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EVALUATION OF FAMILY HISTORY BURDEN IN OBESITY AMONG 6-7-YEAR-OLD CHILDREN AT PRE-SCHOOL SCREENING IN SOUTHERN RUSSIAN CITIES

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ABSTRACT
This cross-sectional cohort study evaluated the frequency and structure of family history burden for obesity, type 2 diabetes mellitus, and thyroid disorders among 1,080 children aged 6-7 years with excess body weight undergoing pre-school medical screening in Volgograd (n=605) and Vladikavkaz (n=475). Children with type 1 diabetes, chromosomal syndromes, and secondary endocrine obesity were excluded, while those with type 2 diabetes secondary to obesity were retained. Obesity severity was assessed using WHO centile charts and BMI Z-scores. Children from Volgograd demonstrated significantly higher BMI, Z-scores, and prevalence of grade 1 obesity compared to their peers from Vladikavkaz. Family history analysis revealed a higher frequency of parental obesity, including bilateral obesity, and type 2 diabetes among relatives in the Volgograd cohort, whereas thyroid pathology was significantly more common in families from Vladikavkaz, particularly along the maternal line. The strongest predictors of severe obesity were the combination of parental obesity and type 2 diabetes (OR = 4.12) and bilateral parental obesity (OR = 3.45), while thyroid pathology showed no significant association with obesity severity. Multivariable regression confirmed bilateral parental obesity, parental type 2 diabetes, and residence in Volgograd as independent predictors of severe obesity. These findings reveal interpopulation differences in obesity patterns and hereditary burden between the two cities. Bilateral parental obesity and combined parental obesity with T2DM are key markers of high risk for severe obesity. Our results support region-specific screening and preventive strategies tailored to regional and population-genetic characteristics.

KEYWORDS: childhood obesity, hereditary burden, family history, type 2 diabetes mellitus, bilateral obesity, interpopulation differences.

INTRODUCTION

Childhood obesity is now recognized as one of the most serious public health threats of the 21st century. According to the World Health Organization, the prevalence of overweight and obesity among children and adolescents has increased more than tenfold over the past four decades, and this trend continues to rise globally, including in the Russian Federation [1, 2]. Particularly concerning is the manifestation of this pathology during preschool and early school age, as this period of ontogenesis is critical for the formation of eating habits, the establishment of metabolic "set points," and the determination of the future trajectory of adipose tissue development [3, 4]. The age period of 6-7 years represents a critical window of opportunity for timely diagnosis and prevention of obesity, since children undergo mandatory pre-school medical examinations at this stage, providing a unique opportunity for screening studies and the identification of high-risk groups for subsequent follow-up [5, 6].

The study of regional characteristics in the prevalence and structure of childhood obesity is of particular scientific and practical interest, as climatic, geographical, ethnic, and socioeconomic factors can significantly contribute to the metabolic profile of a population [7, 8]. In this context, the comparison of two major cities in southern Russia (Volgograd, located in the steppe zone with a temperate continental climate and serving as a major industrial and transport hub, and Vladikavkaz, situated in the foothills of the Central Caucasus with its characteristic multinational population structure and pronounced iodine deficiency) is especially relevant. Differences identified between these populations may reflect both environmental factors (dietary patterns, urbanization levels, physical activity) and population-genetic features related to variations in the frequency of alleles of genes predisposing to obesity and metabolic disorders [9, 10].

The vast majority of childhood obesity cases are multifactorial in nature, where genetic predisposition is expressed through interactions with environmental factors. What is inherited is not the disease itself, but rather the characteristics of metabolic and neuroendocrine responses, which in the context of the modern food environment

(characterized by an abundance of high-calorie, easily digestible food and widespread physical inactivity) can lead to excessive fat accumulation [11, 12]. Modern molecular genetic studies have identified a number of genes and their polymorphic variants associated with the development of obesity. The central role among these is played by genes regulating appetite and energy balance in the hypothalamus, particularly the melanocortin 4 receptor gene (*MC4R*), mutations in which represent the most common cause of monogenic obesity [13, 14], as well as the fat mass and obesity-associated gene (*FTO*), which is considered one of the main susceptibility loci for polygenic obesity in population studies [15, 16]. Also significant are genes of the leptin signaling pathway (*LEPR*, *POMC*, *PCSK1*), disruptions in which lead to diminished satiety, and thermogenesis genes (*UCP3*), polymorphisms of which reduce the efficiency of energy expenditure [17, 18]. Genes associated with the development of insulin resistance, such as atypical protein kinase C isoforms (aPKC) and *PPARG*, deserve particular attention, as their activation under conditions of chronic overeating promotes lipid accumulation in the liver and adipose tissue and triggers a cascade of inflammatory reactions, clinically manifesting as metabolic syndrome [11, 19].

Family history analysis remains one of the classic and most accessible clinical methods for assessing genetic predisposition in population studies [20, 21]. The presence of first- and second-degree relatives with obesity, type 2 diabetes mellitus, or dyslipidemia is a strong predictor of similar conditions in children. Family history reflects the cumulative effect of multiple genetic variants, each contributing relatively little individually, but collectively determining hereditary burden–making this method highly informative for screening and risk group identification in the pediatric population [22]. Of particular importance is the identification of bilateral burden (obesity in both parents) and combined pathology (concurrence of obesity and type 2 diabetes mellitus in parents), as these phenotypic markers indicate high polygenic load and clustering of metabolic disorders within the family [23, 24].

Despite the considerable body of research on the genetic aspects of obesity, comparative population studies among preschool children in southern Russia have not been conducted to date. The structure of hereditary burden in different populations of the region, as well as the relationship between family history and the severity of obesity in children aged 6-7 years, remain insufficiently studied [25, 26]. The aim of this study was to evaluate the frequency and structure of family history burden for obesity, type 2 diabetes mellitus, and thyroid disorders among 6-7-year-old children with excess body weight residing in Volgograd and Vladikavkaz, based on data from pre-school medical examinations.

MATERIALS AND METHODS

This cross-sectional cohort study combined retrospective analysis of medical records with prospective collection of family history data through parental questionnaires. The study was conducted at pediatric clinics and preschool institutions in Volgograd and Vladikavkaz from September 2024 to May 2025. All data were de-identified and analyzed in aggregated form, preventing patient identification. Data collection and processing followed the principles of voluntariness and confidentiality. Written informed consent was obtained from all parents or legal guardians.

Inclusion criteria were age 6-7 years at the time of examination, permanent residency in one of the study cities for at least 5 years, confirmed overweight or obesity on medical examination, and signed informed consent. Exclusion criteria were type 1 diabetes mellitus, chromosomal abnormalities and congenital syndromes (including Down syndrome and Turner syndrome), secondary obesity due to uncompensated endocrine disorders, and parental refusal to participate. Children with type 2 diabetes mellitus secondary to obesity were retained in the analysis as a subgroup with metabolic decompensation.

The initial sample comprised 1,080 children undergoing mandatory pre-school medical examinations, with 605 from Volgograd and 475 from Vladikavkaz. After applying exclusion criteria, 12 children with type 1 diabetes, 4 children with chromosomal syndromes (2 with Down syndrome and 2 with Turner syndrome), and 28 children with incomplete family history data were excluded. The final cohort thus consisted exclusively of children with primary alimentary-constitutional obesity without chromosomal abnormalities or autoimmune endocrinopathies. Children with chromosomal syndromes were excluded from the main analysis due to the different etiology of their obesity and insufficient numbers for statistical analysis; however, their identification was documented, highlighting the need for a differentiated approach to the evaluation of obesity causes in preschool children.

Data collection was performed in two stages. First, medical records (standard pediatric form) were reviewed [27]. Anthropometric measurements, including height in centimeters and weight in kilograms, were recorded, and body mass index was calculated as weight (kg) / height (m)^2. Obesity severity was assessed using WHO growth reference charts (2007) for children aged 5-19 years, stratified by sex and age. The following categories were defined: overweight as BMI $\geq$ 85th percentile, grade 1 obesity as BMI $\geq$ 97th percentile, grade 2 obesity as Z-score > +3, and grade 3 obesity as Z-score > +4 [28]. Associated conditions such as arterial hypertension and dyslipidemia were also recorded when biochemical data were available.

Second, family history was collected through structured interviews with parents or legal guardians, conducted by medical staff on the day of the examination using a specifically designed questionnaire. The questionnaire addressed the presence of obesity (with height and weight for BMI calculation when available), type 2 diabetes mellitus, thyroid pathology (hypothyroidism, hyperthyroidism, autoimmune thyroiditis, nodular goiter), arterial hypertension, and dyslipidemia among first-degree relatives (parents) and second-degree relatives (grandparents on both maternal and paternal sides) [29]. Additional data included parental age at the child's birth, early-onset

obesity (under 30 years of age) among relatives, and episodes of hyperphagia in the child as reported by parents. When respondents expressed uncertainty, investigators verified diagnoses through the relative's attending physician whenever possible. Special attention was paid to the identification of a two-way burden (obesity in both parents at the same time) and a combined pathology (combination of obesity and type 2 diabetes in parents).
Statistical analysis was performed using IBM SPSS Statistics version 26.0 and GraphPad Prism 9. For quantitative variables, means and standard deviations (or medians and interquartile ranges for non-normally distributed data) were calculated. Normality was tested using the Kolmogorov-Smirnov test. Between-group comparisons were made using Student's t-test (or the Mann-Whitney U-test for non-normal distributions). Categorical variables were compared using the chi-square test (or Fisher's exact test when expected frequencies were <5). Odds ratios with 95% confidence intervals were calculated to assess associations between family history factors and severe obesity. Multivariable logistic regression was performed to identify independent predictors of severe obesity, adjusting for potential confounders including city of residence, sex, and age [30]. A p-value < 0.05 was considered statistically significant.

RESULTS

The final sample consisted of 1,080 children with primary alimentary-constitutional obesity who underwent pre-school medical examinations in Volgograd (605 children) and Vladikavkaz (475 children). The mean age was 6.4 ± 0.5 years. Sex distribution was comparable across the total sample, with boys comprising 52.6% and girls 47.4%. No statistically significant differences in age or sex were found between the Volgograd and Vladikavkaz groups, confirming their comparability.
Anthropometric comparisons, detailed in Table 1, revealed that children from Volgograd had significantly higher BMI ($p = 0.04$) and BMI Z-scores ($p = 0.03$) than their peers from Vladikavkaz. No differences in height or weight were observed between groups, indicating that the higher BMI in Volgograd children was attributable to excess fat accumulation rather than differences in linear growth.

Table 1. Anthropometric characteristics of the study children (M ± SD)

Parameter	Volgograd (n=605)	Vladikavkaz (n=475)	p-value
Age, years	6.4 ± 0.5	6.3 ± 0.5	0.42
Height, cm	118.8 ± 6.3	119.7 ± 5.9	0.18
Weight, kg	27.1 ± 5.2	26.4 ± 4.6	0.09
BMI, kg/m²	19.1 ± 2.9	18.4 ± 2.4	0.04
BMI Z-score (WHO)	1.95 ± 0.64	1.81 ± 0.57	0.03

Note: $p < 0.05$ indicates statistically significant differences between cities (Mann-Whitney U test).

Analysis of the distribution of obesity grades (Table 2) showed that Volgograd had a significantly higher proportion of children with grade 1 obesity and a significantly lower proportion of children with overweight without obesity. No statistically significant differences were observed for severe obesity (grades 2 and 3) between cities. Thus, the obesity structure in Volgograd was shifted toward more severe grades, consistent with the higher mean BMI values in this group.

Table 2. Distribution of children by obesity grade, n (%)

Grade	Volgograd (n=605)	Vladikavkaz (n=475)	p-value (χ^2)
Overweight (≥85th percentile)	198 (32.7%)	214 (45.1%)	< 0.001
Grade 1 obesity (≥97th percentile)	277 (45.8%)	171 (36.0%)	< 0.001
Grade 2 obesity (Z-score > +3)	110 (18.2%)	75 (15.8%)	0.29
Grade 3 obesity (Z-score > +4)	20 (3.3%)	15 (3.2%)	0.88

Family history analysis, detailed in Table 3, revealed that more than two-thirds of children had at least one relative with obesity, with significantly higher rates in Volgograd. Notably, bilateral obesity (in both parents) was 1.6 times more common in Volgograd. A similar pattern was observed for type 2 diabetes mellitus, which was reported among relatives of 35.5% of children in Volgograd versus 19.6% in Vladikavkaz. In contrast, thyroid pathology was significantly more common in families from Vladikavkaz (22.1% vs. 14.7% in Volgograd), particularly along the maternal line.

Table 3. Frequency of hereditary burden in families of the studied children, n (%)

Family history feature	Volgograd (n=605)	Vladikavkaz (n=475)	p-value (χ^2)
Obesity in relatives (any line)	462 (76.4%)	280 (58.9%)	< 0.001
- including parental obesity (1st line)	338 (55.9%)	180 (37.9%)	< 0.001
- including grandparental obesity	370 (61.2%)	220 (46.3%)	< 0.001
- including bilateral parental obesity	195 (32.2%)	97 (20.4%)	< 0.001
Type 2 diabetes in relatives	215 (35.5%)	93 (19.6%)	< 0.001
- including T2DM in parents	117 (19.3%)	43 (9.1%)	< 0.001
Thyroid pathology in relatives	89 (14.7%)	105 (22.1%)	0.002
- including maternal hypothyroidism/AIT	54 (8.9%)	67 (14.1%)	0.007
Combined parental obesity and T2DM	85 (14.0%)	28 (5.9%)	< 0.001

To identify factors associated with severe obesity (Z-score > +3), odds ratios were calculated. The analysis included 668 children with BMI ≥ 97th percentile, of whom 220 had grade 2 or 3 obesity. Univariate analysis results are presented in Table 4. The strongest predictors of severe obesity were the combination of parental obesity and type 2 diabetes (OR = 4.12) and bilateral parental obesity (OR = 3.45). Maternal obesity, paternal obesity, and parental T2DM also contributed significantly, though to a lesser extent. Grandparental obesity showed only a trend toward increased risk and did not reach statistical significance. Thyroid pathology in relatives showed no statistically significant association with severe obesity in children.

Table 4. Association of family history factors with severe obesity (Z-score > +3) in children

Factor	OR	95% CI	p-value
Bilateral parental obesity	3.45	2.41 - 4.93	< 0.001
Combined parental obesity and T2DM	4.12	2.68 - 6.33	< 0.001
Parental T2DM (1st line)	1.89	1.40 - 2.55	< 0.001
Maternal obesity	2.11	1.56 - 2.87	< 0.001
Paternal obesity	1.78	1.32 - 2.40	0.002
Grandparental obesity	1.35	0.98 - 1.86	0.07
Thyroid pathology in relatives	1.23	0.89 - 1.72	0.21

Multivariable logistic regression analysis, adjusted for potential confounders, confirmed bilateral parental obesity, parental T2DM, and residence in Volgograd as independent predictors of severe obesity.

During medical record screening, four children with chromosomal syndromes were identified among those with excess body weight (two cases of Down syndrome and two cases of Turner syndrome). In these cases, obesity is secondary and syndrome-related in nature. Given the small size of this group and the fundamentally different etiology of obesity, these patients were excluded from the final analysis in accordance with the exclusion criteria.

DISCUSSION

This study analyzed hereditary burden for metabolic disorders among 1,080 children aged 6-7 years with primary alimentary-constitutional obesity residing in two cities of southern Russia – Volgograd and Vladikavkaz. The findings revealed significant interpopulation differences in family history structure and identified key risk factors for the development of severe obesity in childhood.

Obesity is a classic example of a multifactorial disease in which genetic predisposition is expressed through interactions with environmental factors [31, 32]. What is inherited is not the disease itself, but rather the characteristics of metabolic and neuroendocrine responses that, in the context of the modern food environment (characterized by high-calorie diets and physical inactivity can lead to excessive fat accumulation [33, 34]. The family history collected in our study reflects the cumulative effect of multiple genetic variants, each contributing relatively little individually, but collectively determining hereditary burden [35, 36].

The pathophysiological pathways through which genetic factors exert their effects are illustrated in Figure 1, which presents a schematic diagram of the causal relationships between key genes, their protein products, and the clinical manifestations evaluated in our study.

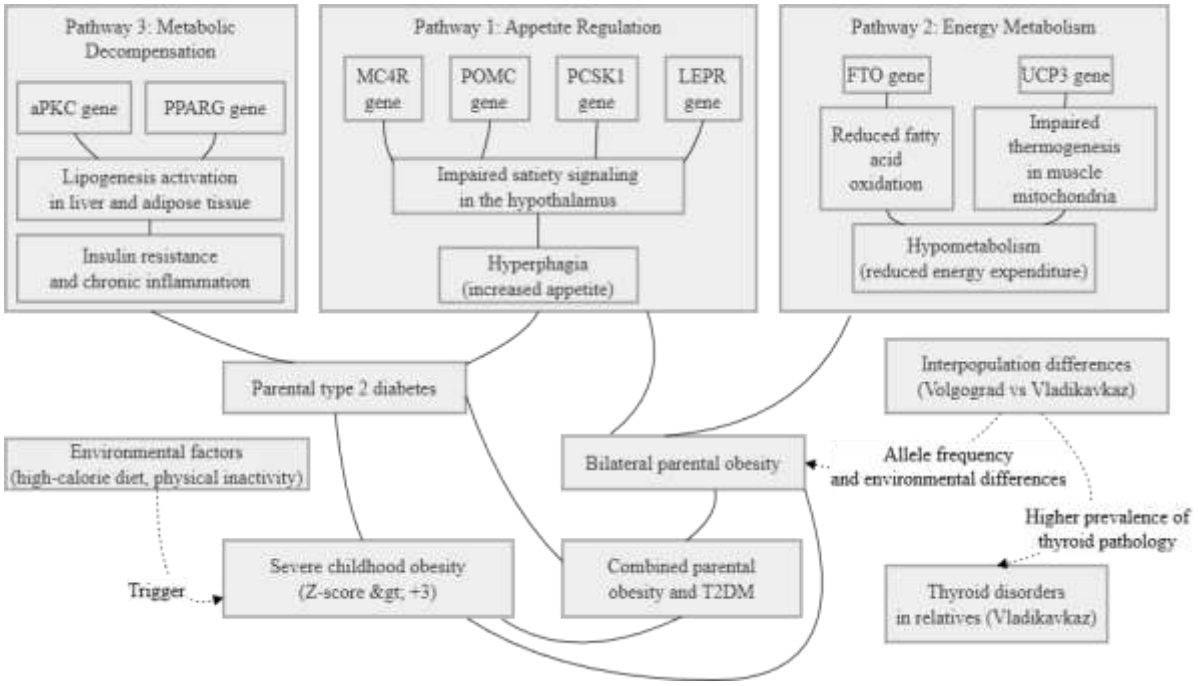

Figure 1. Causal pathway diagram of genetic factors, hereditary burden, and the development of severe obesity in children.

The diagram illustrates three main pathophysiological pathways through which genetic predisposition leads to severe childhood obesity. Pathway 1 (appetite regulation) involves genes *MC4R*, *POMC*, *PCSK1*, and *LEPR*, which control hypothalamic satiety signaling. Pathway 2 (energy metabolism) involves *FTO* and *UCP3*, which regulate fatty acid oxidation and thermogenesis. Pathway 3 (insulin resistance) involves *aPKC* and *PPARG*, which promote lipogenesis and inflammation. These pathways converge on hereditary burden phenotypes (bilateral parental obesity, parental type 2 diabetes, and their combination) which in turn predict severe obesity in children. Environmental factors and interpopulation differences (Volgograd vs. Vladikavkaz) act as additional modifiers.

Interpopulation Differences: Volgograd vs. Vladikavkaz

One of the most notable findings of our study is the differences observed between the two cities. Children from Volgograd had higher BMI and Z-score values, as well as a higher proportion of grade 1 obesity. Concurrently, the Volgograd cohort showed a significantly higher frequency of hereditary burden for obesity and type 2 diabetes mellitus. In contrast, thyroid disorders in family history were significantly more common in Vladikavkaz.

These differences may have several explanations. First, the populations of Volgograd and Vladikavkaz differ in ethnic composition, which may reflect variations in the frequency of alleles of obesity susceptibility genes. Studies by Russian authors have shown that the contribution of *FTO* and *MC4R* genes to metabolic disorders differs among ethnic groups, supporting the need for population-specific approaches to genetic risk assessment [37, 38]. Second, the differences may be related to environmental factors: the level of urbanization, dietary patterns, availability of high-calorie foods, and physical activity levels in industrial Volgograd may differ from those in the foothill city of Vladikavkaz [39, 40]. The persistence of city of residence as an independent risk factor in the multivariable regression model (adjusted OR = 1.42) confirms the presence of both genetic and environmental triggers [41].

Of particular note is the high frequency of thyroid pathology in families of children from Vladikavkaz (22.1% vs. 14.7% in Volgograd), especially along the maternal line (14.1% vs. 8.9%). The foothill regions of the North Caucasus are areas of natural iodine deficiency, which predisposes to the development of autoimmune thyroiditis and hypothyroidism [42, 43]. At the same time, the absence of a statistically significant association between thyroid pathology in relatives and the severity of obesity in children (OR = 1.23; p = 0.21) suggests that this factor is independent and not directly related to alimentary-driven weight gain.

Bilateral Obesity as a Marker of High Polygenic Load

Parental obesity in both parents proved to be one of the strongest predictors of severe obesity in children (OR = 3.45; adjusted OR = 3.02). This finding is fully consistent with current understanding of the polygenic inheritance of obesity, according to which the risk of developing the disease is proportional to the number of inherited risk alleles [44, 45]. In bilateral obesity, the child inherits risk alleles from both parents, resulting in an additive effect and a significantly higher risk of early disease manifestation [46, 47]. Our findings confirm that family history collection with an emphasis on bilateral burden is a highly informative screening method for identifying high-risk groups in the pediatric population.

Combined Parental Obesity and T2DM as an Indicator of Metabolic Syndrome

The strongest predictor of severe obesity in children was the combination of parental obesity and type 2 diabetes mellitus (OR = 4.12). This finding has important clinical significance, as it indicates the presence not of isolated obesity but of a full metabolic syndrome within the family, where genetic factors promoting insulin resistance (such as aPKC, PPARG) interact with factors regulating appetite and energy expenditure (MC4R, FTO) [48, 49]. In such families, the child is exposed not only to genetic predisposition but also to shared environmental factors (dietary patterns, eating habits), creating an extremely high risk of early decompensation [50, 51].

Study Limitations

Several limitations should be considered when interpreting our results. First, family history was collected through questionnaires, which may be subject to reporting bias (incomplete or inaccurate data). To minimize this effect, we verified diagnoses through medical records when possible. Second, the cross-sectional design does not allow causal relationships between hereditary burden and obesity development to be established; prospective cohort studies are needed for this purpose. Third, we did not perform molecular genetic testing, which limits our conclusions to phenotypic markers of heritability. However, this is also a strength of our work: we demonstrated that even at the level of family history, powerful predictors of severe obesity can be identified, which has practical value for pediatric screening. Fourth, the small number of children with chromosomal syndromes (4 individuals) precluded their inclusion in the main analysis, indicating the need for a separate study with a larger sample.

Clinical Significance and Future Directions

Our findings have direct practical implications for pediatric practice. The identification of a child with excess body weight and a positive family history, particularly when combined with obesity in both parents or obesity with T2DM, should prompt in-depth evaluation and early initiation of preventive measures. Such children constitute a high-risk group for the development of severe obesity and metabolic disorders in adolescence and adulthood [52].

At the same time, interpopulation differences highlight the need for region-specific approaches to the prevention of childhood obesity. In industrial cities with high urbanization, such as Volgograd, emphasis should be placed on dietary modification and increased physical activity, whereas in regions with natural iodine deficiency, such as North Ossetia, iodine prophylaxis and thyroid function monitoring are important components of prevention.

A promising direction for future research is molecular genetic analysis (genotyping of polymorphisms in *FTO* (rs9939609), *MC4R* (rs17782313), *LEPR* (rs1137101), and *UCP3* (rs1800849)) in the identified high-risk groups. This would confirm the hypothesis of differences in allele frequencies between populations and enable personalized approaches to obesity prevention based on genetic profiles.

CONCLUSION

This cohort study of 1,080 children aged 6-7 years with primary alimentary-constitutional obesity in Volgograd and Vladikavkaz revealed significant interpopulation differences in obesity patterns and hereditary burden. Children from Volgograd had higher BMI and Z-score values and a higher proportion of grade 1 obesity. Their families more frequently exhibited parental obesity (particularly bilateral) and T2DM, whereas thyroid pathology predominated in Vladikavkaz, especially along the maternal line, consistent with natural iodine deficiency in the region.

The strongest predictors of severe obesity (Z-score > +3) were combined parental obesity and T2DM (OR = 4.12) and bilateral obesity (OR = 3.45). Thyroid pathology showed no association with obesity severity. Residence in Volgograd remained an independent risk factor, indicating the role of both genetic and environmental triggers.

Clinically, it is important to identify children with bilateral obesity and combined parental obesity with T2DM as a high-risk group for early prevention. Regional differences dictate the need for differentiated approaches: dietary modification and physical activity in industrialized cities, and iodine prophylaxis and thyroid function monitoring in iodine-deficient regions. Molecular genetic testing represents a promising direction to confirm the hypothesis of allele frequency differences between populations and to develop personalized prevention strategies.

Acknowledgments: The authors would like to thank the medical staff of the pediatric clinics and preschool institutions in Volgograd and Vladikavkaz for their assistance with data collection.

Authors' contribution: All authors contributed equally to the conception, design, literature review, data analysis, manuscript drafting, and final approval of the version to be published.

Conflict of interest: The authors declare no conflict of interest.

Financial support: This research received no specific grant from any funding agency in the public, commercial, or non-profit sectors.

Ethics statement: This study was conducted in accordance with the principles of the Declaration of Helsinki. All data were de-identified and analyzed in aggregated form, preventing patient identification. Data collection and processing followed the principles of voluntariness and confidentiality. Written informed consent was obtained from all parents or legal guardians.

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