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POINT OF VIEW

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THE INFLUENCE OF DIET AND NUTRITIONAL STEREOTYPES ON THE BIOLOGICAL AGE OF THE INDIGENOUS POPULATION OF THE REPUBLIC OF SAKHA (YAKUTIA)

The study is devoted to assessing the impact of nutrition on accelerating or slowing down biological age in the indigenous population of Yakutia. The study involved 84 participants aged 18 to 89 years living in the central region of Yakutia. The average age of respondents was 58.0 (21.1) years. To analyze the food composition, the frequency questionnaire containing 30 questions were used. Using K-means method of the cluster analysis, two types of the nutrition were identified among the respondents. We assessed the age acceleration, calculating using three biological clock models: Horvath DNAm, Hannum DNAm, GrimAge in these groups of participants. Binary logistic regression showed that the odds of slowing biological ages increased with a moderate diet for Hannum DNAm by 6.3 times, Horvath DNAm by 21 times, and GrimAge by 15.8 times. The frequent overeating had a negative impact on the biological age of respondents. The frequency of consumption of dairy, fried, canned, salted products, and processed meat statistically significantly affected biological age. Acceleration of epigenetic age was observed in respondents with nutritional errors in the form of overeating and frequent consumption of easily digestible, high-calorie, canned foods.

Keywords: epigenetic age, Horvath DNAm, Hannum DNAm, GrimAge, age acceleration, Yakutia, indigenous population, aging, nutrition.

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Introduction. The indigenous population of the Republic of Sakha (Yakutia) is characterized by an evolutionarily developed polar (northern) type of metabolism and a protein-lipid rich diet, which is more physiological in the conditions of the sharply continental subarctic climate of the region [2, 5, 18]. The global transformation from the traditional lifestyles and nutrition, occurring in the last century, has contributed to changes in the structure of prevalent diseases and the increase of chronic non-communicable diseases among the indigenous peoples of the North [1, 3, 5, 6].

Advances in epigenetic research and bioinformatics technologies have led to the creation of "aging clocks" – digital models that allow quantitative assessment of the aging process, health level and adaptive reserve of the body [4, 11, 14]. The most well-known and studied biological clocks are Hannum DNAm [11] Horvath DNAm [12, 13], GrimAge [19], which assess biological age based on the methylation level of the genome CpG sites. Our previous study has revealed differently methylated sites in many areas of the genome when comparing the Yakut population with residents of central Russia. Representatives of the Yakut population have demonstrated a statistically significant acceleration of epigenetic age relative to central Russia for the Horvath DNAm age, Hannum DNAm age, DNAm PhenoAge, GrimAge and their improved models [15].

Studies on model organisms have shown that calorie restriction in nutrition prevents age-related changes in the methylome [8], remodels DNA profiles of genes associated with diabetes mellitus,

inflammation and cardiovascular diseases [16], and significantly improves survival [9]. Intervention studies in humans have confirmed the positive effects of a low-calorie diet, rich in polyphenols (vegetables, fruits, legumes, nuts), as well as limiting the consumption of red meat, sugars and alcohol, on DNA methylation [8-10, 20, 21].

Thus, studying of the relationship between the overall quality and stereotypes of nutrition and epigenetic markers can expand knowledge about the molecular genetic mechanisms of the influence of diet on the quality and duration of people life. The aim of the study was to assess the influence of nutrition on the acceleration or deceleration of biological age in the indigenous population of Yakutia.

Materials and methods. The study was conducted in 2022 among the unorganized indigenous population living in Tattinsky and Churapchinsky districts and in the city of Yakutsk in the Republic of Sakha (Yakutia). The study included data from 84 respondents, including 41 men (48.8%) and 43 women (51.2%). The average age was 58.0 ± 21.1 years (range 18 to 90 years). Participation in the study was voluntary. All participants were representatives of the indigenous population of Yakutia (Yakuts). The study was approved by the local committee on biomedical ethics of the NEFU Medical Institute (protocol No. 34 dated March 30, 2022). Exclusion criteria were acute and chronic diseases in the acute stage, pregnancy.

The survey included an analysis of socio-demographic parameters, a frequency-based assessment of nutrition, and a study of the respondents' lifestyle, including their level of physical activity. Anthropometric parameters, blood pressure and heart rate were also measured and assessed.

DNA methylation analysis was performed using the Illumina Infinium MethylationEPIC BeadChip platform [15]. Methylation data were estimated using the Horvath online calculator (https://dnamage.clockfoundation.org/) [12]. The Hannum DNAm method is based on the analysis of methylation levels of specific CpG sites associated with age-related changes [11]. Horvath DNAm is a multi-tissue age predictor based on 353 CpG sites that allows estimation of DNA methylation age in most tissues and cell types [12, 13]. GrimAge was developed based on 7 CpG sets, 8 plasma proteins and pack-years of smoking [19].

A statistical analysis was performed using IBM SPSS STATISTICS 22 and StatTech v. 4.8.0 packages (StatTech LLC, Russia). The normality of the distributions of quantitative indicators was determined by the Shapiro-Wilk and Kolmogorov-Smirnov tests. Comparison of groups by quantitative indicators was performed using Student's t-test, Mann-Whitney U-test, Welch's t-test. Comparison of percentages was performed using Pearson's chi-square test and Fisher's exact test. The values of $p < 0.05$ were considered statistically significant. The K-means clustering method was also used. The logistic regression method was used to develop the prognostic model.

Results and discussion. Age acceleration Hannum Acc, Horvath Acc, GrimAge Acc was estimated by subtracting chronological from epigenetic ages. The sample characteristics are presented in Table 1. Given the small sample size and the weak acceleration of biological ages, we focused on the median value of age acceleration for each epigenetic clock. When age acceleration is higher than the median value of the corresponding epigenetic clock, it was considered that there is a tendency towards age acceleration, when values are lower than the median - a tendency towards deceleration. The use of the median in such analyses allows to minimize the influence of outliers and increase the accuracy of interpretation.

Using K-means clustering, two groups were identified based on nutritional characteristics: Group 1 included 51 respondents with nutritional errors (overeating, frequent consumption of fried, salted, canned, processed foods), and Group 2 included 26 respondents with a moderate diet. This second type of diet can be characterized as conservative. This approach to clustering is consistent with modern research, in which the analysis of dietary patterns allows us to more accurately determine their impact on biological aging.

Using the binary logistic regression method, predictive models were developed to determine the probability of acceleration or deceleration of the biological clock of Hannum DNAm, Horvath DNAm, GrimAge depending on the nutrition cluster. The resulting regression models were statistically significant ($p<0.001$). The number of observations was 77. In the model for Hannum DNAm R^2 Nigelkirk's was 20.6%, and the chanc-

Socio-demographic characteristics of respondents. frequency of some risk factors and indicators of age acceleration

Parameter	Group	n	Value
Age (years)*	both sexes	84	58.0 (21.1)
Sex#	female	43	51.2 (95% CI 40.0 – 62.3)
	male	41	48.8 (95% CI 37.7 – 60.0)
Marital status#	family	51	60.7(95% CI 49.5 – 71.2)
	not family	33	39.3(95% CI 28.8 – 50.5)
Education#	higher	37	44.0 (95% CI 33.2 – 55.3)
	not higher	47	56.0 (95% CI 44.7 – 66.8)
Body mass index. kg/m2*	both sexes	84	24.8 (21.8 – 28.3)
Weight (kg)**	both sexes	84	66.3 (14.4)
SBP (mmHg) **	both sexes	84	132.1 (17.2)
DBP (mmHg) *	both sexes	84	82.0 (75.7 – 90.0)
Obesity#	there is obesity	16	19.0 (95 % CI 11.3 – 29.1)
	norm	68	81.0 (95 % CI 70.9 – 88.7)
Abdominal obesity#	presence	16	19.0 (95% CI 11.3-29.1)
	absence	50	59.5 (95% CI 48.3 – 70.1)
Adaptation potential#	satisfactory	5	23.8 (95% CI 8.2 – 47.2)
	voltage	10	47.6 (95% CI 25.7 – 70.2)
	unsatisfactory	1	4.8 (95% CI 0.1 – 23.8)
	failure of adaptation	5	23.8 (95% CI 8.2 – 47.2)
Hypodynamia#	there is hypodynamia	11	52.4 (95% CI 29.8 – 74.3)
	no	10	47.6 (95% CI 25.7-70.2)
Hannum Acc**	both sexes	84	-10.25 (7.06)
Horvath Acc**	both sexes	84	4.29 (7.21)
GrimAge Acc**	both sexes	84	-10.59 (5.73)

Note: data are presented: * - as median and interquartile range (Me (Q1 - Q3); ** - as mean and standard deviation (M (SD)); # - as proportions and 95% confidence intervals (CI).

es of slowing biological age increased by 6.3 times with moderate nutrition. For Horvath DNAm R^2 Nigelkirk's was 37.8%, with the odds of slowing biological age increasing 21-fold with moderate nutrition. For GrimAge R^2 Nigelkirk's was 33.0%, with the odds of a slowing trend increasing by 15.8 times in the presence of moderate nutrition.

Modern research confirms the importance of moderate nutrition to slow down aging. Thus, numerous studies have shown that a balanced diet, rich in antioxidants, vitamins and minerals can slow down age-related changes at the molecular level, including through epigenetic mechanisms [5, 7, 8, 18 19]. In our study, we also observe that moderate nutrition is associated with slower biological age across all three epigenetic clock models. Thus, in Figure 1 it is clear that respondents with a moderate type of nutrition tend to slow down their biological age, while respondents with nutritional errors tend to speed it up.

To analyze the food composition, the frequency questionnaire containing 30 questions were used. The frequency of food consumption was assessed according to 4 gradations: daily, 1-2 times a week, rarely, never. When analyzing these data, we found a statistically significant ($p< 0.001$) tendency to accelerate all studied epigenetic ages with frequent consumption of fried, salted, canned foods, and processed meat. The acceleration of all epigenetic ages examined in this study in individuals who frequently consume fried and processed foods is consistent with the idea that diets high in trans fats and preservatives increase inflammation and accelerate aging. A statistically significant trend towards acceleration according to the Hannum DNAm biological clock was also observed with frequent consumption of easily digestible foods such as cakes, cookies, and candies ($p<0.029$) and according to GrimAge with frequent consumption of salty and pickled foods ($p<0.04$).

It is interesting that, according to the results of the study, frequent consumption of dairy products was associated with a slowdown in biological age according to Horvath DNAm ($p<0.005$), Hannum DNAm ($p<0.011$), GrimAge ($p<0.029$). The literature on the relationship between dairy consumption and slower aging is somewhat inconsistent. However, there is some research that suggests dairy may have a positive effect on biological age, due to its calcium, vitamins D and B12, and probiotics that support gut health and metabolic processes. For example, a study conducted in the United States found that moderate dairy consumption was associated with improved metabolic health and reduced signs of aging at the cellular level [15].

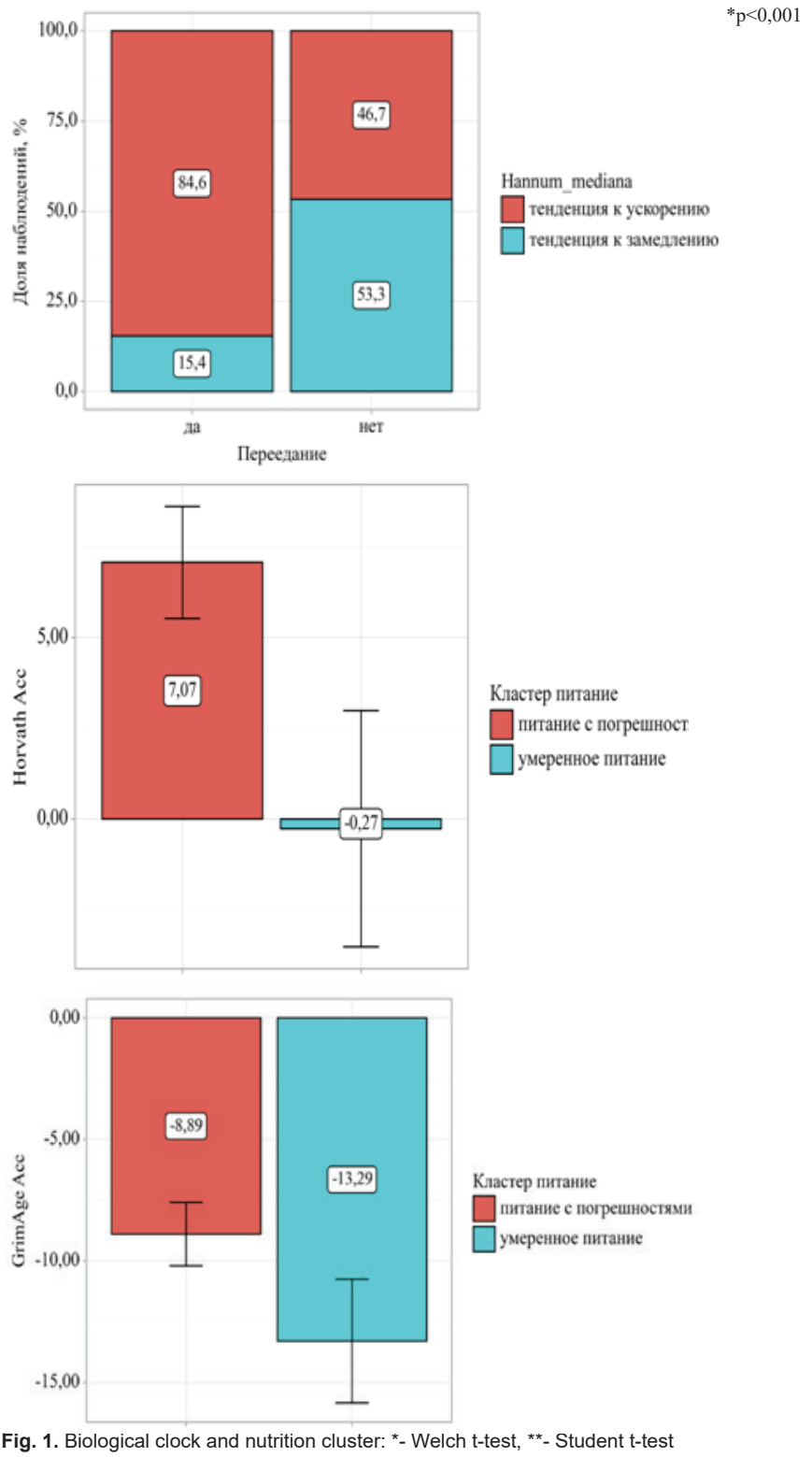

Fig. 1. Biological clock and nutrition cluster: *- Welch t-test, **- Student t-test

The study did not establish statistically significant associations of biological acceleration and the frequency of consumption of fish, vegetables and fruits; this is most likely due to the fact that these products are not consumed very often by observed participants.

A separate analysis of the answers to the question: "Do you think you overeat?" revealed that respondents who had a tendency to overeat had a tendency to accelerate age according to Hannum DNAm in 84.6% versus 46.7% of people who do not overeat, according to Horvath

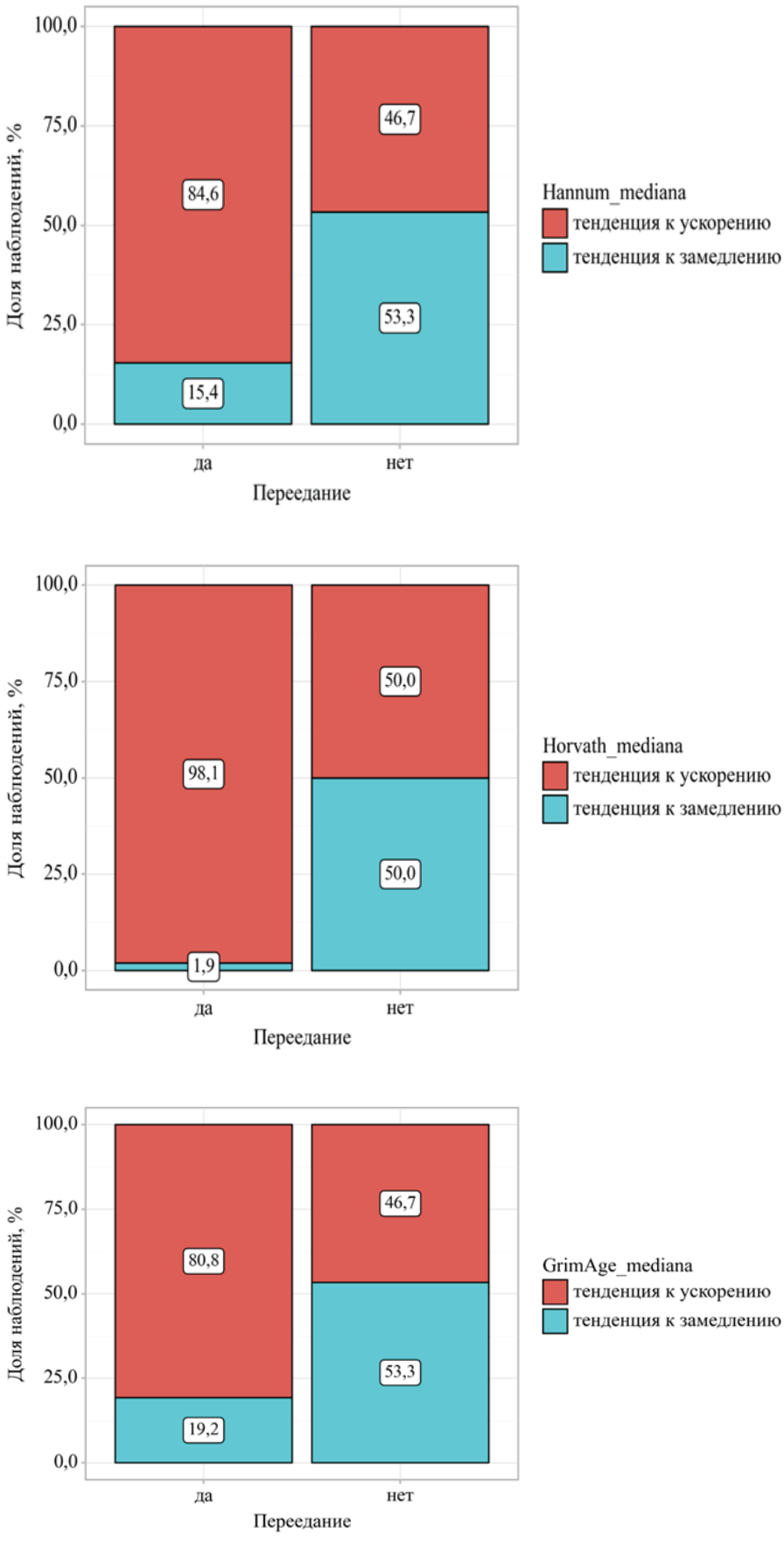

Fig. 2. Age acceleration depending on the answer to the question: “Do you think that you overeat?” (the method used is Fisher's exact test)

DNAm in 98.1% versus 50%, respectively, according to GrimAge in 80.8% versus 46.7%, respectively. This result is consistent with modern studies indicating the negative impact of excessive food consumption on epigenetic aging processes [7, 9, 10, 20, 21].

Conclusion. This study analyzed for the first time the influence of nutrition on age acceleration in the indigenous population of Yakutia. Despite the small size of the study sample, we have established the negative influence of overeating, frequent consumption of fried, canned products, processed meat, and easily digestible products on the epigenetic age. A predictive regression model has been developed to determine the probability of acceleration or deceleration of the epigenetic clock depending on the type of nutrition. Respondents who adhered to a moderate diet had a 6.3-fold chance of slowing down their biological age for Hannum DNAm, 21-fold for Horvath DNAm, and 15.8-fold for GrimAge. Our study confirms that moderate nutrition has a beneficial effect on slowing down biological age, which in the future may form the basis for the development of personalized nutrition programs to prevent aging and increase lifespan.

Further studies with larger sample sizes and more in-depth nutritional studies with the additional clinical parameters will help identify new factors that contribute to accelerated aging.

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The authors declare no conflict of interest in the submitted article.

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CLINICAL CASE

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A CLINICAL CASE OF THE COMBINED ACUTE PROMYELOCYTIC LEUKEMIA AND JUVENILE IDIOPATHIC ARTHRITIS

A clinical case of enteritis-associated juvenile arthritis during the therapeutic stage of consolidation of acute promyelocytic leukemia is presented in the article. It describes the clinical case of a 16-year old teenager. Arthritis in a patient with leukemia is commonly associated either with an exacerbation of the underlying disease or with an infectious process in the joint or the adjacent bone. Leukemic arthritis is commonly manifested by monoarthritis, involving large joints and presented with severe night pain, lymphadenopathy, and hepatosplenomegaly. Joint pain reduction is a sign of a clinical response to chemotherapy.

Musculoskeletal system involvement caused by infection is represented by local inflammatory process accompanied with fever, local hyperemia, hyperthermia, inflammatory changes in blood test results and requires a course of intensive antibacterial therapy with the temporary cessation of chemotherapy. The development of juvenile idiopathic arthritis during leukemia therapy caused diagnostic and therapeutic difficulties due to uncommonly rare association of the both diseases, which required the exclusion of leukemia recurrence and an infectious complication. NSAID therapy brought temporary relief, janus kinase blocker (upadacitinib therapy) was ineffective, only subsequent switching to etanercept allowed the remission of arthritis. Leukemia treatment was carried out in conjunction with JIA treatment.

Keywords: acute promyelocytic leukemia (APL), juvenile idiopathic arthritis, leukemia chemotherapy, myelogram, children and adolescents.

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Introduction. Acute promyelocytic leukemia results from the variant of a gene, caused by abnormal overgrowth of promyelocytes. Acute promyelocytic