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GENETIC LOAD IN HUMAN POPULATIONS THROUGH THE PRISM OF LOCAL INBREEDING

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Background. Assessing genetic load is relevant in connection with active migration and population decline, especially in combat zones. This study aimed to analyse the dynamics of genetic disorder prevalence depending on demographic characteristics in Eastern Ukraine.

Materials and Methods. A cross-sectional population-based impersonal study was performed in four districts of the Kharkiv region as a typical area of Eastern Ukraine. The mean age, mean migration distance, and marital distance of women aged up to 45 years and men aged up to 55 years were assessed from district marriage records of the year 2015. The prevalence of genetic disorders among children aged 0–17 years was estimated based on district medical registries. The genetic structure of the population was estimated through the local inbreeding coefficient F_{ST}.

Results and Discussion. Data for 1427 marriages and 187 children with genetic disorders were analysed. The mean age at marriage, mean migration distance, and marital distance were 27.8 ± 0.1 years, 179.0 ± 15.0 km, and 320.4 ± 28.4 km. F_{ST} accounted for 0.000074–0.012949 and was up to 17.2 times greater (p = 0.0012) in rural areas than in urban ones. The overall F_{ST} across four districts was 0.001292, representing a 1.8-fold increase (p = 0.001477) over seven years. The prevalence of 39 single-gene and 4 chromosome disorders was 0.36 % and 0.08 %, with a positive trend over time. The most common disorders were sensorineural hearing loss (1 : 859), isolated growth hormone deficiency (1 : 3438), ichthyosis vulgaris (1 : 3750), cystic fibrosis (1 : 6875), and Down syndrome (1 : 1331). The prevalence of single-gene disorders in rural populations was 4.3 times greater than in urban ones – 1.29 % and 0.30 % (p = 0.007). F_{ST} was positively correlated with the prevalence of autosomal recessive disorders (r = 0.82, p < 0.001) and chromosomal abnormalities (ρ = 0.90, p < 0.001).

Conclusion. In the region of study, an upward trend was observed in the inbreeding coefficient (F_{ST}), which has doubled across both urban and rural settlements over a seven-year period, reaching a value of 0.001292. This rise in local inbreeding is associated with an increased genetic load within the population, particularly concerning not only single-gene, but also chromosomal abnormalities. Both urban and rural populations exhibited a wide spectrum of genetic disorders, comprising 39 single-gene nosological entities and 4 chromosomal ones. When forecasting healthcare and social support needs, it is advisable to take into account the higher prevalence rates of genetic disorders in rural areas.

Keywords: genetic and demographic characteristics, inbreeding, prevalence, single-gene disorders, chromosomal abnormalities

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INTRODUCTION

Considering the dynamics of demographic indicators in European and world countries (European Commission, 2026), studies of human disorders using genetic, epigenetic, environmental and systems data play a crucial role, in particular, in assessing the ethno-territorial distribution of common and unique genetic determinants of diseases and drug response.

On the one hand, monitoring of single-gene, chromosome and multifactorial disorders as sentinel phenotypes is one of the approaches to evaluate mutation rates and genetic load to assess the genetic and ecological safety of the population (Motsinger-Reif *et al*., 2024; Virolainen *et al*., 2023; Fedota *et al*., 2020a; Fedota *et al*., 2020b). On the other hand, the prevalence of normal and pathological traits in a population is largely determined by marriage patterns, migration distance, and the level of inbreeding (Khayat *et al*., 2024; Yengo *et al*., 2019), and genetic markers provide an objective measure of ancestry that is not influenced by environmental factors (Motsinger-Reif *et al*., 2024).

Characterization of the population structure is necessary for the development and planning of integrated molecular solutions in testing genetic disorders, modelling and understanding evolutionary processes, and establishing guidelines and policies for the appropriate use of genetic information in clinical practice and public health (Swinford *et al*., 2023; Ceballos *et al*., 2021).

In Ukraine, genetic and demographic processes had been studied both in regions as a whole and in small settlements until 2022. It seems relevant to analyse the marriage and migration characteristics of the population with an assessment of its genetic load. In addition, due to the active migration of the population of Eastern Ukraine from combat zones, it is advisable to present its genetic characteristics.

This study aimed to analyse the dynamics of genetic disorders prevalence depending on demographic characteristics in Eastern Ukraine.

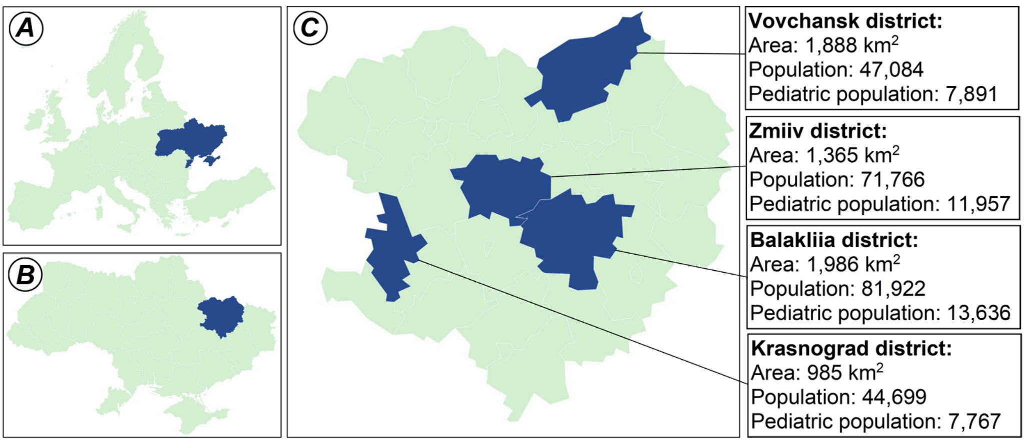
MATERIALS AND METHODS

Study design. The materials for this cross-sectional population-based study were collected in four districts of the Kharkiv region – Balakliya, Krasnohrad, Vovchansk, and

Zmiiv (see **Figure**) from July 2016 to December 2021. The Kharkiv region is located in Eastern Ukraine. Its area is 31,400 km², which is 5.2 % of the total territory of the state. Its population was estimated as 2.7 million in 2015.

The data on the birthplaces and ages of men and women who got married in 2015 were obtained from the marriage records in the state and local government bodies. Marriage records were excluded from the study if women were aged over 45 years, men were aged over 55 years, or both partners were not local residents.

The medical information on patients born from 1999 up to and including 2015, who had been diagnosed and registered at local and regional hospitals with any genetic or congenital disorder, was collected and analysed until 2022 to obtain comprehensive data on the state of health of offspring in marriages contracted in 2015. Only patients with diagnoses confirmed by genetic testing or karyotyping were included in the study.



Characteristics of districts included in the study: Ukraine in Europe (***A***), Kharkiv region in Ukraine (***B***) and the studied districts in Kharkiv region (***C***)

The following indicators of newly married couples were calculated: mean age, mean migration distance, marital distance, and prevalence of genetic disorders. The genetic structure of urban and rural populations was estimated through the local inbreeding coefficient (or fixation index) F_{ST}:

$$F_{ST} = 1/(4Nm + 1),$$

where N is the effective population size of each population and m is the migration rate between populations (Wright, 1931).

The effective population size is estimated as one-third of the census population size (Cavalli-Sforza & Bodmer, 2013).

Statistical analysis. Statistical processing was performed using Statistica Basic Academic (version 13.3, TIBCO Software Inc., Palo Alto, CA, USA). The normality of the distribution of continuous variables was tested by the Shapiro–Wilk test and one-sample Kolmogorov–Smirnov test. Variables were expressed as the mean ± S.E. Means of 2 normally distributed variables were compared by Student's unpaired *t*-test. The Mann–Whitney *U*-test and Kruskal–Wallis *H*-test were used to compare means of 2 and multiple groups of non-normally distributed variables, respectively. The Wilcoxon signed-rank

T-test was performed for two related samples. The Z-score was calculated for 2 population proportions. Correlations between groups were assessed by means of Pearson and Spearman correlation. A two-tailed $p < 0.05$ was considered statistically significant.

Ethics approval statement. The study was carried out in compliance with the basic provisions of the "Rules of ethical principles of scientific medical research with human participation", approved by the Declaration of Helsinki (1964–2013), ICH GCP (1996), EEC Directive No. 609 (dated 24.11.1986), Orders of the Ministry of Health of Ukraine No. 690 (dated 23.09.2009), No. 944 (dated 14.12.2009), No. 616 (dated 03.08.2012). The protocol for this study was approved by the Ethics Committee of Kharkiv National Medical University (registration number 21, date: 02.04.2025). The materials obtained for the study were completely anonymous and did not contain personal information by which individuals could be identified.

RESULTS

Marriage age. Among the 1582 aggregate marriage records collected, data for 1427 (90.2 %) records were analysed after exclusions. The mean age at marriage in Eastern Ukraine was 27.8 ± 0.1 years, with figures varying from district to district (**Table 1**). In Zmiiv district, this indicator was 1.5 years higher than in Vovchansk district ($p = 0.0001$). There were no statistically significant differences in the mean age at marriage in urban populations between the districts, but in rural areas it approached 2.0 years ($p < 0.05$). In Vovchansk and Krasnohrad districts, the mean age at marriage was lower in rural areas than in urban areas ($p < 0.05$) (**Table 1**).

The mean age of women at marriage was 26.3 ± 0.2 years (with the interval between 25.6 ± 0.4 years in Vovchansk district and 27.3 ± 0.3 years in Zmiiv district). Women in urban areas got married at an older age than those in rural areas – 26.7 ± 0.3 and 26.1 ± 0.2 years ($p = 0.018034$), respectively. That value ranged within 1.3 years in towns and 2.5 years in villages (**Table 1**). The mean age of men at marriage was 29.2 ± 0.2 years, from 28.4 ± 0.4 years in Vovchansk district to 29.8 ± 0.3 years in Zmiiv district. Despite the fluctuations of those figures at approximately 1.3 years in towns and 1.9 years in villages, the values did not differ significantly in those settlements: 29.6 ± 0.3 years and 28.9 ± 0.2 years, respectively (**Table 1**). The mean age at marriage gap between men and women was the largest in the town of Krasnohrad and amounted to 3.5 years (**Table 1**).

Marriage migration. The mean migration distance of the population was 179.03 ± 14.95 km and varied between the districts. In Vovchansk district it was 76.20 km longer than in Balakliya district ($p = 0.0073$) (**Table 2**). The values in urban areas were greater than those in rural areas: 191.77 ± 25.14 and 171.64 ± 18.59 km ($p < 0.000001$), respectively. In the towns, which are the administrative district centers, they ranged from 125.43 ± 36.99 km in Balakliya to 244.66 ± 71.49 km in Vovchansk, and in villages ranged from 152.74 ± 27.43 km in Zmiiv district to 218.94 ± 52.59 km in Krasnohrad district ($p < 0.05$) (**Table 2**).

In marriage-related migration, women moved over 151.83 ± 16.68 km, with extreme values from 108.69 ± 21.44 km in Balakliya district to 218.27 ± 62.64 km in Vovchansk district ($p = 0.0398$) (**Table 2**). In towns, the migration distance for women varied between 82.09 ± 31.24 km in Balakliya and 218.09 ± 65.58 km in Zmiiv, while in villages it varied

Table 1. **Mean and median age at marriage in Eastern Ukraine in 2015**

Gender	Area						
	Urban		Rural		*p*-value	District in total	
	Mean ± S.E., years	Median (IQR), years	Mean ± S.E., years	Median (IQR), years		Mean ± S.E., years	Median (IQR), years
Balakliya district							
Women	26.5 ± 0.5	25.0(22.0–30.0)	25.9 ± 0.4	24.0(21.0–29.0)	0.160384	26.1 ± 0.3	24.0(22.0–29.0)
Men	29.6 ± 0.6	28.0(24.0–33.0)	29.1 ± 0.4	27.0(24.0-33.0)	0.573591	29.3 ± 0.3	28.0(24.0–33.0)
p-value	0.000053		<0.00001		–	< 0.000001	
Total	28.1 ± 0.4	27.0(23.0–32.0)	27.5 ± 0.3	26.0(23.0–32.0)	0.187290	27.7 ± 0.2	26.0(23.0–32.0)
Krasnohrad district							
Women	26.3 ± 0.5	24.5(22.0–30.0)	25.3 ± 0.4	24.0(21.0–28.0)	0.193588	25.8 ± 0.3	24.0(21.0–29.0)
Men	29.8 ± 0.6	27.5(25.0–32.0)	27.8 ± 0.5	26.0(24.0–30.0)	0.017211	28.7 ± 0.4	27.0(24.0–31.0)
p-value	0.000011		0.000017		–	< 0.000001	
Total	28.0 ± 0.4	26.0(23.0–31.0)	26.6 ± 0.3	25.0(22.0–29.0)	0.017477	27.2 ± 0.3	26.0(23.0–30.0)
Vovchansk district							
Women	26.7 ± 0.6	25.0(22.0–31.0)	24.7 ± 0.6	23.0(20.0–28.0)	0.006031	25.6 ± 0.4	24.0(21.0–29.0)
Men	28.8 ± 0.7	27.0(24.0–32.0)	28.1 ± 0.6	27.0(23.0–31.0)	0.421918	28.4 ± 0.4	27.0(24.0–31.0)
p-value	0.011727		0.000006		–	0.000001	
Total	27.7 ± 0.5	26.0(23.0–31.0)	26.4 ± 0.4	25.0(22.0–29.0)	0.014475	27.0 ± 0.3	26.0(22.0–30.0)
Zmiiv district							
Women	27.6 ± 0.6	25.5(23.0–32.0)	27.2 ± 0.4	25.0(22.0–31.0)	0.366836	27.3 ± 0.3	25.0(22.0–31.0)
Men	30.1 ± 0.6	28.0(25.0–32.0)	29.7 ± 0.4	28.0(24.5–33.0)	0.355832	29.8 ± 0.3	28.0(25.0–33.0)
p-value	0.001630		< 0.000001		–	< 0.000001	
Total	28.8 ± 0.4	27.0(24.0–33.0)	28.4 ± 0.3	27.0(23.0–33.0)	0.218559	28.5 ± 0.2	27.0(24.0–32.0)

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Table 2. **Mean and median migration distance in Eastern Ukraine, km**

Gender	Area						
	Urban		Rural		*p*-value	District in total	
	Mean ± S.E., km	Median (IQR), km	Mean ± S.E., km	Median (IQR), km		Mean ± S.E., km	Median (IQR), km
Balakliya district							
Women	82.09 ± 31.24	0.00(0.00–23.50)	124.84 ± 28.76	11.00(0.00–48.70)	0.000027	108.69 ± 21.44	6.50(0.00–40.30)
Men	168.76 ± 67.01	0.00(0.00–31.80)	184.67 ± 60.65	0.00(0.00–67.80)	0.046221	178.66 ± 45.40	0.00(0.00–58.30)
p-value	0.446856		0.000451		–	0.001060	
Total	125.43 ± 36.99	0.00(0.00–27.60)	154.75 ± 33.56	6.3(0.0–51.7)	0.000010	143.68 ± 25.12	0.00(0.00–47.25)
Krasnohrad district							
Women	149.68 ± 50.53	4.20(0.00–59.60)	218.26 ± 69.46	13.80(4.20–66.00)	0.005861	188.24 ± 44.86	10.30(0.00–59.60)
Men	242.58 ± 87.28	0.00(0.00–23.40)	219.62 ± 79.20	4.20(0.00–39.80)	0.025600	229.67 ± 58.58	0.00(0.00–34.70)
p-value	0.013844		0.000378		–	0.000019	
Total	196.13 ± 50.41	0.00(0.00–40.85)	218.94 ± 52.59	7.25(0.00–52.00)	0.000477	208.96 ± 36.87	4.50(0.00–47.60)
Vovchansk district							
Women	182.84 ± 89.31	0.00(0.00–76.70)	248.94 ± 87.89	17.40(0.00–89.70)	0.020896	218.27 ± 62.64	10.60(0.00–76.70)
Men	306.49 ± 111.77	0.00(0.00–76.70)	147.93 ± 29.42	6.00(0.00–69.90)	0.081146	221.49 ± 54.32	0.00(0.00–76.70)
p-value	0.293998		0.117091		–	0.068833	
Total	244.66 ± 71.49	0.00(0.00–76.70)	198.44 ± 46.36	12.30(0.00–80.80)	0.004517	219.88 ± 41.41	7.80(0.00–76.70)
Zmiiv district							
Women	218.09 ± 65.58	3.50(0.00–77.20)	110.77 ± 18.55	8.20(0.00–43.70)	0.382342	138.91 ± 22.04	7.30(0.00–44.80)
Men	258.00 ± 76.69	0.00(0.00–37.50)	194.71 ± 51.56	0.00(0.00–40.20)	0.946187	211.31 ± 43.01	0.00(0.00–39.20)
p-value	0.343456		0.001520		–	0.001372	
Total	238.05 ± 50.36	0.00(0.00–40.25)	152.74 ± 27.43	5.40(0.00–43.00)	0.580147	175.11 ± 24.18	4.35(0.0–43.00)

between 110.77 ± 18.55 km in Zmiiv district and 248.94 ± 87.89 km in Vovchansk district ($p < 0.05$) (**Table 2**). In rural areas of all the districts, except Zmiiv district, the female migration distance was 42.75–68.58 km longer than in towns ($p < 0.01$) (**Table 2**). The male migration distance was 206.24 ± 24.81 km, ranging from 178.66 ± 45.40 km in Balakliya district to 229.67 ± 58.58 km in Krasnohrad district ($p = 0.0053$). Men moved over greater distances to towns than to villages (234.24 ± 41.64 km and 189.98 ± 30.87 km, respectively). In the urban areas, these values ranged from 168.76 ± 67.01 km in Balakliya to 306.49 ± 111.77 km in Vovchansk, and in rural areas they ranged from 147.93 ± 29.42 km in Vovchansk district to 219.62 ± 79.20 km in Krasnohrad district ($p > 0.05$) (**Table 2**).

Comparison of the migration distance based on sex revealed that in three of the four studied districts, men migrated at a distance 1.2–1.6 times greater than women (**Table 2**). For towns separately, it was typical only of Krasnohrad – 1.6 times, and for villages – Balakliya and Zmiiv districts – 1.5–1.8 times (**Table 2**).

At the same time, 56.1 % of men and 38.6 % of women did not change their residence after marriage, and in urban areas these percentages were even higher than in rural areas, therefore, the median migration distance was equal to zero or extremely short (**Table 2**).

The marital distance in the Kharkiv region was 320.40 ± 28.41 km, ranging from 263.17 ± 48.39 km in Balakliya district to 400.12 ± 79.97 km in Vovchansk district ($p = 0.0034$). In the town of Krasnohrad it exceeded that in the town of Balakliya by 1.6 times, 378.91 ± 98.20 km and 237.98 ± 73.94 km, respectively ($p = 0.0177$). In villages, it ranged from 278.46 ± 63.58 km in Balakliya district to 374.80 ± 99.02 km in Krasnohrad district.

A comparison of marriage patterns in urban and rural areas showed that the inbreeding coefficients F_{ST} ranged from 0.000074 in the town of Balakliya to 0.012949 in the village of Zmiiv district.

Prevalence and spectrum of genetic disorders. The study, after excluding patients with nongenetic birth defects, considered 187 subjects: 152 with single-gene disorders and 35 with chromosome abnormalities.

The prevalence of single-gene diseases among children and adolescents was 0.37 %, ranging from 0.25 % in Vovchansk district to 0.41 % in Krasnohrad district.

The profile of single-gene disorders in the studied districts included 39 nosological entities: 12 entities in Vovchansk district, 17 in Krasnohrad district, 17 in Zmiiv district, and 22 in Balakliya district.

Four diseases were common to the paediatric populations of all districts: sensorineural hearing loss, isolated growth hormone deficiency, cystic fibrosis, and ichthyosis vulgaris (**Table 3**). Twelve single-gene disorders occurred among children and adolescents in two or three districts simultaneously (**Table 3**), but were also recorded in other age groups in the other districts. Some orphan diseases were linked to a certain district: diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (hemophilia A, X-linked agammaglobulinemia), endocrine, nutritional and metabolic diseases (mucopolysaccharidoses types I and IIIA, Wilson disease, acrodermatitis enteropathica, hypoparathyroidism), diseases of the nervous system (periodic paralysis), diseases of the eye and adnexa (Stargardt disease, coloboma of

Table 3. **Prevalence of the most common single gene disorders among the pediatric population in Eastern Ukraine**

Disorder	District				European countries	Reference
	Balakliya	Krasnohrad	Vovchansk	Zmiiv		
Sensorineural hearing loss	1 : 974	1 : 1110	1 : 1578	1 : 544	1 : 500–1 : 1000	(Ivarsdottir *et al.*, 2021)
Isolated growth hormone deficiency	1 : 13636	1 : 2589	1 : 2630	1 : 2391	1 : 4000–1 : 10000	(Casteràs *et al.*, 2014)
Cystic fibrosis	1 : 13636	1 : 3884	1 : 7891	1 : 11957	1 : 1400–1 : 25000	(Guo *et al.*, 202)
Hypothyroidism	1 : 3409	1 : 1942	1 : 3946	–	1 : 1660–1 : 2828	(Olivieri, 2015)
Adrenal hyperplasia	1 : 13636	1 : 7767	–	1 : 11957	1 : 13000–1 : 15000	(Parsa & New, 2017)
Spinal muscular atrophy	1 : 3409	–	1 : 7891	1 : 5979	1 : 6000–1 : 10000	(MacDonald *et al.*, 2014)
Ehlers-Danlos syndrome	1 : 13636	–	1 : 7891	1 : 11957	1 : 5000	(Busch *et al.*, 2016)
Ichthyosis vulgaris	1 : 1705	1 : 7767	1 : 7891	1 : 11957	1 : 100–1 : 250	(Süßmuth *et al.*, 2020; Veropotvelyan *et al.*, 2015)
Cataract	1 : 6818	1 : 7767	–	1 : 5979	1 : 7874	(Sheeladevi *et al.*, 2016)
Primary congenital glaucoma	1 : 13636	1 : 3884	–	1 : 11957	1 : 1250–1 : 30000	(Kaur *et al.*, 2025)
Diabetes insipidus	1 : 13636	1 : 7767	–	–	1 : 25000	(Di Iorgi *et al.*, 2012)
Phenylketonuria	1 : 3409	–	1 : 3946	–	1 : 10000	(Chen & Weinstein, 2016)
Glycogen storage disease	1 : 13636	–	1 : 7891	–	1 : 100000	(Zerjav Tansek *et al.*, 2015)
Duchenne muscular dystrophy	1 : 6991*	–	–	1 : 6194*	1 : 3500	(Kravchenko *et al.*, 2017)
Neurofibromatosis	–	1 : 7767	–	1 : 11957	1 : 2000–1 : 6000	(Uusitalo *et al.*, 2015)
Ectodermal dysplasia	–	1 : 7767	1 : 7891	–	1 : 17000	(Trzeciak & Koczorowski, 2015)

Note: * – prevalence in men only

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optic nerve), diseases of the digestive system (Hirschsprung disease), congenital malformations, deformations and chromosomal abnormalities, etc.

In all the districts, the most prevalent single gene disorder was sensorineural hearing loss, from 1 : 1578 in Vovchansk district to 1 : 544 in Zmiiv (p = 0.0165) (**Table 3**).

The inbreeding coefficient F_{ST} was positively correlated with the prevalence of autosomal recessive disorders (Pearson correlation r = 0.82, p < 0.001) and the prevalence of sensorineural hearing loss (Spearman's correlation ρ = 0.85, p < 0.001).

The prevalence of chromosome abnormalities was 0.08 %, varying from 0.05 % in Vovchansk district to 0.14 % in Krasnohrad.

The profile of chromosome diseases comprised 4 nosological entities in total, but only Down syndrome was common to the paediatric populations of all four districts. Its prevalence ranged from 1 : 1996 to 1 : 863 in the studied areas. Other chromosome abnormalities were found in a single district: Turner and Klinefelter syndromes in Balakliya (1 : 6645 girls and 1 : 6991 boys, respectively) and Prader–Willi syndrome in Krasnohrad (1 : 3884).

There was a positive correlation between the prevalence of chromosome abnormalities and the inbreeding coefficient F_{ST} in the settlements of the studied districts (Spearman's correlation ρ = 0.90, p < 0.001).

DISCUSSION

The decrease in the effective population size due to changes in its age-sex structure in favour of older people or one sex is one of the factors that causes the genetic load. Those processes have been inherent in Ukraine for the last decades due to geopolitical transformations and socioeconomic hardship (Ceballos *et al*., 2021). It is known that an increase in not only maternal age at childbearing, but also both parents' age is a risk factor for children's disorders including genetic ones (Flores-López *et al*., 2023; Hvide *et al*., 2021; Moorthie *et al*., 2018).

Since the age of marriage could help to predict the average age of parents at a child's birth, we studied the mean age at marriage. In general, the average age at marriage in the studied settlements corresponded to that in Ukraine – 25.0 years for women and 27.6 years for men, and in the Kharkiv region – 25.9 years for women and 28.3 years for men, in 2015*. The obtained results are comparable with the average maternal age at childbearing – 27.4 years and age at first birth – 25.1 years in Ukraine in 2015, and with European data on maternal age at childbearing. It is known that the mean age of women at childbirth in the EU has been increasing since 2001, from an average of 29.0 to 31.2 years in 2023. The same trend is observed for the mean age of women at birth of the first child during the same period, from the value of 28.8 in the EU in 2013 to the value of 29.8 in 2023 (European Commission, 2026). The data obtained are comparable with data from neighboring countries in Eastern and South-Eastern Europe. The lowest mean age at birth of a first child can be found in Bulgaria – 26.9 years, and Romania – 27.1 years. At the same time, the highest values were in Italy – 31.8 years and Ireland – 31.6 years (European Commission, 2026). As European scientists currently note, the optimal age range for successful conception and healthy

* According to the data provided by the State Statistics Service of Ukraine

childbirth is 20–34 years (Ahmad *et al*., 2024). According to clinical and demographic data, the best age for having children with the least risk of complications during pregnancy and the postpartum period is 25–29 years (Cavazos-Rehg *et al*., 2015).

Since our study of these populations in 2008, the mean age at marriage for both men and women increased only in Balakliya district by 1.0 years (p = 0.000420) due to its rise by 2.3 years in rural settlements (p = 0.000089). In the villages of Zmiiv district, that figure decreased by almost 2.0 years (p = 0.001156). During the same period, the mean age of women at marriage increased by 1.8 years in Krasnohrad district (p = 0.035727). For men, the mean age at marriage increased by 1.3 years in Balakliya district (p = 0.000113) and decreased by 2.6 years in Zmiiv district (p = 0.000009). In urban areas, those indicators were comparable, but in rural areas, the changes were different: they increased by 2.0 years for women (p = 0.001953) and by 2.5 years for men in Balakliya district (p = 0.000116), while in Zmiiv district, the latter decreased by almost 3.0 years (p = 0.000015). In both 2008 and 2015, the mean age of men at marriage was higher than that of women in all districts and settlements ($p < 0.01$).

Thus, the established average age of parents at marriage and childbearing in Eastern Ukraine hardly contributes substantially to the genetic load of the population, at least at the birth of the first child.

Another risk factor for having a child with genetic disorders is considered to be assortative mating, in particular endogamy, the degree of which is inversely proportional to the marital distance, and is associated with accidental inbreeding (Marchi *et al*., 2018; Motsinger-Reif *et al*., 2024). Inbreeding leads to an increased homozygosity of pathological alleles, which raises the risk of not only recessive disorders, but also dominant ones, especially with incomplete penetrance and variable expressivity (Smolen *et al*., 2023). The obtained results demonstrate the predominance of ambilocality over migration within neighboring regions, the same region or even neighboring districts and settlements (**Table 2**). The highest figures of mean migration distance obtained for Vovchansk and Zmiiv districts are probably due to the shorter distance to the regional center and more intensive labor migration. Such restricted marital practices can negatively affect patterns of genetic variation.

It is obvious that economic ability determines the possibilities of change in life, the possibilities of educational, labor, marriage migration, and, as a consequence, the prevention of inbred marriages. In this regard, it is important to note the possible effects of epigenetic drift in people with persistent environmental stressors, such as stress and insufficient or improper nutrition. Historical and current experience shows that low socioeconomic status and toxic effects can contribute to chronic stress and environmental influences that can affect gene expression and increase the risk of disease (Virolainen *et al*., 2023). On the other hand, a hereditary disease can lead to a deterioration in economic well-being over several generations (Johansson *et al*., 2022).

Analysis of the dynamics indicators showed that seven years after previous research in this area, the migration distance decreased by 1.5 times in Balakliya district and increased by 5.4 and 5.5 times in Zmiiv and Krasnohrad districts ($p < 0.05$), respectively.

During the same period, the distance increased among rural residents of Vovchansk, Zmiiv, and Krasnohrad districts by 2.2, 9.2, and 15.4 times ($p < 0.05$), respectively. In Zmiiv district, the dynamics were due to the increase in migration distance for both men and women, while in Vovchansk district, it resulted from just male migration, and in Krasnohrad district, it was attributable to female migration.

However, both partners could have come from the same area, so it was worth exploring their origins. The marital distance in all the districts was less than the sum of the migration distances of both newlyweds ($p < 0.05$), thus migrants mostly originated from different places. Since 2008, the marital distance increased statistically significantly by 3.3–8.5 times in settlements of Krasnohrad district, and decreased in Balakliya district by 1.7 times ($p < 0.05$).

It is known that populations with negligible marital migration have a high level of endogamy and consanguineous marriages, one of the indicators of which is the inbreeding coefficient F_{ST} (Cavalli-Sforza, Bodmer, 2013). Despite the increase in the percentage of long-distance migrations during the study period, religious and legal restrictions of consanguineous marriages in Ukraine, the inbreeding coefficient F_{ST} = 0.001292 was up to 17.2 times greater in rural areas than in urban areas. For seven years, the value of F_{ST} increased by 1.8 times ($p = 0.001477$).

Because increasing inbreeding rates affect population genetic load (Ceballos *et al*., 2021; Motsinger-Reif *et al*., 2024), it is advisable to analyse population aspects of genetic disorders in the studied districts.

The prevalence of single-gene diseases in the paediatric population was comparable to that of other European countries (**Table 3**) (Busch *et al.*, 2016; Casteràs *et al*., 2014; Chen & Weinstein, 2016; Di Iorgi *et al*., 2012; Guo *et al*., 2023; Ivarsdottir *et al*., 2021; Kaur *et al*., 2025; Kravchenko *et al*., 2017; MacDonald *et al*., 2014; Olivieri, 2015; Parsa & New, 2017; Sheeladevi *et al*., 2016; Süßmuth *et al*., 2020; Trzeciak & Koczorowski, 2015; Uusitalo *et al*., 2015; Zerjav Tansek *et al*., 2015). Both the profile and the prevalence of the registered nosological entities were comparable to those in in other regions of Ukraine and in the European Union (**Table 3**) (Berglund *et al*., 2020; Busch *et al*., 2016; Casteràs *et al*., 2014; Chen & Weinstein, 2016; de Graaf *et al*., 2021; Di Iorgi *et al*., 2012; Guo *et al*., 2023; Ivarsdottir *et al*., 2021; Kaur *et al*., 2025; Kravchenko *et al*., 2017; MacDonald *et al*., 2014; Olivieri, 2015; Parsa & New, 2017; Popa & Ghiorghiţă, 2015; Sheeladevi *et al*., 2016; Shaikh *et al*., 2024; Süßmuth *et al*., 2020; Trzeciak & Koczorowski, 2015; Uusitalo *et al*., 2015; Veropotvelyan *et al*., 2015; Zerjav Tansek *et al*., 2015). For example, in the Dnipropetrovsk and Zaporizhzhia regions of Ukraine, the prevalence of sensorineural hearing loss was estimated as 1 : 1923 (Veropotvelyan *et al*., 2015). According to our previous studies in the southeastern part of the Kharkiv region, the prevalence of sensorineural hearing loss was 1 : 1331, isolated growth hormone deficiency was 1 : 3,629, and ichthyosis vulgaris was 1 : 3,629. Qualitative and quantitative indicators of the genetic load in the population of the southeastern districts were comparable to those of other districts and the region as a whole. There were 36 nosological forms of single-gene disorders with various patterns of inheritance and 3 nosological forms of chromosomal disorders in the studied population (Fedota *et al*., 2019).

From 2015 to 2022, 17 nosological entities of single-gene disorders were registered among the paediatric population of Krasnohrad district, showing an increase compared to 13 in 2008. Comparison of the profiles of the diseases showed that 7 disorders were no longer represented in that age group in 2015 as they were in 2008. However, other new nosological entities were registered in 2015. Among them were coloboma of the optic nerve, primary congenital glaucoma, neurofibromatosis, osteogenesis imperfecta, Hirschsprung disease, ectodermal dysplasia, and cystic fibrosis. The changes in the profile of single-gene disorders may result from the small population size in the district, its natural and migration movements, low prevalence of the disorders, reduced survival in patients, and *de novo* mutations.

The strong correlation of the F_{ST} value with the prevalence of autosomal recessive disorders in the region (Pearson correlation $r = 0.82$, $p < 0.001$) was comparable to that in Krasnohrad district in 2008 (Pearson correlation $r = 0.99$). The correlation coefficient between the prevalence of sensorineural hearing loss and the inbreeding coefficient F_{ST} in the settlements of the district did not change significantly either (Spearman's correlation $\rho = 0.61$ in 2008 and Spearman's correlation $\rho = 0.85$ in 2015). However, despite the maintenance of the load of autosomal recessive disorders in the district – 0.19 % in 2008 and 0.30 % in 2015, the possibility of its increase cannot be excluded because of a delayed effect of inbreeding.

The prevalence of chromosome abnormalities also corresponded to that in European countries, for example, 0.88 % in Romania (Popa & Ghiorghiţă, 2015). In particular, in Europe the prevalence of Down syndrome is 1 : 1000 (de Graaf *et al*., 2021), Klinefelter syndrome is 1 : 1470 among newborn boys (Berglund *et al*., 2020), Turner syndrome is 1 : 1700 among newborn girls (Berglund *et al*., 2020), and Prader–Willi syndrome is 1 : 10000–1 : 30000 (Shaikh *et al*., 2024).

A similar or lower prevalence of chromosome diseases in Kharkiv region than in European countries may be explained by the effective prevention of these diseases in Ukraine. Current national guidelines for prenatal screening, especially the Standards of Medical Care "Normal Pregnancy" (2022), recommend sonography in the first and second trimesters of pregnancy and double biochemical screening for fetal genetic disorders and congenital malformations.

Thus, the pattern of genetic and demographic processes in small settlements has contributed to the homozygosity of the population. This in turn results in an increased prevalence of not only single-gene disorders but also chromosome abnormalities. Analysis of parameters and trends of genetic-demographic processes and data on genetic pathology allows predicting the dynamics of genetic parameters of the population. The results can be used to assess the needs for medicines, medical and social assistance for the population, the development of educational and social programs, infrastructure and economic projects.

Our study has several limitations. In this article, we present a study of four districts of the region, although data for eight out of 27 districts were analysed. It should be noted that occasional cases of patient under-registration may occur, as some families, particularly in rural areas, do not seek timely medical attention from specialized facilities. Furthermore, the results of genetic laboratory testing are not included in this work because findings have not been obtained for all patients. While military operations continue in the region, we intend to resume our research in certain areas in the future, given that the study's primary value is its longitudinal perspective.

The established direction of genetic-demographic processes, alongside rising inbreeding levels, facilitates the forecasting of genetic load dynamics in the Kharkiv region. Additionally, it allows for the extrapolation of these results to populations sharing comparable population-demographic profiles, processes, and sociocultural attributes.

CONCLUSION

In the region of study, an upward trend was observed in the inbreeding coefficient (F_{ST}), which has doubled across both urban and rural settlements over a seven-year period, reaching a value of 0.001292. This rise in local inbreeding is associated with an increased genetic load within the population, particularly concerning not only single-gene, but also chromosomal pathologies (r = 0.82 and ρ = 0.90). Both urban and rural populations exhibited a wide spectrum of genetic disorders, comprising 39 single-gene nosological entities and 4 chromosomal ones. When forecasting healthcare and social support needs, it is advisable to take into account the higher prevalence rates of genetic disorders in rural areas.

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Human Rights: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

AUTHOR CONTRIBUTIONS

Conceptualization, [O.F.]; methodology, [I.S.; O.F.]; validation, [I.S.; V.M.]; formal analysis, [I.S.; V.M.]; investigation, [I.S.; O.F.]; resources, [I.S.; O.F.]; data curation, [I.S.; O.F.]; writing – original draft preparation, [I.S.]; writing – review and editing, [I.S.; V.M.; O.F.]; visualization, [I.S.; V.M.; O.F.]; supervision, [V.M.; O.F.]; project administration, [O.F.]; funding acquisition, none.

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ГЕНЕТИЧНИЙ ТЯГАР У ПОПУЛЯЦІЯХ ЛЮДИНИ КРІЗЬ ПРИЗМУ ЛОКАЛЬНОГО ІНБРИДИНГУ

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Вступ. Визначення генетичного тягаря є актуальним у зв'язку з активною міграцією та зменшенням чисельності населення, зокрема, в зонах бойових дій. Метою цього дослідження було проаналізувати динаміку показників поширеності генетичних захворювань залежно від демографічних характеристик населення на сході України.

Матеріали та методи. У чотирьох районах Харківської області як типового регіону сходу України проведено знеособлене популяційне дослідження. Середній вік, дальність міграції та шлюбну відстань у жінок віком до 45 років і чоловіків до 55 років визначали за інформацією про шлюби по районах за 2015 рік. Поширеність генетичних захворювань серед дітей віком 0–17 років визначали на основі районних медичних реєстрів. Генетичну структуру популяції визначали за коефіцієнтом локального інбридингу F_{ST}.

Результати. Проаналізовано дані щодо 1427 шлюбів і 187 дітей із генетичними захворюваннями. Середній шлюбний вік, дальність міграції та шлюбна відстань становили 27,8 ± 0,1 року, 179,0 ± 15,0 км і 320,4 ± 28,4 км. F_{ST} становив 0,000074–0,012949 і був до 17,2 раза більшим (p = 0,0012) у сільських районах, ніж у міських. Загальний F_{ST} по чотирьох районах становив 0,001292, збільшившись у 1,8 раза (p = 0,001477) протягом 7 років. Поширеність 39 моногенних і 4 хромосомних порушень становила 0,36 % і 0,08 % з позитивною динамікою в часі. Найпоширенішими захворюваннями були нейросенсорна втрата слуху (1:859), гіпофізарний нанізм (1:3438), іхтіоз звичайний (1:3750), муковісцидоз (1:6875) та синдром Дауна (1:1331). Поширеність моногенних захворювань у сільських популяціях була у 4,3 раза вищою, ніж у міських: 1,29 % і 0,30 % (p = 0,007). F_{ST} мав позитивний зв'язок із поширеністю аутосомно-рецесивних розладів (r = 0,82, p < 0,001) та хромосомних аномалій (ρ = 0,90, p < 0,001).

Висновки. В обстеженому регіоні спостерігали позитивну динаміку коефіцієнта локального інбридингу (F_{ST}) зі збільшенням удвічі до 0,001292 протягом 7 років, притаманну як міським, так і сільським поселенням. Зростання показника інбридингу асоційовано зі збільшенням генетичного тягаря популяції, зокрема, у вигляді не лише моногенної, а й хромосомної патології. Як у міських, так і у сільських популяціях зазначено широкий спектр генетичних хвороб – 39 моногенних нозологічних одиниць і 4 хромосомних. Прогнозуючи потреби у медичній допомозі та соціальній підтримці, доцільно брати до уваги вищі показники поширеності генетичних захворювань у сільській місцевості.

Ключові слова: генетичні та демографічні характеристики, інбридинг, поширеність, моногенні захворювання, хромосомні аномалії

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