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Increased 25(OH)D3 level in redheaded people: Could redheadedness be an adaptation to temperate climate?

Jaroslav Flegr[1] | Kateřina Sýkorová[1] | Vojtěch Fiala[1] | Jana Hlaváčová[1] | Marie Bičíková[2] | Ludmila Máčová[2] | Šárka Kaňková[1]

[1]Department of Philosophy and History of Sciences, Faculty of Science, Charles University, Prague, Czech Republic

[2]Institute of Endocrinology, Prague, Czech Republic

Correspondence
Jaroslav Flegr, Laboratory of Evolutionary Biology, Department of Philosophy and History of Sciences, Faculty of Science, Charles University, Vinicna 7, 128 00 Prague 2, Czech Republic.
Email: flegr@cesnet.cz

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Abstract

About 1-2% of European population are redheaded, meaning they synthesize more pheomelanin than eumelanin, the main melanin pigment in humans. Several mutations could be responsible for this phenotype. It has been suggested that corresponding mutations spread in Europe due to a founder effect shaped either by a relaxation of selection for dark, UV-protective phenotypes or by sexual selection in favour of rare phenotypes. In our study, we investigated the levels of vitamin D precursor 25(OH)D3 (calcidiol) and folic acid in the blood serum of 73 redheaded and 130 non-redheaded individuals. In redheaded individuals, we found higher 25(OH)D3 concentrations and approximately the same folic acid concentrations as in non-redheaded subjects. 25(OH)D3 concentrations correlated with the intensity of hair redness measured by two spectrophotometric methods and estimated by participants themselves and by independent observers. In non-redheaded individuals, 25(OH)D3 levels covaried with the amount of sun exposure and intensity of suntan while in redheaded individuals, this was not the case. It suggests that increased 25(OH)D3 levels in redheaded individuals are due to differences in physiology rather than in behaviour. We also found that folic acid levels increased with age and the intensity of baldness and decreased with the frequency of visiting tanning salons. Our results suggest that the redheaded phenotype could be an evolutionary adaptation for sufficient photosynthesis of provitamin D in conditions of low intensity of UVB radiation in central and northern parts of Europe.

KEYWORDS

baldness, cancer, human evolution, pigmentation, UVB, vitamin D

1 | INTRODUCTION

On average, less than 2% of all Europeans (but 6-13% of population of Ireland, Wales and Scotland) express the redheaded phenotype.[1,2] Mutations in the gene for receptor protein *MCIR*, the most important regulator of melanogenesis,[3] which is responsible for low levels of eumelanin in the affected subjects, probably spread in human populations after the arrival of modern *Homo sapiens* to Europe. Nevertheless, the most common allele, Val92Met, seems to have introgressed into our gene pool from *Homo neanderthalensis*.[4] In redheaded subjects, the eumelanin (black pigment) is, for the most part, substituted with a related pigment pheomelanin (yellow-red pigment) in melanin-containing granules in the skin, hair and iris.[3,5,6] However, pheomelanin cannot protect the body against

UV radiation and can even have mutagenic and cancerogenic influences, depending on the context.[7] The type of pigments and their concentration therefore influence the susceptibility of individuals to cancer, especially (but not only[8]) to melanoma.[9] It has been speculated, therefore, whether in higher latitudes, the pheomelanogenesis is linked to some beneficial effect able to compensate its adverse effects.[7] It has been also suggested that the redheaded phenotype and corresponding alleles spread due to sexual selection, in particular, by selection in favour of a rare phenotype.[10,11]

Many anecdotal observations[12-16] and one systematic large-scale study[11] reveal that redheaded persons, especially women, tend to suffer from various symptoms of impaired health and from a higher frequency of certain diseases, including colorectal, cervical, uterine and ovarian cancer than their non-redheaded peers. It has been suggested that the resulting selection against redheaded individuals counterbalances the positive sexual selection in favour of redheaded women, thereby maintaining the corresponding alleles at a low but stable frequency.[11]

Another study which used a similar population later showed that it is not the red hair as such but rather the pale skin frequently associated with redheaded phenotype that is responsible for the observed signs of impaired health of redheaded persons.[17] Pale skin can be the result of either congenitally low eumelanin concentrations in the skin or a sign of absence of suntan, usually due to avoidance of sun exposure.[18] The authors suggest that the impaired health[7,19] observed primarily in pale-skinned individuals and secondarily also in many redheaded persons is caused either by photolysis of folic acid in naturally pale individuals or by insufficient photosynthesis of vitamin D in persons who are pale due to avoidance of sun exposure. It has been shown that a large fraction of the genes that influence skin pigmentation (11 of 29 under study) affect the concentration of vitamin D in modern human.[20] However, the regulation of melanogenesis[21] as well as the relation between skin pigmentation and vitamin D synthesis[7,22] is rather complex. Moreover, no direct data concerning the concentration of folic acid in pale-skinned or redheaded participants of the study[17] were available.

Rather surprisingly, we found only two studies with information about vitamin D concentrations[23,24] and no study with information on folic acid concentrations in redhaired individuals in scientific literature. The study performed on subjects living in the United Kingdom showed that their 25(OH)D3 levels were on average 50.5 nM/L, which was significantly lower than in controls, including subjects with blond hair, for whom the value stood at 56.1 nM/L.[23] Another study showed virtually no difference in vitamin D concentrations between redhaired and non-redhaired Finnish men (33.6 vs 33.5 nM/L).[24] Both studies, as well as our present study, were conducted on European populations. Comparisons with populations of Asian origin were not possible since so far, there is to the best of our knowledge no study that dealt with this subject in these populations, where fair-skinned and redhaired phenotypes originated independently and different alleles and different genes are involved.[25]

The aim of the present case-control study performed on a population of 203 subjects (73 of whom are redheaded) was to test the proposed hypotheses by searching for possible correlations between the intensity of natural hair redness, natural and by sun exposure acquired skin tone, and 25(OH)D3 and folic acid concentrations. In previous studies, the intensity of hair redness was rated by subjects themselves. To check the reliability of such data and their usefulness for future studies, we compared self-rated hair redness, redness rated by two independent observers and exact measurements acquired by two different spectrophotometric methods.

2 | MATERIALS AND METHODS

The project included a laboratory investigation which took place at the Faculty of Science of Charles University on September 17—October 3, 2018. The second part, an online questionnaire survey, was completed by the same set of participants within the following 35 days.

2.1 | Participants

Participants were recruited mostly via a Facebook-based snowball method. Initially, an invitation to participate in a "study of health and personality of redheads" was posted on the timeline of the Facebook page Labbunnies, an approximately 18 000 strong group of Czech and Slovak nationals willing to participate in evolutionary psychology experiments. Further recruitment of redheads was carried out by invitations on Facebook, selective invitation of registered members of Labbunnies who completed our earlier questionnaires on the scale of redheadedness and scored four to six on a six-point scale, and by handing out flyers in the streets of Prague to people looked like natural redheads. We invited only people who confirmed that they had not dyed or bleached their hair for at least 6 months. This enabled us to measure natural hair colour near the hair roots. Only subjects who provided informed consent were included in the study. In the end, we assembled a sample of 110 women and 93 men. Participants received no remuneration, only a commemorative badge and a haircare gift set (costing 53 CZK, that is app. 2.3 USD). The project was approved by the Ethics Committee of the Faculty of Science, Charles University (No. 2018/30).

2.2 | Experimental design

Participants were instructed to wash their hair the evening before or morning of the day of the laboratory measurement and to refrain from using any postshampoo products. At the beginning of the session, participants obtained a paper questionnaire, which they could complete while waiting for individual measurements. First, participants were tested with an electronic dynamometer (not part of the present study). Then, we measured the natural red colour of participants' hair and their skin hue by using a spectrophotometer to obtain a standardized scale of redheadedness and skin hue. Subsequently,

participants were tested with a mechanical dynamometer. While the dynamometer and spectrophotometer measurements were performed in two separate rooms, two observers (a woman and a man) independently rated the intensity of subjects' redheadedness and freckledness using an ordinal scale of zero to five. At the end of the laboratory part of the study, we asked participants whether they consent to having a blood sample taken to determine the concentration of 25(OH)D3 and folic acid. The sampling was performed in an adjacent room by a qualified nurse. Several days after the laboratory part of the study, we sent all participants a link to another electronic questionnaire with a request to complete it within the following 35 days. After two rounds of e-mail reminders, 198 (97.5%) of participants completed this questionnaire.

2.3 | Questionnaires

All participants were asked to complete one printed questionnaire and one electronic questionnaire, distributed via Qualtrics platform, which aimed at collecting their basic anamnestic information and information related to their and their relatives' hair and body pigmentation, as well as their tanning or sun avoidance behaviours. Specifically, we asked the participants to rate the following:

- Natural redness of their hair and hair colour in childhood on a six-point scale anchored with "absolutely non-red" (code 1)—"bright red" (code 6);
- Natural lightness of their hair and complexion on a six-point scale anchored with "very light" (code 1)—"very dark" (code 6);
- Hair length on a four-point scale anchored with "very short, does not cover the forehead, ears or neck" (code 1)—"medium length or long, covering forehead, ears and neck, mostly worn loose" (code 4);
- Intensity of baldness on a seven-point scale, where degrees were shown by black and white pictures (no responder chose code 7, the highest degree of baldness);
- Current intensity of suntan on a six-point scale anchored with "no suntan" (code 1)—"very dark suntan" (code 6);
- Tendency to tan to brown and tendency to tan to red on six-point scales anchored with "definitely not" (code 1)—"definitely yes" (code 6);
- Intensity of chemical self-protection from sun by creams or oils with UV filters, intensity of self-protection by mechanical means (by shelters and clothing) on six-point scales anchored with "not at all" (code 1)—"yes, very carefully" (code 6);
- Frequency of sun exposure on a seven-point scale anchored with "almost never" (code 1)—"over 3 hours a day" (code 7); no responder chose code 7;
- Frequency of visits to tanning salons on a five-point scale anchored with "never" (code 1)—"yes, almost throughout the year" (code 5);
- Frequency of taking vitamin D supplements on a six-point scale anchored with "never" (code 2)—"yes, almost constantly" (code 6). Here, responders could also check "I do not know" (code 1: "missing value").

Participants were also asked whether they had red hair on other parts of their body (eg facial hair, body hair) and whether they had redheaded relatives (binary variables). The other two binary variables of red hair (no/yes) and red hair in childhood (no/yes) were obtained by splitting the corresponding ordinal variables (0:1, 2 vs 1:3, 4, 5, 6). We also monitored potential confounding variables such as sex, age and size of place of residence (six categories: <1000 inhabitants, 1000-5000, 5000-50 000, 50 000-100 000, 100 000-500 000, Prague or Bratislava).

2.4 | Measuring skin and hair pigmentation with a spectrophotometer

Measurements of the natural red colour of participant's hair and darkness or lightness of their skin tone were performed with a spectrophotometer (Ocean Optics FLAME-S). The device was white-calibrated using a WS-1 Diffuser Reflectance Standard. Before commencing the measurement, the experimenter asked whether participant's hair had been dyed and then cleaned the participant's cheeks and forehead with a make-up removal pad. Then, he took three spectrophotometric measurements of skin colour on the inner upper arm of the less dominant hand (depending on participants' self-reported handedness), one on the left cheek, one on the right cheek and one on the forehead above nasal root. To measure hair colour, the experimenter moved aside the crown hair to get to the hair in the occipital region and made sure that the scalp was not visible. Then, he took three spectrophotometric measurements of hair colour in different areas around the occipital region. The occipital region and inner upper arm are the areas least exposed to sunlight, which is why hair and skin colour found there correspond most closely to the natural colour. We used two methods to determine the total level of redheadedness. The first was Reed's function[26]:

$$R = \frac{100\,(y_{530} - 0.243y_{400})}{y_{650}},$$

where y_{400}, y_{530} and y_{650} are the arithmetical means of three measurements of percentage reflectance values at wavelengths in the subscript. The second was the CIE L*a*b* colour space: it provided the a* parameter which ranges from −100 (green) to +100 (red).[27,28]

2.5 | Measurements of 25(OH)D3 and folic acid concentrations

25(OH)D3 concentration was measured using high-performance liquid chromatography by ClinRep® Complete Kit for 25-OH-Vitamin D2/D3 (RECIPE Chemicals+ Instruments GmbH). Folic acid was measured with ID-Vit®Folic acid microtitre plate kit

(Immundiagnostik AG). After incubation at 37°C for 48 hours, the growth of *Lactobacillus rhamnosusis* was measured turbidimetrically at 620 nm using ELISA-reader Spark™ 10 mol/L (Tecan).

2.6 | Statistics

Statistica v. 10.0 was used to explore the data and R v. 3.3.1[29] for confirmatory statistical tests. Associations of sex with age, and 25(OH)D3 and folic acid concentrations were estimated by a t test and correlation of sex, age and urbanization with all focal variables by a Kendall correlation test. Partial Kendall correlation test (R package ppcor 1.1[30]) with age, urbanization and in some analyses also sex as potential covariates was used for the main analysis. This multivariate non-parametric test allows for measuring the significance and strength of correlations between any combination of binary, ordinal and continuous variables while controlling for any number of confounding variables. In the confirmatory part of the study, that is to test the hypothesized effect of redheadedness on 25(OH)D3 and folic acid concentrations, we performed a correction for multiple tests by Benjamini-Hochberg procedure with false discovery rate preset to 0.20.[31] In the exploratory parts of the study, we performed no correction for multiple tests.

3 | RESULTS

The final population consisted of 110 women (mean age 27.4, SD = 7.5) and 93 men (mean age 34.0, SD = 9.0). The age difference between men and women was highly significant ($t_{180} = -3.92$, $P = .0001$, Cohen's $d = 0.563$). Table 1 shows the descriptive statistics for our ordinal and binary data. Kendall correlation test showed that men and women, the old and the young, people residing in small and large settlements, and redheaded versus non-redheaded people differed in their responses to hair and body pigmentation-related variables as well as in behavioural variables related to sun exposure (Table 1, the last four columns). Average 25(OH)D3 concentrations were higher in 105 women (75.1 nmol/L, SD = 22.8) than in 88 men (70.2 nmol/L, SD = 21.8), but the difference was not statistically significant ($t_{186} = 1.54$, $P = .124$, Cohen's $d = -0.224$). Folic acid concentrations were also non-significantly higher in 99 women (7.48 μg/L, SD = 5.71) than in 78 men (7.11 μg/L, SD = 4.78) ($t_{174} = 1.54$, $P = .643$, Cohen's d = −0.069). Table 2 shows correlations between 25(OH)D3 and folic acid concentrations and age and urbanization. Except for a strong positive correlation between folic acid concentration and age (Tau = 0.210, $P < .00001$), none of these correlations reached the formal level of statistical significance.

The effect of hair redness and other variables related to hair and body pigmentation as well as sun exposure behaviours on the concentration of 25(OH)D3 and folic acid in the serum was analysed primarily with non-parametric partial Kendall correlations controlled for age and urbanization. Nevertheless, similar results were obtained also when sex, hair and skin tone (light to dark), and even the frequency of sun exposure and intensity of suntan were controlled for. Our results suggest that hair redness has the strongest effect on 25(OH)D3 concentrations (positive and significant after correction for multiple tests) and a negligible effect on folic acid concentrations (see Figure 1, Table 2). The strongest correlation was observed when analyses used the binary variable hair redness obtained from hair redness estimated by the subjects on an ordinal scale of 1-6 split to 0 (responses 1 and 2) and 1 (responses 3-6). Nonetheless, effects of a similar strength were detected when the intensity of hair redness was measured spectrophotometrically and that held regardless of which index, including raw reflectance at 650 nm, of hair redness was applied.

Separate partial Kendall analyses for redheaded and non-redheaded subjects showed that sun exposure had a minimal effect on 25(OH)D3 and folic acid concentrations in redheaded subjects, except for a very strong negative (sic!) effect of frequency of tanning salon visits on 25(OH)D3 levels. In non-redheaded subjects, sun exposure did have the expected positive effect on 25(OH)D3 levels (see Figure 2, Table 3). Frequency of visiting tanning salons had a negative effect on the level of folic acid (relatively strong in all subjects but significant only in non-redheaded subjects) (Table 3).

4 | DISCUSSION

Redheaded subjects had higher 25(OH)D3 concentrations and approximately the same folic acid concentrations as non-redheaded subjects. Results of partial correlations suggest that redheaded subjects need less sun exposure to achieve satisfactory 25(OH)D3 levels—and thereby probably also satisfactory levels of a biologically active vitamin D—than non-redheaded subjects do.

Differences between redheaded and non-redheaded subjects are likely to be due to differences in their physiology than an effect of their sunbathing-related behaviour. For example, we observed no differences in the intensity of sun exposure between redheaded and non-redheaded subjects but redheaded subjects were less tanned at the time of the study. Redheaded subjects also reported that they use more intensive chemical and mechanical sun protection than their non-redheaded peers. In contrast to the situation in non-redheaded persons, redheaded persons' 25(OH)D3 concentrations seemed independent of the intensity of sun exposure or protection from solar radiation. Redheaded subjects used vitamin D supplements less frequently but it should be noted that while the effect of these supplements on 25(OH)D3 levels was positive, it was at best modest and always non-significant. This absence of effect of vitamin D supplement use could be due to the fact that they tend to be used by persons with a diagnosed vitamin D deficiency.

There are several hypotheses whose aim is to explain the spread of genes for fair skin and red hair, that is the shift of the eumelanin-pheomelanin ratio, in populations inhabiting higher latitudes. It has been, for example, suggested that a relaxation of selection for protection against photolysis of folic acid or against

TABLE 1 Distributions of responses of participants (or observers) to particular questions

	1		2		3		4		5		6						
	n	%	n	%	n	%	n	%	n	%	n	%		Sex	Age	Urban.	Redness
Urbanization																	
Women	11	10.00	14	12.73	9	8.18	2	1.82	1	0.91	73	66.36	Tau	0.072	0.082	NA	0.085
Men	3	3.23	10	10.75	10	10.75	1	1.08	3	3.23	66	70.97	*P*	.13	.08	NA	.07
Hair redness																	
Women	50	45.45	16	14.55	7	6.36	17	15.45	13	11.82	7	6.36	Tau	−0.088	−0.082	0.085	NA
Men	49	52.69	15	16.13	9	9.68	8	8.60	7	7.53	5	5.38	*P*	.06	.08	.07	NA
Redness childhood																	
Women	53	49.07	9	8.33	4	3.70	7	6.48	10	9.26	25	23.15	Tau	−0.117	−0.084	0.095	0.801
Men	56	60.22	4	4.30	7	7.53	6	6.45	8	8.60	12	12.90	*P*	**.01**	.08	**.05**	**.00**
Body hair redness																	
Women	70	63.64	40	36.36									Tau	0.089	0.053	0.100	0.680
Men	51	54.84	42	45.16									*P*	.06	.26	**.03**	**.00**
Red hair relatives																	
Women	71	65.74	37	34.26									Tau	0.013	−0.016	0.062	0.523
Men	60	64.52	33	35.48									*P*	.79	.73	.19	**.00**
Hair redness observer 1																	
Women	52	47.27	16	14.55	2	1.82	3	2.73	15	13.64	22	20.00	Tau	−0.151	−0.127	0.047	0.745
Men	59	63.44	11	11.83	5	5.38	1	1.08	3	3.23	14	15.05	*P*	**.00**	**.01**	.32	**.00**
Hair redness observer 2																	
Women	5	4.55	12	10.91	18	16.36	33	30.00	24	21.82	18	16.36	Tau	−0.103	−0.087	0.010	0.574
Men	11	11.83	15	16.13	14	15.05	22	23.66	18	19.35	13	13.98	*P*	**.03**	.07	.83	**.00**
Hair darkness																	
Women	1	0.91	17	15.45	33	30.00	33	30.00	24	21.82	2	1.82	Tau	0.108	0.073	−0.021	−0.277
Men	0	0.00	9	9.68	26	27.96	28	30.11	27	29.03	3	3.23	*P*	**.02**	.12	.66	**.00**
Baldness																	
Women													Tau	NA	0.229	0.146	−0.104
Men	41	44.09	40	43.01	6	6.45	2	2.15	0	0.00	0	0.00	*P*	NA	**.00**	**.04**	.15
Hair length																	
Women	0	0.00	6	5.45	56	50.91	48	43.64					Tau	−0.666	−0.105	−0.006	0.155
Men	39	42.39	38	41.30	9	9.78	6	6.52					*P*	**.00**	**.03**	.89	**.00**

(Continues)

TABLE 1 (Continued)

	1		2		3		4		5		6						
	n	%	n	%	n	%	n	%	n	%	n	%		Sex	Age	Urban.	Redness
Natural skin darkness																	
Women	22	20.00	49	44.55	26	23.64	12	10.91	1	0.91	0	0.00	Tau	0.161	0.123	−0.098	−0.406
Men	13	13.98	31	33.33	29	31.18	16	17.20	3	3.23	1	1.08	*P*	**.00**	**.01**	**.04**	**.00**
Suntan																	
Women	11	10.00	35	31.82	30	27.27	25	22.73	8	7.27	1	0.91	Tau	0.057	0.059	−0.113	−0.157
Men	8	8.60	31	33.33	16	17.20	26	27.96	10	10.75	2	2.15	*P*	.23	.21	**.02**	**.04**
Brown tanning																	
Women	21	19.09	25	22.73	18	16.36	18	16.36	21	19.09	7	6.36	Tau	0.083	0.077	−0.036	−0.407
Men	12	12.90	20	21.51	16	17.20	15	16.13	22	23.66	8	8.60	*P*	.08	.10	.44	**.00**
Red tanning																	
Women	18	16.36	24	21.82	15	13.64	13	11.82	22	20.00	18	16.36	Tau	0.001	−0.016	0.150	0.432
Men	10	10.75	22	23.66	18	19.35	14	15.05	17	18.28	12	12.90	*P*	.99	0.73	**.00**	**.00**
Freckledness observer 1																	
Women	54	49.09	17	15.45	17	15.45	7	6.36	4	3.64	11	10.00	Tau	−0.196	−0.045	0.053	0.518
Men	61	65.59	19	20.43	5	5.38	6	6.45	0	0.00	2	2.15	*P*	**.00**	.34	.26	**.00**
Freckledness observer 2																	
Women	5	4.55	12	10.91	18	16.36	33	30.00	24	21.82	18	16.36	Tau	−0.150	−0.023	0.082	0.542
Men	11	11.83	15	16.13	14	15.05	22	23.66	18	19.35	13	13.98	*P*	**.00**	.63	.08	**.00**
Protection by sun creams																	
Women	9	8.18	13	11.82	11	10.00	28	25.45	26	23.64	23	20.91	Tau	−0.163	−0.122	0.171	0.250
Men	15	16.13	15	16.13	14	15.05	20	21.51	18	19.35	11	11.83	*P*	**.00**	**.01**	**.00**	**.00**
Protection by shelters																	
Women	21	19.09	24	21.82	20	18.18	22	20.00	15	13.64	8	7.27	Tau	−0.099	−0.006	0.015	0.177
Men	20	21.51	26	27.96	17	18.28	20	21.51	10	10.75	0	0.00	*P*	**.04**	.91	.76	**.00**
Sun exposure																	
Women	3	2.73	1	0.91	13	11.82	17	15.45	27	24.55	49	44.55	Tau	−0.020	−0.019	−0.061	0.001
Men	0	0.00	1	1.08	6	6.45	17	18.28	37	39.78	32	34.41	*P*	.67	.69	.20	.99
Tanning salons																	
Women	103	93.64	4	3.64	2	1.82	1	0.91	0	0.00			Tau	−0.173	−0.001	0.072	−0.010
Men	93	100.00	0	0.00	0	0.00	0	0.00	0	0.00			*P*	**.00**	.98	.13	.84

(Continues)

TABLE 1 (Continued)

	1		2		3		4		5		6							
	n	%	n	%	n	%	n	%	n	%	n	%		Sex	Age	Urban.	Redness	
Vitamin D supplements																		
Women	21	19.27	56	51.38	24	22.02	0	0.00	7	6.42	1	0.92	Tau	−0.096	0.130	0.015	−0.088	
Men	27	29.03	44	47.31	16	17.20	0	0.00	2	2.15	4	4.30	*P*	**.04**	**.01**	.75	.06	

Note: This table shows the distribution of responses of our subjects (and observers) to particular questions. The last four columns show the strength and significance (Tau and p) of Kendall correlations between variables listed in the first column and sex, age, urbanization and intensity of hair redness (controlled for age and urbanization), respectively. Positive Tau means that men, older subjects, residents of larger cities and more redheaded subjects provided higher codes of responses than women, younger subjects, residents of smaller cities and less redheaded subjects (see Material and methods). Significant correlations are printed in bold. Statistical significance below 0.005 is coded 0.00.

skin cancer in regions with lower intensity of solar radiation allowed for the spread of such alleles by a genetic drift.[32] Recent results, however, suggest that this explanation is probably incorrect, because the corresponding alleles show clear signs of positive selection.[25]

Another hypothesis suggested that red hair—similarly to other conspicuous traits, such as blond hair and blue or green eyes—had spread not due to its effects on viability but sexual selection, in particular, selection in favour of carriers of rare and conspicuous traits.[10,11] A new and more elaborate version of this hypothesis suggests that unlike alleles for other traits subjected to this form of selection, the frequency of alleles for red hair stayed very low in most populations because sexual selection was counterbalanced by natural selection associated with worse health in both male and, especially, female redheads.[11] Our results contradict these sexual selection-based hypotheses by showing that redheadedness could increase the viability of individuals in higher latitudes and may have therefore spread by natural selection. This conclusion finds further support in the results of a recent case-control study performed on a sample of 24,000 Swedish women, which showed that women with red hair or freckles have a survival advantage in low UV environment.[33] It is possible that the positive effects of redheadedness prevail over this trait's negative effects only in high latitudes, for instance in Sweden and Scotland, countries situated largely north of the 55° parallel,[34] while in other parts of the world, they are sustained by gene flow[35] and/or sexual selection.[10,11]

The currently most popular hypothesis regarding the persistence of redheadedness and fair skin suggests that the decrease of eumelanin concentration in fair-skinned subjects and decrease of the eumelanin-pheomelanin ratio in redheaded individuals (who are mostly but not always fair-skinned) are an adaptation for synthesis of sufficient amount of provitamin D in regions with low, seasonally fluctuating intensity of UVB radiation.[36-38] Our results, possibly for the first time, confirmed a higher concentration of 25(OH)D3 in the serum of redheaded subjects. On the other hand, they also showed that the situation is probably more complicated: the association between redheadedness and 25(OH)D3 concentration remained unchanged when the skin tone (light to dark) and even frequency of sun exposure and intensity of suntan were controlled for. This suggest that a factor other than eumelanin concentration (and skin fairness) is responsible for higher concentrations of 25(OH)D3 in redheaded individuals and that both traits, that is both red hair and fair skin, may well be two independent adaptations for life in environments with low UVB radiation.

Indeed, the results of genetic studies suggest that the concentration of 7-dehydrocholesterol, precursor of both vitamin D3 and cholesterol, rather than the concentration of 25(OH)D3, could be more important for the survival of humans in low UV radiation environment. The gene for 7-dehydrocholesterol reductase, the enzyme responsible for synthesis of cholesterol and therefore indirectly also the synthesis of previtamin D from their common substrate, was positively selected for rather recently in populations inhabiting higher latitudes, while genes responsible for the synthesis of

TABLE 2 The effects of variables related to body pigmentation and sun exposure behaviours on 25(OH)D3 and folic acid concentrations

	ALL				MEN				WOMEN			
	25(OH)D3		Folic acid		25(OH)D3		Folic acid		25(OH)D3		Folic acid	
	Tau	*P*	Tau	*P*	Tau	*P*	Tau	*P*	Tau	*P*	Tau	*P*
Age	−0.061	.210	0.210	**.000**	−0.070	.339	0.113	.148	−0.015	.820	0.285	**.000**
Urbanization	−0.062	.201	0.018	.722	0.024	.739	0.028	.723	−0.120	.072	0.016	.819
Hair redness	0.142	**.004**	0.002	.968	0.138	.060	−0.134	.086	0.149	**.027**	0.089	.195
Hair redness binary	0.229	**.000**	−0.017	.737	0.222	**.002**	−0.172	**.028**	0.239	**.000**	0.077	.265
Redness childhood	0.141	**.004**	0.004	.931	0.198	**.007**	−0.126	.107	0.110	.105	0.074	.286
Redness childhood binary	0.173	**.000**	−0.010	.851	0.252	**.001**	−0.167	**.033**	0.124	.064	0.099	.151
Body hair redness	0.203	**.000**	−0.018	.722	0.186	**.011**	−0.101	.196	0.236	**.000**	0.043	.537
Red hair relatives	0.072	.145	−0.091	.075	0.116	.114	−0.227	**.004**	0.036	.595	0.011	.875
Hair redness observer 1	0.192	**.000**	0.007	.884	0.165	**.025**	−0.112	.154	0.206	**.002**	0.062	.369
Hair redness observer 2	0.167	**.001**	−0.015	.763	0.185	**.012**	−0.097	.214	0.160	**.017**	0.047	.492
Reflect. 400	0.128	**.009**	−0.011	.833	0.159	**.030**	−0.118	.131	0.114	.090	0.084	.225
Reflect. 530	0.177	**.000**	0.016	.750	0.226	**.002**	−0.085	.275	0.146	**.029**	0.110	.112
Reflect. 650	0.204	**.000**	0.015	.768	0.231	**.002**	−0.062	.429	0.179	**.008**	0.082	.235
Hair redness R	−0.202	**.000**	−0.004	.937	−0.189	**.010**	−0.002	.978	−0.185	**.006**	0.014	.839
Hair redness a*	0.205	**.000**	0.012	.807	0.200	**.006**	−0.039	.614	0.189	**.005**	0.041	.552
Hair darkness	−0.117	**.016**	−0.006	.899	−0.132	.071	0.110	.159	−0.097	.147	−0.091	.185
Hair length	0.045	.357	0.039	.441	−0.074	.317	−0.108	.171	0.072	.283	0.149	**.031**
Baldness	0.048	.511	0.208	**.008**	0.048	.511	0.208	**.008**	NA	NA	NA	NA
Natural skin darkness	−0.036	.464	0.072	.159	0.031	.674	0.152	.052	−0.102	.127	0.010	.880
Suntan	0.151	**.002**	0.067	.189	0.191	**.009**	0.079	.311	0.111	.099	0.074	.286
Brown tanning	−0.035	.474	0.005	.925	−0.031	.672	0.102	.193	−0.051	.445	−0.047	.499
Red tanning	0.049	.317	0.007	.898	0.101	.167	−0.076	.334	0.024	.726	0.049	.477
Freckledness observer 1	0.120	**.014**	−0.024	.631	0.062	.395	−0.154	**.049**	0.142	**.034**	0.033	.628
Freckledness observer 2	0.121	**.013**	−0.031	.541	0.121	.099	−0.125	.110	0.121	.072	0.018	.789
Facial skin fairness	−0.066	.173	−0.016	.746	−0.202	**.006**	−0.136	.082	−0.087	.194	0.031	.658
Arm skin fairness	−0.079	.106	0.038	.460	−0.124	.091	−0.031	.687	−0.066	.323	0.055	.423
Protection by sun creams	0.043	.373	−0.032	.534	0.087	.238	−0.144	.066	−0.009	.898	0.023	.734
Protection by shelters	−0.079	.107	−0.039	.439	−0.084	.253	−0.107	.173	−0.086	.200	−0.006	.936
Sunbathing	0.114	**.020**	0.033	.521	0.208	**.005**	0.048	.543	0.052	.435	0.030	.666
Tanning salons	−0.016	.743	−0.140	**.006**	NA	NA	NA	NA	−0.043	.526	−0.209	**.002**
Vitamin D suppl.	0.003	.956	0.026	.659	0.010	.913	0.065	.493	−0.007	.928	−0.010	.894

Note: This table shows the strength and direction of partial Kendall correlations (controlled for age and urbanization) between variables listed in the first column (see Material and methods) and 25(OH)D3 and folic acid concentrations. Significant correlations are printed in bold. Statistical significance below 0.005 is coded 0.00.

25(OH)D3 from cholecalciferol carry no signs of recent positive selection.[39] Another study showed that redheaded men carry a lower risk of prostate cancer although their concentrations of 25(OH)D3 did not differ from control population.[24] All this suggests—but of course does not prove—that it is some molecule or molecules synthesized in parallel with 25(OH)D3, rather than 1,25-(OH)2D3, the biologically active product of 25(OH)D3, that is or are responsible for the beneficial effect of UV radiation.

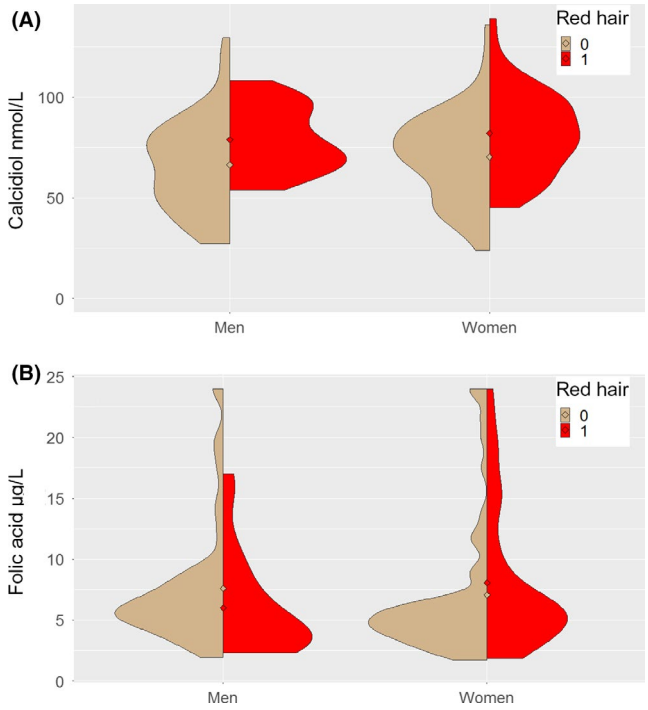

FIGURE 1 The effect of sex and red hair colour on 25(OH)D3 (calcidiol) and folic acid concentrations. The split violin plots for 25(OH)D3 (A) and folic acid (B) show the means and distribution computed as kernel probability density

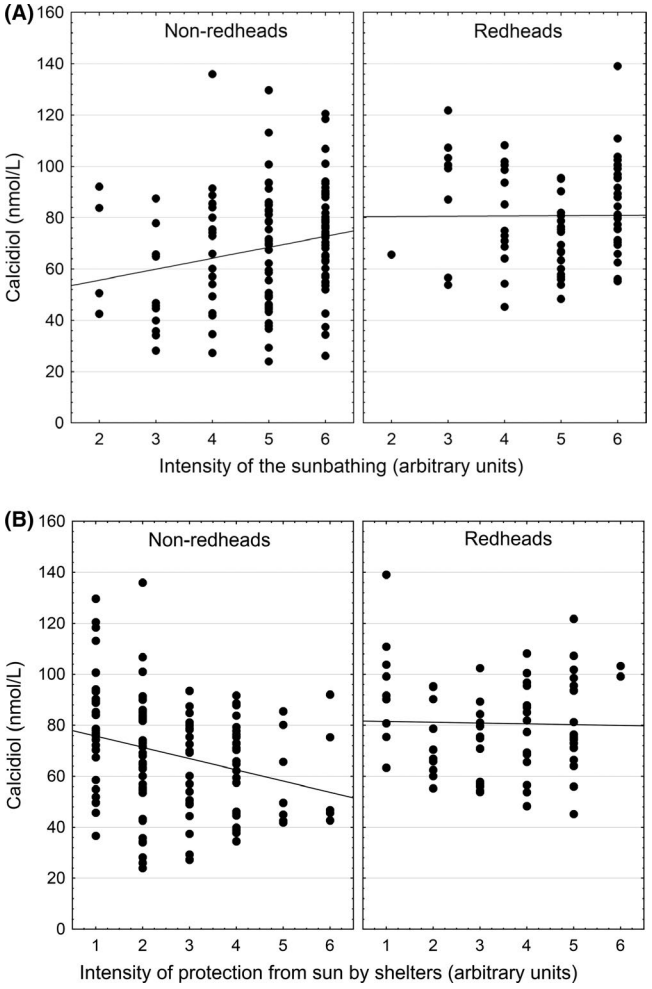

FIGURE 2 The effect of sun exposure on 25(OH)D3 (calcidiol) concentrations

Darker hues of natural hair but not of natural skin, both self-rated and measured spectrophotometrically, had a relatively strong negative effect on 25(OH)D3 concentrations. The two questions concerning natural skin hue and current tan were placed alongside each other in the questionnaire: it is therefore likely that responders rated the intensity of natural skin fairness or darkness as it looks untanned. The question on the darkness of natural hair, on the other hand, was in a different part of the questionnaire. It can be speculated that hair darkness actually reflects both the amount of eumelanin (positively) and intensity of sun exposure in the past (negatively). 25(OH)D3 levels, meanwhile, could be negatively affected both by high eumelanin levels and by absence of sun exposure. With respect to skin (but not hair), sun exposure promotes darker hues. The opposite effect of eumelanin levels, which are positively correlated with darker natural skin hues and suntan intensity (acquired skin darkness), on 25(OH)D3 concentrations cancel each other. The result is an absence of correlation between darker skin hues and 25(OH)D3 levels.

It is known that solar radiation destroys folic acid by photolysis.[40,41] One could thus expect that folic acid concentrations would negatively correlate with the intensity of sun exposure and intensity of suntan. Actual data, however, show only weak positive correlations, none of which reach the formal level of significance. The only significant (and relatively strong) negative correlation with folic acid concentrations was found with respect to the frequency of visiting tanning salons. This pattern is in agreement with current theories[42] according to which in human populations there exist two mutually independent skin darkness latitudinal gradients, the results of two distinct selection pressures. The first gradient is found in populations which originated between subtropical and subpolar latitudes, that is in the temperate climate. This gradient is the result of insufficient photosynthesis of vitamin D precursor in areas with low and seasonal solar UV radiation. The second gradient is found in populations which originated between the tropics and the subtropics, and its development was driven by excessive photolysis of folic acid in areas with intense solar radiation. The Czech Republic lies for the most part between 48° and 51° of northern latitude, where insufficient UV radiation rather than excess radiation could pose a problem, especially during the winter and spring months. It is indicative and perhaps clinically relevant that in our study, folic acid concentrations negatively correlated with the frequency of tanning salon visits.

We also found a rather strong positive correlation between the intensity of baldness and folic acid concentrations in men. Baldness intensity was not self-rated by women because our previous studies showed a minimal variability in this variable in young women. In men, however, both folic acid concentrations and baldness intensity strongly correlated with age. The strength of the correlation between folic acid concentration and baldness, however, was similar in

TABLE 3 The effect of sun exposure-related variables on 25(OH)D3 and folic acid concentrations and suntan intensity

	Redheaded subjects			Non-redheaded subjects		
	25(OH) D3	Folic acid	Suntan	25(OH) D3	Folic acid	Suntan
Natural skin darkness	0.015	0.097	**0.475**	0.091	0.050	**0.431**
Suntan	0.079	−0.010	NA	**0.241**	0.098	NA
Protection by sun creams	−0.073	−0.061	**−0.295**	0.012	−0.022	**−0.145**
Protection by shelters	0.050	0.068	−0.156	**−0.202**	−0.091	**−0.296**
Sun exposure	0.014	0.082	**0.337**	**0.168**	−0.009	**0.404**
Tanning salons	**−0.211**	−0.120	0.113	0.099	**−0.161**	−0.079

Note: The table shows the strength and direction (Taus) of partial Kendall correlations (controlled for age and urbanization) between variables listed in the first column (see Material and methods) and 25(OH)D3 and folic acid concentrations as well as suntan. Significant correlations are in bold.

cases where the age was (Tau = 0.21) and was not (Tau = 0.22) controlled for. In contrast to a general expectation, published data show no empirical evidence for an involvement of folic acid deficiency in alopecia.[43,44] Some studies even seem to support the notion of a positive association between folic acid and alopecia. For example, Rushton[45] shows that among 200 healthy women complaining of increased hair shedding for over 6 months, only one had a "bellow range" folic acid level, while 57 had "above range" folic acid levels. Another study reported no significant difference in folate concentrations in a population of 91 female patients diagnosed with diffuse hair loss and 74 controls.[46] Authors of that study did not, however, report folate concentrations in both groups, which may indicate that they had some unexpected results, such as lower folate concentrations in their controls.

As far as we know, our study is the first to have compared several methods of measuring the intensity of hair redness. Our results suggest that even the simplest method, that is the self-rating by participants, is satisfactory. Both methods of spectrophotometric measurement of hair redness worked similarly well, although the correlation between hair redness as estimated by subjects or other observers and hair redness as measured by the CIE L*a*b* colour space method as the a* parameter (and possibly also the reflectance at 650 nm) was slightly higher than the correlation with redness as R calculated from reflectance according to Reed's function. For example, partial Kendall correlation of self-rated hair redness with hair redness as a*, R and reflectance at 650 nm was 0.528, 0.461 and 0.484, respectively. Similarly, correlation with 25(OH)D3 concentration was stronger for hair redness measured as the a* parameter than with hair redness measured as R (Table 2).

The main aim of this study was to test the vitamin D deficiency hypothesis of impaired health of people with red hair.[17] This hypothesis suggests that, in the Czech population, many redheaded subjects avoid excessive sun radiation, which results in their fair skin and insufficient opportunity for the photosynthesis of precursor of vitamin D. Our results confirmed the first part of the hypothesis, but strongly contradicted its second part. The redheaded subjects indeed protected themselves more from direct sun radiation by chemical and mechanical means and had more pale hues of skin. But the same data also showed that they had higher, not lower, levels of 25(OH)D3 than non-redheaded subjects. In humans, photosynthesis from 7-dehydrocholesterol by classical[47,48] and non-classical pathways[9,49,50] is the main source of vitamin D, the hormone which plays the principal role in many health-related processes.[51] However, skin, the largest immune/endocrine organ in human body (about 15% of body weight), has an exceptionally complex metabolism and produces a broad spectrum of important bioactive molecules that act both locally and at the systemic level.[22,51] Solar radiation plays a direct or an indirect role in the synthesis of several of them.[52,53] We can modify the original hypothesis to suggest that it is not the lack of vitamin D but lack of another molecule which is normally synthetized in irradiated skin that is responsible for the impaired health of redheaded, fair-skinned subjects.

The main limitation of the present study is that our subjects cannot be considered a random sample of general Czech population. About half of the subjects who were asked to come to our laboratory to participate in an about 40-minute-long experiment politely refused. A few also refused to provide a blood sample for serological analysis. It is possible that persons who consented to participation and actually came to the experimental session form a specific population, for instance a group of highly altruistic subjects in good mood and good physical and mental condition. It is known that certain genetic and environmental factors influence variance more than physiological variables do.[54] Such factors may have, for example, negative effects on the health of a specific part of the population and positive effects on the health of others in the same population. If subjects who enjoy good health are more likely to be enrolled in the study (as may have been the case here), we may end up concluding that a particular factor, for instance redheadedness, has a positive effect on health and health-related variables although it has either no effect or even a negative effect on most members of a fully general population. Similarly, if subjects in poor health are more likely to be enrolled in a study—which is often the case with studies performed

on patients with and without a particular disorder—a study can show that a particular factor has a negative effect on health although in majority of general population, its effect is positive.

Our data suggest that such a sieve effect operated in our study, too. Firstly, latent infection with the common *Toxoplasma* parasite has a wide range of negative effects on the health of most members of the general population.[55,56] In our study, however, *Toxoplasma*-infected subjects enjoyed significantly better health than those who were *Toxoplasma*-free. (The effect of toxoplasmosis on health and well-being was a subject of another study performed on the same population of volunteers.) Secondly, a visual inspection of the violin plots for 25(OH)D3 and folic acid concentrations suggests that the distribution is truncated at the bottom and a subpopulation of individuals with a low concentration of these vitamins is missing from our sample. In a democratic country where people can refuse to participate in a study, the issue of non-representativeness of a sample due to sieve effect linked to the requirement of obtaining informed consent is hard or even impossible to avoid. It can be merely mitigated by making participation as easy and convenient as possible. It would be therefore most advisable to repeat our study on different populations of subjects who would not be selected or self-selected for better health.

5 | CONCLUSION

Based on previous observations of impaired health in fair-skinned people,[17] we predicted that redheaded subjects, who can be expected avoid sun exposure because of their sensitive skin, would have lower 25(OH)D3 levels. We confirmed that they indeed protect their skin from the sun by chemical and mechanical means. Nevertheless, we also found that in our self-selected sample, redheaded individuals had significantly higher 25(OH)D3 levels regardless of intensity of sun exposure. This discovery suggests that hair redness, the result of eumelanin synthesis downregulation and pheomelanin upregulation, could be an evolutionary adaptation to life in higher latitudes where the photosynthesis of vitamin D precursor in skin is inadequate for large part of the year due to a low intensity of solar radiation. Our results suggest that redheaded individuals are capable of synthesizing sufficient amounts of 25(OH)D3 even when their sun exposure is minimal. Nonetheless, we should be cautious about generalizing this observation. This phenomenon was observed in two medium-sized samples of 93 men and 110 women who passed a relatively stringent self-selection process.

Until this phenomenon is demonstrated in other, more representative populations, especially those living north of the 55° parallel, such as Scotland or Sweden, our conclusions must be considered merely preliminary.

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CONFLICT OF INTEREST

The authors have declared no conflicting interests.

AUTHOR CONTRIBUTIONS

JF and KS designed research. KS, VF, JH, MB, LM and ŠK performed research. JF analysed data and wrote the paper.

DATA AVAILABILITY STATEMENT

The final raw data set is available at figshare: https://figshare.com/s/50f5d6145b93a9892801.

ORCID

Jaroslav Flegr https://orcid.org/0000-0002-0822-0126

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