500-8400 BP) of Nemrik in Tigris Valley Molleson (2006) recorded the occurrence of small vastus notch in patellae of three individuals suggesting that the squatting on the heels could be a resting position, although the condition could also be induced by sartorial position. Furthermore, a small patella of a young female from the Neolithic settlement

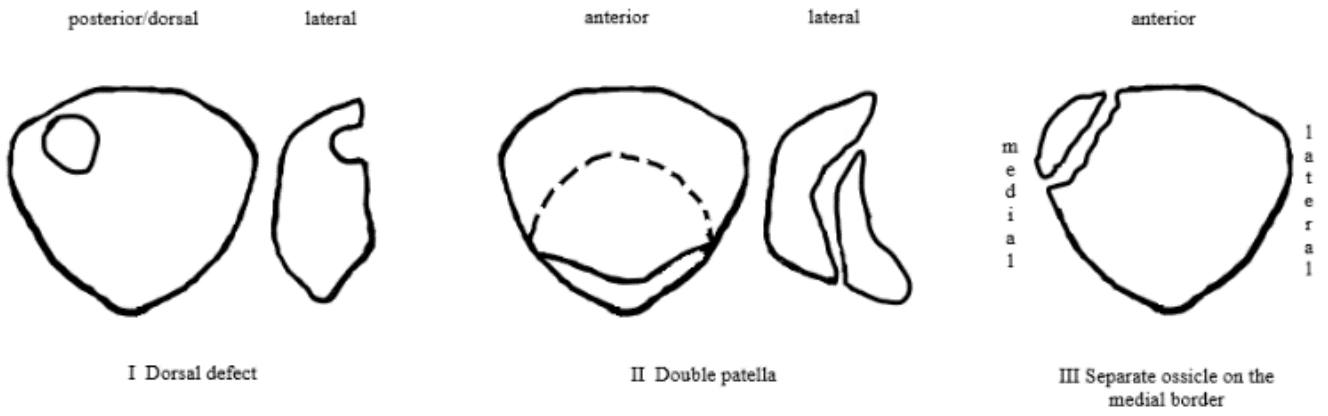

Figure 9. Defects mistaken for bipartite patella and/or vastus notch; schematics.

of Abu Hureyra in Syria displays vastus notch on the superolateral border suggesting that she as well as the other women from the group may have squatted in the 'hocker' position to carry out the certain tasks (Molleson, 2016). And finally, the study of various Islamic period skeletal assemblages from Medieval Iberia Habitual indicates that the adoption of praying resulted in patella alterations and development of vastus notch (Inskip, 2013).

Prehistoric people cultivated a whole range of domestic cereals which required mechanical preparation before they could be eaten. The preparation of grain such as grinding and dehusking was the most demanding and labor-intensive activity, and it usually took much time. Since the seed could not be kept once dehusked, the grain had to be pounded every day (Molleson, 2006). Repetitive activity of kneeling while grinding could have led towards chronic knee injuries. Frequent habitual activities of kneeling and/or squatting due to cereal preparation were surely practiced by prehistoric inhabitants of Kneževići - Malo Libinje and these could have resulted in high prevalence of vastus notch observed in this skeletal assemblage.

Today, few distinct defects associated with patella are acknowledged, some of which might be mistaken for bipartite patella and/or vastus notch (Figure 9). In example, dorsal defect of the patella presents a cavitation or a depression on the posterior (dorsal) surface of the bone (Owsley & Mann, 1990) which distinguishes the condition from vastus notch and bipartite patella, since the latter two only occur on the superolateral side. It is a concave, round-shaped defect and appears to be self-limiting (Resnick & Niwayama, 1981). Dorsal defect can occur in a conjunction with bipartite patella, or as a separate anomaly (Todd & McCally, 1921). Another rather rare condition is called a double patella. The term is used for the condition in which the bone is divided into a superior portion and an inferior portion, which usually overlap (Anderson, 2002). The superior portion is usually larger and can occasionally completely overlap the smaller element, resulting in anterior and the posterior patella (Brailsford, 1945). Most commonly, double patella occurs as a part of genetic condition termed multiple epiphyseal dysplasia (Silverman et al., 1993; Sutton, 1998). Lastly, a separate ossicle can be located on the medial border of the patella (Halpren & Oakley, 1978), appearing to represent an unfused additional ossification center. This, however, is not consistent with Saupe's (1921) classification of bipartite patella and therefore should be observed as a distinct condition. As far as traumas are concerned, injury almost invariably occurs unilaterally, whilst an anatomical condition would more frequently be bilateral (Anderson, 2002). When both patellae are available for examination, it is easier to distinguish a trauma from bipartite patella or vastus notch; when not, defect should be examined for a new bone overgrowth or callus formation that is expected with a healing fracture (Anderson, 2002).

Based on the provided differential diagnosis, the most probable explanation for the studied conditions observed in the patellae from Malo Libinje is bipartite patella and vastus notch.

Conclusion

This study presents the first documented case of joint occurrence of bipartite patella and vastus notch in a Croatian skeletal assemblage, but also the largest amount of patellae with vastus notch in an archaeological population from Croatia recorded so far. Conditions associated with patella are sparse in general, so the fact that two similar and at the same time etiologically distinct patellar lesions were recorded at the same archaeological site is rather intriguing. Even rarer find is vastus notch defect observed on the left patella belonging to an adult whose right patella exhibits bipartition at the same time. High prevalence of vastus notch in Kneževići - Malo Libinje assemblage may indicate that these individuals regularly performed activities involving kneeling and/or squatting, possibly associated with some type of manual labor (e.g. cereal grinding and dehusking). In any case, the presented research contributes to the study of these conditions in ancient populations, but also provides a broader insight into the lives of the prehistoric inhabitants of the Velebit Mountain region.

Acknowledgements

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Pregnancy and birth cohorts in Europe: An overview

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Abstract

A birth cohort study is a form of study that uses expectant mothers and their subsequent newborns as research participants. Data is collected in order to identify health consequences and overall health outcomes of environment and lifestyle on pregnancy and childbirth. The main aim of this paper is to review and summarize all cohort studies that have been carried out or are still being conducted in Europe in last 80 years, as well as general information such as aim of the study, number of participants and duration of follow-up. Gathering information was made easier by websites such as Birthcohorts, CHICOS and LifeCycle, where many of the cohorts and their sources are listed. The remaining data was found by searching Google Scholar, PubMed and similar webpages, using keywords 'birth and pregnancy cohorts', 'infants', 'pregnancies', 'allergies' and 'childhood obesity'. Overall, 137 cohorts in 27 countries were found. Cohort studies are an efficient method for assessing cause and effect. The focus is on the general health and well-being of mothers and children and as such provides a good approach to establishing a link between risk factors and outcomes. In epidemiological research, especially those concerning some of the biggest problems of the 21st century, such as obesity, type II diabetes and coronary heart disease, cohort studies make a valuable contribution. In last 80 years the number of studies has been increasing and with it the number of new insights. Collaboration between different birth cohorts is crucial for further harmonization of collected data and their use in the public health systems worldwide.

Introduction

Recently, it has become increasingly apparent that new and modern lifestyles have considerably greater adverse and long-term health effects that it has been perceived previously. Health issues such as metabolic diseases, mental health, and respiratory system diseases and alike, which in most cases are preventable, are becoming more common due to the sedentary lifestyle, unhealthy dietary patterns, polluted environment and everyday stress. Although many studies investigate the causes and consequences of these problems, in recent decades the prevailing research models have become cohorts. Such studies have a sample that represents a specific segment of the population (share the same characteristics such as age, gender, place of residence etc.) as a study subject and they can be prospective and retrospective. Prospective studies look for outcomes of certain exposures, whereas retrospective studies look backwards comparing two groups of people, one under a certain exposure and the other unexposed. Birth cohort studies are especially suitable study methods for understanding the influence of the environment in which a child develops during pregnancy, on its development later in life and its overall health. The main advantage is that there are no limits to follow-ups and health outcomes can be monitored until adulthood or even further in life (Brandstetter et al., 2019). In addition, because of the large difference between children in different regions, even within the same country, a general approach is an excellent tool for

comprehensive research. Possible adverse outcomes of pregnancy are very important to identify early on in order to prevent them in the future or in other risk groups. In that way, many public health issues can be monitored and prevented. Most of European populations have a problem with low birth rates and an ageing population and it is becoming an increasing burden for the social and health systems. Childhood is the best period for action because it is the most effective time to promote good health and healthy life choices, which can then also be passed on to next generations (Golding, 2006; Larsen et al., 2013).

The number of cohort studies in Europe has been growing in the last 80 years. Generally, they start in the prenatal period and end after birth with one or several follow-ups of children. Although extremely useful, this research model is time and money consuming. Therefore, collaboration and data sharing between study groups is expected. The aim of this paper is to list all cohort studies of pregnancy and birth that have taken place in Europe, as well as to offer a general overview. Data shared between cohorts can reduce time and resources needed for the studies. The strength in drawing conclusions and causal effects on a larger number of participants is also one of the advantages of collaboration and data sharing. Not only that, the challenges and obstacles in individual research can provide useful information for improving future research models. (Larsen et al., 2013).

Materials and methods

Pregnancy and birth cohorts' data was collected from multiple sources. Online databases such as PubMed and Google Scholar were inspected, as well as Google with keywords 'birth cohort', 'pregnancy cohort', 'newborns', 'pregnancies', 'childhood asthma', 'childhood obesity', 'illness in early childhood', 'epidemiological study of newborns'. Pages https://www.birthcohorts.net/, http://chicosproject.eu/ and https://lifecycle-project.eu/ were reviewed. Birthcohorts.net is a database that collects information about birth cohorts worldwide. It was established to enable easier access to data and study designs and to promote collaboration between distinct study groups. Cohorts in this database have at least one year of follow-up, have been established before/during pregnancy or at birth and have at least 300 mother-child pairs (Birthcohorts, 2021). 'CHICOS: Developing a Child Cohort Research Strategy for Europe' is a project funded by the European Union's 7th Framework Programme for Research and Technological Development. The aim of CHICOS is to improve child health by evaluating existing data about mother-child cohorts, determining gaps in research and focusing on future studies (CHICOS project, 2021). The 'EU Child Cohort Network: A Europe-wide network of cohort studies started in early life' has been developed to bring together cohort studies in Europe. Its overall aim is to determine the effect of early-life environment and possible stressors on developing health problems later in life (LifeCycle, 2021). Each of the mentioned databases and articles is created according to certain own criteria. This review brings together data from databases and articles, with the intent of harmonizing and making data more accessible.

Inclusion criteria for cohorts were that the study population was based in Europe and that the subjects of studies were pregnant women and subsequently their children, or that newborns were included in the study. There was no time or size limit on found cohorts. Therefore, only studies that have an extended period of observation and continuity were taken into consideration due to the fact that it was sometimes hard to separate what is a continuous study and what is a one-time study of one cohort. Europe as inclusion criteria imply countries that are part of the continent using defined natural borders.

The majority of data and information on subjects was found on the Birthcohorts website, where the researchers submit information themselves. For other studies, official websites of research groups and their published articles were reviewed. Data collected from websites and articles comprise the name of the cohort, its country of origin, main aim, number of subjects in the cohort, other family members included in the study and duration of the follow-up period with parents and child.

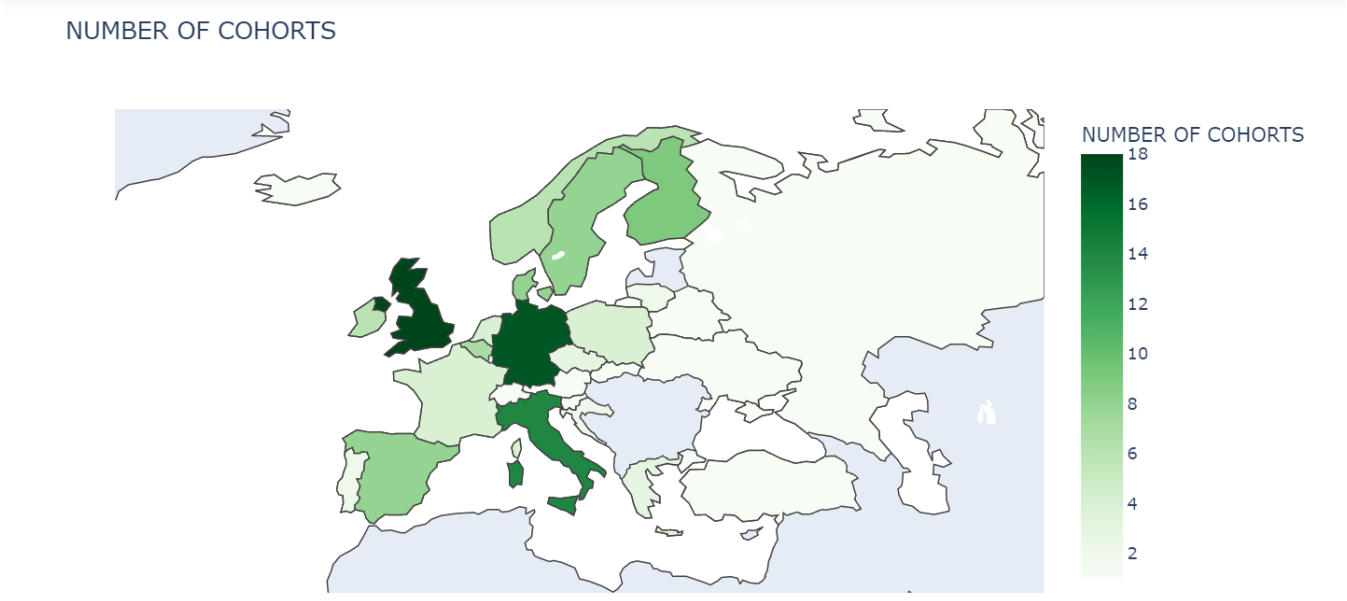

Figure 1.: Number of cohorts per country

Results and discussion

As expected, the most developed European countries have the largest and most extensive studies. Of all the cohorts, more than half (n = 113) are in the countries of Northwest and Central Europe. Italy, Germany and the United Kingdom have the greatest number of cohorts and the most diverse studies (Figure 1.). 127 studies consisting of 137 cohorts spread out in 27 countries were found (Table 1, at the end of the paper). 29 cohorts are a part of bigger consortium, where cohort studies are being conducted simultaneously in several partner countries (AMICS, ELSPAC, EuroPrevall study, CHOPIN, PHIME, SPACE studies). CHOPIN has cohorts in Belgium, Germany, Italy, Poland and Spain and is concentrated on early life nutrition and its possible influence on obesity later in life (Koletzko et al., 2009). PHIME focuses on early life nutrition but aims to investigate the level of heavy metals in blood and breast milk accumulated through the nutrition. Cohorts are in Croatia, Greece, Italy and Slovenia (Miklavčič et al., 2013). Both SPACE and AMICS are focused on the development of asthma and atopy in childhood. AMICS has two cohorts in Spain, and one in Germany and the United Kingdom (Fríguls et al., 2009; Iliadou et al., 2019). The EuroPrevall study is also investigating allergy but from a nutritional aspect. In addition, data related to the cost of food allergies and quality of life was also obtained. The study was conducted in the following countries: Germany, Greece, Iceland, Italy, Lithuania, the Netherlands, Poland, Spain and the United Kingdom. To improve epidemiological knowledge of factors influencing children's health in European countries, WHO started ELSPAC. ELSPAC consists of four studies: ALSPAC in the UK, FCOU in Ukraine, one on the Island of Man and one in the Czech Republic. Other cohorts collected data in Slovakia and the Russian Federation but encountered political and financial problems, while Greece and Estonia stopped collecting data because of the lack of funds (WHO, 1997, 1998, 1999).

The most common method of collecting data is via questionnaires. Interviews and educational assessments are used later in the child's life. Information includes the socio-demographic status of parents, their lifestyle and environmental exposures, as well as mother's pregnancy characteristics, depending on the main aim of the study. Most common participants are mother-child pairs. Half of them included fathers as well, but only a few included siblings, grandparents or other family members. Their inclusion is often associated with the main goal of a study, for example in allergies and atopic diseases

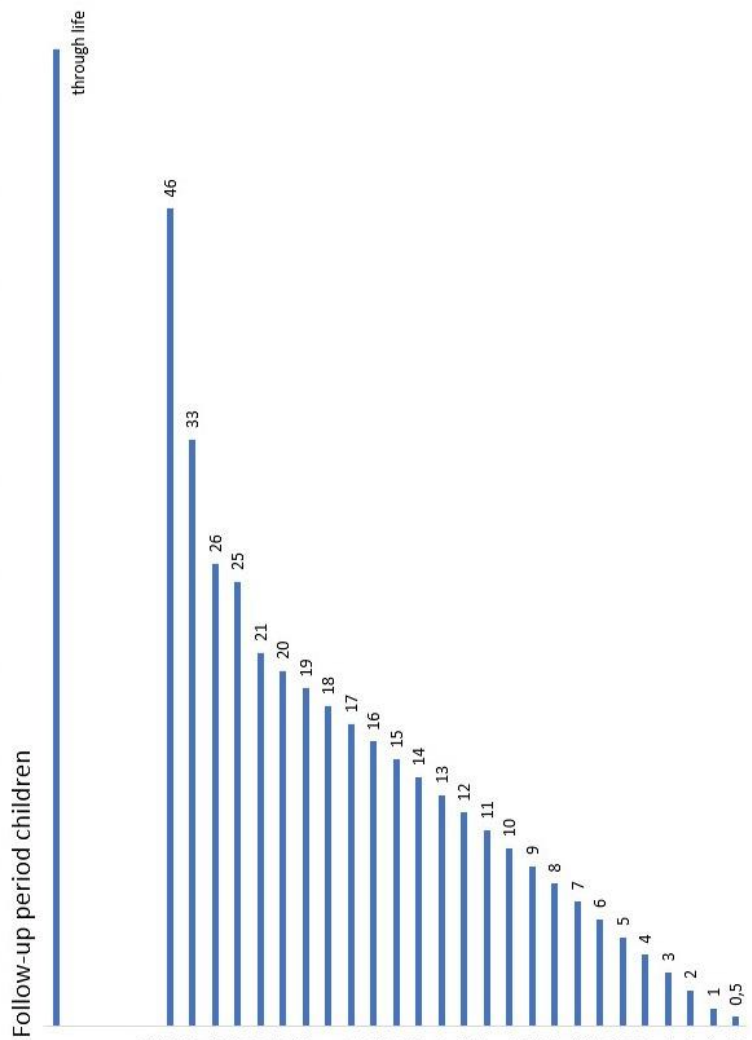

Figure 2.: Follow-up period children

research, family medical history and current living conditions are useful information for the evaluation of infants' health.

Most of the cohorts have specific enrolment criteria, such as mothers over 18 years of age that are native language speakers (for the comprehension of study procedures), healthy mothers without a history of chronic diseases, singleton pregnancy etc. If a study has a specific aim, the inclusion and exclusion criteria are formed accordingly. Examples include MUBICOS in Italy, a cohort study that researches only twins so their inclusion criteria are only twin pregnancies (Brescianini et al., 2013, 2016). When investigating allergies, cohorts

Figure 3.: Follow up period parents

like SPACE have their own inclusion criteria such as the parent's medical history of respiratory diseases or parental IgE results or for children, a manifestation of atopic diseases (Tsitoura et al., 2002). The most common criteria are still healthy mothers living in a specific area in which the study is taking place. For most of the studies, the enrolment period begins at pregnancy and follow-up continues at least a couple of years after birth (Figure 2.). Enrolment usually starts with the pregnancy or after the birth of a child (Figure 3.). Only a few studies differ, including the Southampton Women's Survey. In the survey, the parental data is collected before the pregnancy so that their associations to perinatal and infant outcomes can be evaluated (Inskip et al., 2006). In addition, the UppSTART study from Sweden recruits couples undergoing assisted reproductive techniques to determine if parental lifestyle has an influence on conception, pregnancy or assisted reproduction procedure-specific outcomes. UppSTART also investigates possible epigenetic alterations in infants conceived via assisted reproductive techniques, compared with infants conceived spontaneously (Iliadou et al., 2019). The Swedish BASIC study follows women's experiences during and after pregnancy. in order to offer timely and appropriate help to women who feel unwell. Biosamples from both mother and child are also collected for further analyses (BASIC, 2021).

Factors that have an influence on general health and the wellbeing of mother-infant pairs are cited as the main goal in almost half of the studies (n=61) (Figure 4.). The objective is generally to describe and understand how lifestyles, environment, education and other socio-economic factors affect the course of pregnancy and childbirth. The child's development and growth are examined later on. The respiratory system and its development, diseases and risk factors for their occurrence are among the most researched subjects. It has been noted that several factors have an impact on the development of childhood asthma. Besides genetic factors, environmental influence also has an important role in the etiology of a disease, the most prominent one being socio-economic status and housing. Blood samples, which are used for detecting the level of IgE, family history of atopic diseases, number of siblings or people in the household, parental education and indoor pollution (types of heating, pets, mold etc.), are correlated to the allergies of young children (Bisgaard, 2004; de Korte-de Boer et al., 2015; Martindale et al., 2005). Most of the cohorts that investigate atopic

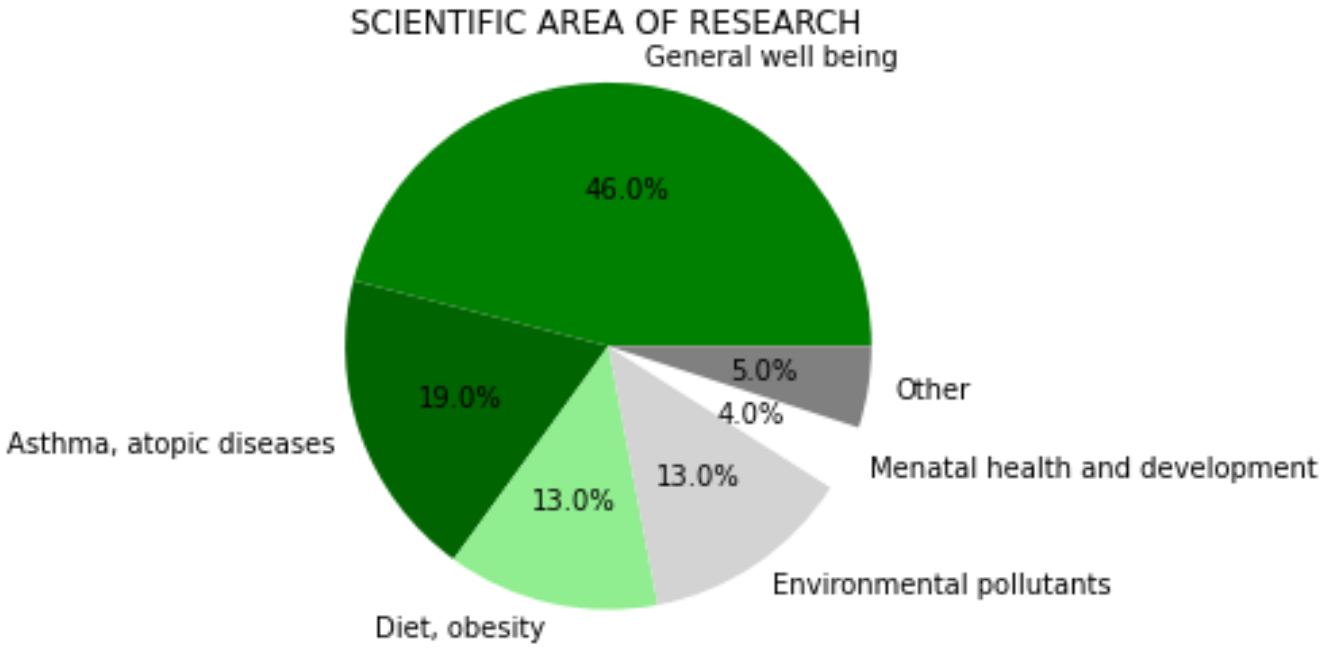

Figure 4.: Scientific area of research

diseases and allergies have the same pattern regarding cohort size due to the fact that children with a family history of atopic diseases have a larger risk for developing the same. It is for this reason that cohorts usually include other family members such as the Russian Moscow newborns 2011 eczema study. This cohort included both parents, grandparents, siblings and all first relatives. Data collected includes allergy manifestation to determine if there is gender or some other pattern of incidence of atopic diseases in newborns whose family has a history of such diseases (Treneva et al., 2015). Another major health concern is obesity whose percentage in the population is growing each year. That is why metabolic diseases, such as diabetes and metabolic syndrome, as well as nutrition and gut microbiome are very often part of a cohort's research. Many studies investigate different aspects of nutrition and diet-related issues. HELMI study focuses on factors that modify intestinal microbiome in infants and its relation to its health and well-being. This subject is becoming increasingly popular as there is more and more evidence of gut microbiome having potential long-term consequences on health in individuals (HELMi, 2019). CRIBS is focused on biological, environmental and behavioral risk factors for metabolic syndrome and study results serve as a base for the development of intervention strategies (Havaš Auguštin et al., 2020; Zajc Petranović et al., 2018). In addition to nutrition and allergies, studies concerning exposure to chemicals, pollutants and tobacco smoke have been investigated with a similar frequency. Environmental pollutants can have an immense impact on children's health, especially on development during the gestation period. Chemicals such as organochlorines, polycyclic aromatic hydrocarbons (PAHs), dioxins and heavy metals have an adverse effect on neurological development and the immune system. These pollutants are known to accumulate in marine food chains and are closely monitored in populations where the diet is based on seafood, namely the Mediterranean countries and the Faroe Islands. Both PHIME and CHEF research long-term, low-level environmental exposure to toxic and essential metals via food. CHEF also focuses on the health of children and adults with an emphasis on the impact of a seafood diet and on marine contaminants (Miklavčič et al., 2013). Particulate matter (PM) is measured as an air pollutant since it covers all liquid and solid particles suspended in the air. Dust, pollen, smoke, soot and liquid drops are all considered PM and are highly concentrated in industrial areas and heavy traffic areas. The Portuguese GISA study is a retrospective cohort study, which tries to assess the relationship between air pollution and low birth weight and preterm birth outcomes. Similarly, in the Czech Republic, PM in air was measured in a highly industrial region and its impact on the retardation of fetal growth was examined. Results were compared to those of a mountain region, without pollution (Dejmek et al., 2000). Problems concerning mental health and neurological development have also been analyzed and several studies focus only on this topic. CCCC 2000 investigates mental health problems and associated factors in infancy and their association with psychopathology in later childhood, as well as possibilities of intervention from infancy onwards (Skovgaard et al., 2005). FinnBrain investigates the effects of prenatal and early life stress exposure on child health and brain development. It has primarily neurodevelopmental focus and aims at identifying biomarkers related to early life and prenatal stress exposures as well as trajectories for common psychiatric and somatic illnesses such as depression, anxiety and cardiovascular illnesses (Karlsson et al., 2018). Very often all of the above-mentioned problems are interconnected, for instance many studies that investigate atopic diseases consider environmental pollution or nutrition as factors that could cause problems with the respiratory system. The GINI study investigates whether the development of allergic diseases can be influenced by early childhood nutrition (von Berg et al., 2003). Breastfeeding and dietary habits, including organic food and a vegetarian diet, are also mentioned in the KOALA birth cohort study which tries to identify factors that influence the clinical expression of atopic disease (Kummeling et al., 2005). The Swedish ALADDIN study also has a unique view on the allergy development in childhood. The population in this study practices anthroposophical lifestyle which is characterized by organic diet, home deliveries, restricted use of medicines and alike (Stenius et al., 2011). Besides metabolic syndrome, the CRIBS study also focused on psychological health and quality of life

of pregnant women (Delale et al., 2021), while the Kraków Cohort tries to connect all three key problems, nutrition during pregnancy, exposure to environmental pollutants and the manifestation of eczema in children (Jedrychowski et al., 2003).

In addition to regular cohort studies, fertility studies, biobanks, and prevention programs were also included in this review. Each collects a sizable amount of data, but only several cover a broader variety of research subjects. BabyCare in Germany is a program to prevent preterm birth with an extensive database which is used for follow-up surveys (Kirschner & Friese, 2012). Nascere in Friuli Venezia Giulia is not an official cohort study, but data routinely collected by the Regional Health Authority and is used for studies such as asthma, allergies, diet during pregnancy and mercury levels (Pitter et al., 2016). Some birth cohorts are a part of bigger cohort groups who include people of different age. Lifelines in the Netherlands is a large, multigenerational cohort study that has been on-going for 30 years, over three different generations and has over 167,000 participants (Lifelines, 2021). Likewise, Swedish LifeGene is both a cohort study and a database consisting of whole families of different age groups. The project offers an opportunity to involve couples prior to and during pregnancy, meaning children that are going to be born into the cohort are going to have complete pre- and perinatal data from both the mother and father (Almqvist et al., 2011).

Although pregnancy and birth cohorts are usually established to detect future outcomes, there are few that use older data and records for retrospective research. The Helsinki Birth Cohort Study includes people who were born 80 years ago. Old medical records are used to compare childhood data to health outcomes in old age such as coronary diseases, cancer and mental health (Maelstrom Research, 2021). The Newcastle 1000 Families started as a study of health in newborns, continuing over a few decades and now researches the health of its original newborns in their 70s. Similarly, PLASTICITY follows the lives of children born from 1971 to 1974 and aims to explore how the neonatal risk factors modulate neurodevelopmental and neurodegenerative processes such as learning disabilities, ADHD, ageing, the early onset mild cognitive impairment, dementia and like. It is believed that perinatal adverse events have an unexpectedly deleterious effect on the brain at a middle and older age (Hokkanen et al., 2013). These cohort studies are excellent for determining long-term consequences on health, but its problem is tracking down all of the participants after such a lengthy period (Thousand Families, 2009).

Most common restrictions and limitations in cohort studies are time-consuming methods and results which depend on the honesty of the participants and their willingness to respond to follow-ups. The number of children decreases with each follow-up in every cohort, which can alter results and make comparisons difficult. In addition, collecting biosamples is a challenging and demanding process, which must be specifically coordinated and conducted according to strict ethical guidelines. Nonetheless, study design of the birth cohort studies is suitable for estimating an association between risk factors during prenatal period and the possible health problems in newborns, potentially up to adulthood. New insights from these studies can be implemented in health interventions or used in specific medical cases. The biggest advantage is the wide range of information collected such as psychosocial, genetic and epigenetic, as well as exposure data. Problems arising from having such multitude of information is harmonizing data over multiple studies because each have their own methods. On the other hand, having a variety of methods can be advantageous in estimating which one is most suitable for different field of interest. There is also a discrepancy in number and multitude of cohorts between progressive countries from Northwest and rest of the Europe. While some of the countries are just beginning their research, the UK, Denmark and Germany, to name a few, have been doing researches for many years, some even decades. In such cases, collaboration and shared knowledge are useful to avoid problems that others have already encountered and to establish a good study design that will provide solid data that can be shared later without harmonization problems.

Conclusion

The main aim of this paper is to review and summarize all cohort studies that have been carried out or are still being conducted in Europe. More than 137 cohorts have been found in 27 countries. Exact number of studies is 127 due to the number of them had been or are being conducted internationally, meaning that they collect information from multiple cohorts in different European countries. General concern is well being of mother and child pairs. Numerous cohorts are trying to resolve common health problems in childhood, main being respiratory diseases. Occurrence of allergy in infants has been connected to family history of atopic diseases, number of siblings or people in the household, parental education and indoor pollution. New problem arising in recent years is obesity. Many cohorts are researching connections of pre and postnatal exposures that may have influence on obesity later in life. Mother's BMI and eating habits during pregnancy, smoking and socioeconomic status are implied to have an impact on child's weight later in life. Another problem that has arisen with modern lifestyle is pollution. Connection between PM and retardation of fetal growth have been made. Chemical pollution also has great impact on health, showing that they can alter neural development. Many studies have combined all of these problems and are trying to find connection between obesity, childhood respiratory problems and environmental pollution from the early age. It is known that obesity is a risk factor for asthma and that obese asthmatics have more severe symptoms, as well as polluted environment, indoors and outdoors, having impact on respiratory system and general health. However, early indications for these connections are still not well understood and therefore relevant research subject. Such problems are an excellent example of the benefits of cohort study design and collaboration among research groups. Birth cohorts are an important source of information, excellent for comparing regional differences between cohorts, discovering impacts on people's health and causes of diseases. Collaboration between different birth cohorts is crucial for further harmonization of collected data and their use in the public health systems worldwide for prevention and education.

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Table 1. Pregnancy and birth cohorts in Europe and their characteristics. All data are participants on the baseline. Source: website birtcohorts.eu and stated references.

Country	Birth cohort name	Abbreviation	Participants			Other family members	Scientific area
			Children	Mothers	Fathers		
Austria	Study on the Prevention of Allergy in Children in Europe – Vienna (Halmerbauer et al., 2003)	SPACE- Vienna	4,309				Atopic disease
Belarus	The Promotion of Breastfeeding Intervention Trial (Patel et al., 2014)	PROBIT	17,046	17,046	17,046	+siblings	Breastfeeding
Belgium	Childhood Obesity - Early Programming by Infant Nutrition(Koletzko et al., 2009)	CHOPIN- Belgium	255	255	255		Childhood obesity
	Flemish Environment and Health Study I-VI (Birthcohorts, 2021; Schoeters et al., 2017)	FLEHS I	1,196	1,196			Determinants of exposure
		FLEHS II	255	255			
		FLEHS III	281	281			
		FLEHS IV **					
	Perinatal factors on the Occurrence of asthma and allergies (Hagendorens et al., 2005; Oostveen et al., 2010)	PIPO	1,128	1,128			Asthma
	3xG study (Gezondheid, Gemeenten, Geboorten) (3xg studie, 2021; Birthcohorts, 2021)	3xG study	301	301			Environmental pollutants and health outcomes
Croatia	Croatian Islands Birth Cohort Study (Birthcohorts, 2021; Sarac et al., 2019; Zajc Petranović et al., 2018)	CRIBS	500	500			Metabolic Syndrome
	Public health impact of long-term, low-level mixed-element exposure in susceptible population strata: Mediterranean Cohort- Croatia(Miklavčič et al., 2013)	PHIME- Croatia	234	234			health risk-assessment of long-term, low-level environmental exposure to toxic and essential metals
Czechia	Central European Longitudinal Studies of Parents and Children: The Next Generation	CELSPAC: TNG**	500	500			Pregnancy, childbirth and its development
	Czech Early Childhood Health (Birthcohorts, 2021; Dejmek et al., 2000)	CZECH	7,577	7,522			c-PAHs and fine particles and intrauterine growth
	European Longitudinal Study of Pregnancy and Childhood	Czech ELSPAC	7,589	5,151	4,653		Epidemiological factors influencing children's health
Denmark	Aarhus Birth Cohort (Birthcohorts, 2021; Mortensen et al., 2013)	ABC	100,000	100,000			Data resource for research; various aspects of pregnancy, birth, and neonatal care
	Copenhagen Child Cohort 2000 (Birthcohorts, 2021; Skovgaard et al., 2005)	CCC2000	6,090	6,090			Mental health problems
	Copenhagen Prospective Studies on Asthma in Childhood (Bisgaard, 2004; Bisgaard et al., 2013)	COPSAC2000	411	394	385		Atopic diseases
		COPSAC2010	743	733	733		Chronic inflammatory diseases (asthma, etc.)

	The Danish Allergy Research Centre cohort (Birthcohorts, 2021; Christiansen et al., 2017)	DARC	562				allergic diseases
	Danish National Birth Cohort	DNBC	95,000	100,418			Exposures in early life
	Healthy Habits for two	HHf2	11,144	11,980	11,500		Risk behaviours and their impact (campaign)
	Odense Child Cohort (Birthcohorts, 2021; Odense Child Cohort, 2021)	OCC	2,553	2,874	2,693		Determinants for health and disease
Faroe Islands	Children's Health and the Environment in the Faroes	CHEF 1	1,022	1,022			Exposure to environmental chemicals
		CHEF 3	656	656			
		CHEF 5	491	491	282		
Finland	FinnBrain Birth Cohort Study (Birthcohorts, 2021; Karlsson et al., 2018)	FinnBrain	4,040	4,011	2,800		Stress exposures on child (brain) development
	Health and Early Microbiota	HELMi	1,055	1,063	1,039		Intestinal microbiota development
	Helsinki Birth Cohort Study (Eriksson, 2006; Helsinki Birth Cohort Study, 2021)	HBCS	13,345				Health influences of early growth
	Kuopio Birth Cohort	KuBiCo	4,700	4,700			Multiple factors and health and disease
	LUKAS		442	442	418		Exposures and respiratory symptoms and development of the immune system
	The Northern Finland Birth Cohort Studies (NFBC, 2021)	NFBC 1966	12,231	12,055			Genetic, biological, social or behavioral risk factors for diseases
		NFBC 1986	9,479	9,362			
	Perinatal Adverse events and Special Trends in Cognitive TrajectorY	PLASTICITY	22,359				Perinatal adverse events and brain at middle and older age
	Steps to the Healthy Development and Well-being of Children	STEPS	1,827	1,797	1,658		Problems in child health and well-being
France	Endocrine disruptors: Longitudinal study on pregnancy abnormalities, infertility, and childhood	PÉLAGIE	4,000	4,000			Chemical exposure and defects and diseases
	Etude Longitudinale Francaise depuis l'Enfance	ELFE	20,000				Early life exposures and their outcomes
	Pollution and Asthma Risk: An Infant Study	PARIS	3,840	3,840			Respiratory and allergic symptoms and behavioural/environmental factors
	Study on the pre and early postnatal determinants of child health and development	EDEN	1,900	2,000	1,800		Pre- and post-natal determinant of the development and health
Germany	Asthma Multicentre Infants Cohort Study- Perinatal Asthma and Environment Longterm Allergy Study(Illi et al., 2014)	AMICS- PAULA	526	513			Asthma and atopy

	Baby Care Cohort (Kirschner & Friese, 2012)	Baby Care	12,555	12,555			Program for the prevention of preterm birth
	Berlin Pregnancy Cohort	BPC	623	978			Pregnancies at risk and allergy risk
	Bielefeld Birth cohort study (Spallek et al., 2017)	BaBi study	995	995			Health inequalities; mental development; allergies
	Childhood Obesity - Early Programming by Infant Nutrition (Koletzko et al., 2009)	CHOPIN- Germany	281	281	281		Childhood obesity
	Dortmund Nutritional and Anthropometric Longitudinally Designed Study	DONALD	1,300	1,300	1,300		Nutrition
	Duisburg (Birthcohorts, 2021; Wilhelm et al., 2008)		234	234			Exposure to environmental chemicals
	The EuroPrevall birth cohort- Berlin (Keil et al., 2010; McBride et al., 2012)		1,570	1,570	1,570	+siblings	Allergies
	German Infant Study on the influence of Nutrition Intervention (Birthcohorts, 2021; von Berg et al., 2003)	GINIplus	5,991				natural course of atopic diseases and metabolic disorders; mental health, nutrition
	Influence of life-style factors on the development of the immune system and allergies in East and West Germany	LISAplus	3,097				Atopic diseases
	Kids birth cohort study (Brandstetter et al., 2019)	KUNO	2,492	2,462	1,412		Various aspects of child health
	LIFE Child		3,500	2,500	1,000		Causes of important widespread diseases
	Lifestyle and environmental factors and their influence on Newborns Allergy risk	LINA	629	622			Allergies
	Loewen KIDS		783				Infections and the development of the Immune System
	Multizentrische Allergie Studie	MAS-90	1,314	1,314	1,314		Allergic disease
	Prenatal Identification of Children's Health	PRINCE	750	750			Factors during pregnancy can and children's health
	Study on the Prevention of Allergy in Children in Europe – Freiburg (Halmerbauer et al., 2003)	SPACE- Freiburg	862				Atopic disease
	Survey of Newborns in Pomerania	SNiP-study	4,840				Neonatal health
Greece	The EuroPrevall birth cohort- Athens (Keil et al., 2010; McBride et al., 2012)		1,080	1,080	1,080	+siblings	Allergies
	Mother Child Cohort in Crete	RHEA	1,590	1,610	37		Prenatal exposures and outcomes, mother's health
	Public health impact of long-term, low-level mixed-element exposure in susceptible population strata:	PHIME- Greece	484	484			health risk-assessment of long-term, low-level environmental exposure to toxic and essential metals

	Mediterranean Cohort- Greek Islands (Miklavčič et al., 2013)						
Iceland	The EuroPrevall birth cohort- Reykjavik (Keil et al., 2010; McBride et al., 2012)		1,341	1,341	1,341	+siblings	Allergies
Ireland	Babies After SCOPE: Evaluating the Longitudinal Impact using Neurological and Nutritional Endpoints	BASELINE	2,185				Development of diseases
	The Cork Nutrition Maternal-Infant Cohort Study	COMBINE	456	456			Nutrition and gut bacteria
	Growing Up in Ireland (Infant Cohort/Cohort '08) (Williams et al., 2012)	Cohort '08	11,100	11,100	11,100		Child well-being
	Lifeways Cross-Generation Cohort Study	Lifeways Cross-Gen.	1,074	1,061	325		Health information system
	Maternal health And Maternal Morbidity in Ireland (MAMMI, 2021)	MAMMI		2,503			Health problems during pregnancy and the first year after the birth
	Randomized control trial of Low glycemic index diet	ROLO	720	720			Low glycemic index diet and postnatal weight
Italy	Bologna Birth Cohort	Co.N.ER	654	651	593		Early life exposure and mother and child health
	Childhood Obesity - Early Programming by Infant Nutrition (Koletzko et al., 2009)	CHOPIN- Italy	415	415	415		Childhood obesity
	The EuroPrevall birth cohort- Milan (Keil et al., 2010; McBride et al., 2012)		1,486	1,486	1,486	+siblings	Allergies
	Genetica e Ambiente: Studio Prospettico dell'Infanzia in Italia	GASPII	708	693	693		Early life exposure and mother and child health
	Italian prospective Cohort of term and late preterm Newborns	ICON	2,314				Lower respiratory tract infection during childhood
	Mamma & Bambino		274	411			Early life exposure and mother and child health
	Public health impact of long-term, low-level mixed-element exposure in susceptible population strata: Mediterranean Cohort- Italy (Miklavčič et al., 2013)	PHIME- Italy	900	900			health risk-assessment of long-term, low-level environmental exposure to toxic and essential metals
	Multiple Births Cohort Study Pansieri 2020	MUBICOS	1,000	500	500		Heritability and gene-environment interaction in twins
	NAscere e creSCere in ITAlia	NASCITA	5,000				Health status of Italian children early on
	Nascita e INFanzia: gli Effetti dell'Ambiente	NINFEA	6,832	6,798			Exposures during pre-natal and early post-natal life
	Nascere in Friuli Venezia Giulia (prospective studies on children in Italian region of Friuli Venezia Giulia-FVG region) (Pitter et al., 2016)		All children that were born in this region and are in administrative data				Wellbeing and health of the children (Region-wide control for well-being and public health)

	Neonatal Environment and Health Outcomes	NEHO	860	860	860		environmental risk factors for placental function, pregnancy outcomes and newborns' health outcomes
	Piccolipiù		3,338	3,338	3,300		Environmental exposures and infant and child health and development
	Trieste child development cohort	Trieste cohort	900	900			Environmental, social, and genetic factors and neurocognitive development
Lithuania	The EuroPrevall birth cohort- Vilnius (Keil et al., 2010; McBride et al., 2012)		1,556	1,556	1,566	+siblings	Allergies
	Kaunas cohort	KANC	4,405	4,329	4,300		Risk factors for adversely pregnancy outcomes
Netherlands	Amsterdam Born Children and their Development	ABCD	6,161	8,266	2,270		Prenatal exposures and the child's health
	Dutch famine birth cohort study	DFBCS	741	741			Prenatal exposure to the Dutch famine and health
	The EuroPrevall birth cohort- Amsterdam (Keil et al., 2010; McBride et al., 2012)		976	976	976	+siblings	Allergies
	Generation R		10,000	97,780	6,500		Factors that influence the health of children in Rotterdam
	Groningen Expert Center for Kids with Obesity	GECKO Drenthe	2,997				Childhood obesity
	KOALA Birth Cohort Study (Birthcohorts, 2021; Kummeling et al., 2005)	KOALA	2,843	2,900	2,900		Allergies and asthma; growth and development
	Lifelines NEXT (Birthcohorts, 2021; Lifelines, 2021)		three-generation cohort: 15,000 children (aged 0-18 years) 140,000 adults (aged 18-65 years) 12,000 elderly (65+ years).				Early life factors and health (biobank)
	The LucKi Birth Cohort Study (Birthcohorts, 2021; de Korte-de Boer et al., 2015)	LucKi	5,000				Exposures; atopic diseases; obesity
	Maastricht essential fatty acid birth cohort (Birthcohorts, 2021; Wurff et al., 2015)	MEFAB	1,203	1,203			Early essential fatty acid status and development and health
	PRegnancy and Infant DEvelopment Study	PRIDE Study	3,200	5,300	2,100		Exposures and health outcomes
	Prevention and Incidence of Asthma and Mite Allergy (Birthcohorts, 2021; PIAMA, 2012)	PIAMA	3,963	4,146	4,116		Asthma, allergies and lung function
	Prevention of Asthma in Genetically Susceptible Children (Kuiper et al., 2005)	PREVASC	888	888			Asthma
	Rotterdam Periconception Cohort	Predict Study	1,500	2,000	1,500		Exposures and health outcomes
	Wheezing Illnesses Study in LEidsche Rijn (Birth cohorts, 2021; Katier et al., 2004)	WHISLER	2,500	1,000	1,000		Determinants for wheezing illnesses

Norway	ArcRisk-Norway: Northern Norway mother-and-child contaminant cohort study (Veyhe et al., 2012)	MISA – Arctic Norway	515	515			Pollutant levels in maternal blood during pregnancy and in mother's milk
	Environment and Childhood Asthma Study in Oslo (Lødrup Carlsen, 2002; Lødrup Carlsen et al., 2006)	ECA	3,754				Air pollution and asthma development
	Norwegian Human Milk Study	HUMIS	2,500	2,500	2,400		Levels of environmental toxicants in breast milk
	The Norwegian Influenza Pregnancy Cohort Study (NorFlu, 2021)	NorFlu	4,500	4,500			Effects of maternal influenza infection on the fetus
	Norwegian Microbiota Study (Eggesbø et al., 2011)	NoMIC	601	601			Gut microbiota in infancy and its development
	Norwegian Mother, Father and Child Cohort Study	MoBa	108,500	90,700	72,100		Causes of disease
Poland	Childhood Obesity - Early Programming by Infant Nutrition (Koletzko et al., 2009)	CHOPIN- Poland	275	275	275		Childhood obesity
	The EuroPrevall birth cohort- Lodz (Keil et al., 2010; McBride et al., 2012)		1,513	1,513	1,513	+siblings	Allergies
	Kraków Cohort		505	528			PAH exposure and birth outcomes
	Polish Mother and Child Cohort Study	REPRO_PL	1,800	1,800			Exposure and health outcomes
Portugal	Geração XXI (Alves et al., 2011; Birthcohorts, 2021)	G21	8,270	8,127	4,351		Child health and development
	Gestão Integrada Saúde e Ambiente	GISA	1,645	1,645			Environmental air pollution and birth weight and gestational age
Russian Federation	Russian Moscow newborns 2011 eczema	RuMos	393	393	393	2,748	Allergy manifestation in relatives of newborns and their tendency for atopic disease
Slovakia	Slovak PCB study		1,134	1,134			Pollutant exposure and neurobehavioral and immunologic development
Slovenia	Public health impact of long-term, low-level mixed-element exposure in susceptible population strata : Mediterranean Cohort- Slovenia (Miklavčič et al., 2013)	PHIME- Slovenia	584	584			health risk-assessment of long-term, low-level environmental exposure to toxic and essential metals
Spain	Asthma Multi-centre Infants Cohort Study (Friguls et al., 2009)	AMICS- Barcelona	487	480			Atopy and asthma
		AMICS- Menorca	482	475			
	Childhood Obesity - Early Programming by Infant Nutrition (Koletzko et al., 2009)	CHOPIN- Spain	452	452	452		Childhood obesity
	ECLIPSES		400	700	500		Environmental factors, during pregnancy and newborn cognitive development

	The EuroPrevall birth cohort- Madrid (Keil et al., 2010; McBride et al., 2012)		1,387	1,387	1,387	+siblings	Allergies
	Genetics, Environmental, Exposures and Infant Development in Andalucia (Aguilar-Lacasaña et al., 2021; Birthcohorts, 2021)	GENEIDA	800	800			Exposure to environmental pollutants and the fetal growth and development, neurodevelopment; biomarkers
	INfancia y Medio Ambiente	INMA	3,768	3,944	3,944		Environmental pollutants and children's' growth and development
	Nutrition in Early Life and Asthma (Birthcohorts, 2021; Suárez-Martínez et al., 2021)	NELA	738	738			Nutrition during pregnancy and early postnatal life and health outcomes
Sweden	All Babies in Southeast Sweden	ABIS	17,000	17,000	17,000		Environmental and genetic factors and Type 1 Diabetes, and other immune-mediated diseases
	Assessment of Lifestyle and Allergic Disease During Infancy (Stenius et al., 2011)	ALADDIN	330	330	330	+siblings	Exposure during pregnancy and infancy in children of families with an anthroposophic lifestyle
	Biology, Affects, Stress, Imaging and Cognition (BASIC, 2021)	BASIC	2,866	6,387			Women's experience during and after pregnancy
	Born into Life (Smew et al., 2018)		107	107			Maternal stress during pregnancy and fetal growth
	Children (Barn), Allergy, Milieu, Stockholm, Epidemiological study	BAMSE	4,089	4,089	4,089		Asthma, allergic diseases and lung function
	Helsingborg Birth Cohort 1964-1967	HbgBC	4,982	4,982			Health of Mothers and Offspring
	LifeGene (Almqvist et al., 2011; LifeGene, 2021)		50 799 participants				population and health registry
	The Uppsala-Stockholm Assisted Reproductive Techniques Study (Iliadou et al., 2019; UppStART, 2011)	UppSTART		514(129 pregnancies)	457		Epigenetic alterations in infants conceived via ART and those conceived spontaneously; lifestyle factors and ART procedure-specific outcomes and pregnancy outcomes
Switzerland	Bern-Basel Infant Lung Development Cohort	BILD	400	400			Physiological properties of the respiratory system; environmental and genetic risk factors and lung development
Turkey	Bogazici Mother-Baby Relationship Project	BABIP	150	150			Prenatal environment and fetal development and health

Ukraine	Family and Children of Ukraine (European Longitudinal Study of Pregnancy and Childhood)	FCOU	4,510	4,510	4,510		Epidemiological factors influencing children's health
United Kingdom	Asthma Multi-centre Infants Cohort Study (Fríguls et al., 2009)	AMICS- Ashford	642	634			Atopy and asthma
	Avon Longitudinal Study of Parents & Children/Children of the 90s (European Longitudinal Study of Pregnancy and Childhood)	ALSPAC	14,000	14,000	20,000	1,000	Epidemiological factors influencing children's health
	Baby Biome Study	BBS	3,401	3,401			Microorganisms, the immune system, and clinical, social, and behavioural factors during pregnancy and early life influence later health and disease
	Born in Bradford (BiB, 2018)	BiB	14,000	14,000	3,000		Reasons for ill health; improving child health and wellbeing
	The EuroPrevall birth cohort- Southampton (Keil et al., 2010; McBride et al., 2012)		1,140	1,140	1,140		Allergies
	Gateshead Millennium Study	GMS	1,029	1,011			Child health; growth and development in childhood
	Growing Up in Scotland (GUS, 2017)	GUS Birth cohort 1	5,502				Children's wellbeing in Scotland
		GUS Birth cohort 2	6,127				
	Growing Up in Wales: Environments for Healthy Living	EHL	420	420			Environmental and behavioural exposures on the health of offspring
	European Longitudinal Study of Pregnancy and Childhood: Isle of Man Birth Cohort Study (Birthcohorts, 2021; Goodfellow et al., 2013)	ELSPAC: Isle of Man	1,314	1,384	1,384		Epidemiological factors influencing children's health
	Isle of Wight Birth Cohort (Arshad et al., 2018)	IOWBC	1,536	1,509			Asthma and allergic diseases
	Leicester Respiratory Cohorts	LRC	10,350				Wheezing disorders and other common respiratory problems
	Merthyr Allergy Study		497	491			Allergies and infant feeding and various environmental factors
	Newcastle Thousand Families Study (Pearce et al., 2009)	1000 Families Study	1,146				Infections in infancy and other health outcomes, educational performance and family life
	Study of eczema and asthma to observe the effects of nutrition (Martindale et al., 2005)	SEATON	1,924	2,000			Mother's diet during pregnancy and child's risk for getting asthma and allergies
	Study on the Prevention of Allergy in Children in Europe (Halmerbauer et al., 2003; Tsitoura et al., 2002)	SPACE- Newport	430				Atopic disease
	Southampton Women's Survey	SWS	3,158	12,583	3,158		Maternal pre-conception and pregnancy factors and child's health
	Wirral Child Health and Development Study (Sharp et al., 2012)	WCHADS	1,233	1,233	1,014		Early social, emotional and biological risks and processes and childhood conduct problems

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