DOI: https://doi.org/10.30841/2786-720X.4.2024.320822
УДК 616-053.2-056.7-039:612.397.8

# Vascular microcalcification: diagnostic approach, statistical modeling, and the need for comprehensive management of children from the Ukrainian familial hypercholesterolemia registry

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**Familial hypercholesterolemia (FH) is a genetic disorder that significantly increases the risk of cardiovascular disease (CVD) in children. The identification of early predictors of cardiovascular pathology is crucial for effective management.**
***The objective:*** **to develop a statistical model that significantly predicts the mGla protein level, a marker of vascular microcalcification, in children with FH by analyzing the relationships between dietary habits, health-related quality of life, physical activity energy expenditure, extended lipid profile, dp-uc MGP protein levels, and results from instrumental examinations.**
***Materials and methods*****. Food habits, quality of life, energy expenditure for physical activity, lipid profiles, and dp-uc MGP protein levels were assessed in children from the Ukrainian FH registry. A multivariate regression model was developed to identify significant predictors of cardiovascular pathology, namely the level of the vascular microcalcification biomarker.**
***Results*****. The regression model demonstrated that the predictors explained 91.01% of the variance ($R^2 = 0.91$; $p < 0.0001$). Age and cholesterol intake were significant predictors ($\beta = 19.16$; $p = 0.0039$ and $\beta = 0.70$; $p = 0.0013$, respectively). These results highlight the impact of chronic cholesterol exposure on cardiovascular health in children with HF.**
***Conclusions*****. The study emphasizes the need for a comprehensive approach to the treatment of HF, combining medical and psychosocial support, to reduce the risk of cardiovascular complications in pediatric patients.**
***Keywords:*** *children, familial hypercholesterolemia, predictors of damage of the cardiovascular system, low-density lipoprotein, cholesterol.*

## Мікрокальцифікація судин: діагностичний підхід, статистичне моделювання та необхідність комплексного лікування дітей з Українського реєстру сімейних гіперхолестеринемій

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Сімейна гіперхолестеринемія (СГ) є генетичним захворюванням, що значно підвищує ризик серцево-судинних захворювань (ССЗ) у дітей. Виявлення ранніх предикторів серцево-судинної патології є ключовим для ефективного лікування.
***Мета дослідження:*** розроблення статистичної моделі, яка значущо передбачає рівень білка mGla, маркера судинної мікрокальцифікації, у дітей із СГ шляхом аналізу взаємозв'язків між харчовими звичками, якістю життя, пов'язаною зі здоров'ям, витратами енергії на фізичну активність, розширеним ліпідним профілем, рівнями білка dp-uc MGP та результатами інструментальних досліджень.
***Матеріали та методи.*** Дітям з українського реєстру СГ було проведено оцінку харчових звичок, якості життя, витрат енергії на фізичну активність, ліпідних профілів та рівнів білка dp-uc MGP. Для виявлення значущих предикторів серцево-судинної патології, а саме рівня біомаркера судинної мікрокальцифікації, було створено багатофакторну регресійну модель.
***Результати.*** Регресійна модель продемонструвала, що предиктори пояснюють 91,01% дисперсії ($R^2 = 0,91$; $p < 0,0001$). Значущими предикторами були вік та споживання холестерину ($\beta = 19,16$; $p = 0,0039$ та $\beta = 0,70$; $p = 0,0013$ відповідно). Ці результати підкреслюють вплив тривалого впливу холестерину на серцево-судинне здоров'я дітей із СГ.
***Висновки.*** Дослідження наголошує на необхідності комплексного підходу до лікування СГ, що поєднує медичну та психосоціальну підтримку, для зниження ризику серцево-судинних ускладнень у педіатричних пацієнтів.
***Ключові слова:*** *діти, сімейна гіперхолестеринемія, предиктори ураження серцево-судинної системи, ліпопротеїди низької щільності, холестерин.*

Familial hypercholesterolemia (FH) is a hereditary condition characterized by elevated low-density lipoprotein cholesterol (LDL-C) levels, significantly increasing the risk of early cardiovascular disease (CVD), even in children [1]. Early detection and management of cardiovascular pathology in pediatric FH patients are crucial to mitigating long-term health risks. Despite the availability of lipid-lowering therapies, understanding the interplay between dietary habits, physical activity, and biochemical markers remains essential for comprehensive care.

The study by Jaminon (2020) and others [11] confirmed the level of mGla protein as an independent predictor of intimal and medial calcification, as well as a factor influencing arterial stiffness [10] and cardiovascular morbidity and mortality. One of the potential preventive measures against microcalcification is the use of vitamin

K2 (or menaquinone-7) [12], which is essential for the carboxylation of the mGla protein, thereby preventing the mineralization of the intima and media of blood vessels. The effective impact on involutional processes of microcalcification in the vascular wall has been demonstrated in animal models in vitro [13–20], whereas only a few studies in adult patients have been successful [21–24].

Literature data had shown that dietary habits, such as high intake of saturated fats and low intake of fruits and vegetables, can exacerbate LDL-C levels and contribute to atherosclerosis [1]. Physical activity, on the other hand, is known to improve lipid profiles and reduce cardiovascular risk through mechanisms such as enhanced endothelial function and reduced arterial stiffness [4, 5, 10]. Furthermore, biochemical markers such as apoB, which reflects the number of atherogenic particles, have been identified as significant predictors of cardiovascular events in both children and adults [1].

This study aims to comprehensively analyze the relationships between dietary habits, health-related quality of life, physical activity energy expenditure, extended lipid profile data, dp-uc MGP protein levels, and instrumental study findings, with the goal of developing a statistical model to predict the that significantly predicts the mGla protein level, a marker of vascular microcalcification, in children with FH. Understanding these relationships is critical, as they may provide insights into the multifactorial nature of cardiovascular disease development and help tailor preventative and therapeutic strategies for affected children.

## MATERIALS AND METHODS

A retrospective study was conducted of pediatric patients from all regions of Ukraine who were seen in the Department of Cardiology at Kiev City Children's Clinical Hospital #1 [26].

Inclusion criteria for the study were: a confirmed diagnosis of familial hypercholesterolemia for at least 6 months, age between 5 and 18 years, adherence to prescribed lipid-lowering therapy and an appropriate diet (CHILD-1), signed informed consent by a child and parent(s) (or legal guardian(s)). Exclusion criteria were withdrawal of informed consent, age less than 5 years, interruption of lipid-lowering therapy >1 month, presence of an confirmed disease or condition other than FH that causes lipid metabolism disorders (diabetes mellitus, hypothyroidism, nephrotic syndrome, chronic kidney disease, primary cholangitis, obstructive jaundice, obesity, Cushing's syndrome, pheochromocytoma and etc.); intake of medications that cause lipid metabolism disorders (amiodarone, thiazide diuretics, beta-blockers, glucocorticoids, estrogens, androgens, immunosuppressants, anticancer agents, antipsychotics, HIV-1 protease inhibitors, anticonvulsants, retinoids, growth hormones and others) [26].

118 children were assessed between January and December 2021. 15 of these met the inclusion criteria and agreed to participate in the study, with informed consent given by both the children and their parent(s) (or legal guardian(s)). 3 patients withdrew their informed consent [26].

Children with familial hypercholesterolemia were included in the patient group (hereinafter referred to as "Patients" or "FH group") (n = 15). The Dutch Lipid Clinic Network criteria were used to establish the diagnosis of familial hypercholesterolemia [1].

The FH group children were mostly in the age range 5–17 years (55% boys and 45% girls). The control group consisted of healthy peers (n = 21, 47.7% girls and 52.3% boys). Subsequently, the children were stratified by age and sex. The following age groups were identified according to WHO guidelines: 5 to 9 years, 10 to 14 years, and 15 to 18 years. Both groups were representative of age and sex.

Additional clinical and demographic data related to the FH patients can be found in Table 1.

The overall clinical characteristics of the control group are detailed in Table 2.

Blood samples for measurement of biochemical parameters including total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) obtained by Friedewald's formula [2], high-density lipoprotein cholesterol (HDL-C),

*Table 1*

**Clinical characteristics of children with FH at study enrollment (M±s)**

| Parameter | 5–9 age group | 10–4 age group | 15–18 age group |
|---|---|---|---|
| Age (years) | 7.0 ± 1.22 | 12.4 ± 1.14 | 16.0 ± 1.00 |
| Weight (kg) | 25.4 ± 9.84 | 40.6 ± 7.30 | 62.9 ± 13.34 |
| BMI | 17.0 ± 3.45 | 19.0 ± 2.75 | 20.7 ± 3.42 |
| CHILD diet | prescribed | prescribed | prescribed |
| Anti-lipid therapy | dietary supplements (omega-3 fatty acid supplement) | statin or statin + ezetimibe | statin or statin + ezetimibe |
| Target LDL-C achieved | by 20% of group | by 60% of group | by 60% of group |

*Table 2*

**Overall clinical characteristics of the control group (M±s)**

| Parameter | 5–9 age group, n = 5 | 10–14 age group, n = 8 | 15–18 age group, n = 8 |
|---|---|---|---|
| Age (years) | 6.60 ± 1.40 | 11.87 ± 1.45 | 16.25 ± 0.88 |
| Weight (kg) | 24.42 ± 5.78 | 46.35 ± 9.29 | 62.46 ± 20.32 |
| BMI | 18.34 ± 2.40 | 20.71 ± 5.67 | 20.31 ± 5.42 |

triglycerides (TG), apolipoprotein A1, apolipoprotein B and lipoprotein (a) were taken after at least 8 hours fasting. Non-high-density (non-HDL-C) cholesterol was calculated TC minus HDL-C. Remnant cholesterol (rC) calculated from the standard lipid profile as TC minus LDL-C minus HDL-C. Subjects' blood plasma was also used to quantify the inactive dephosphorylated-uncarboxylated (dp-uc) isoform of matrix Gla protein (IDS-iSYS InaKtif MGP® UK) on the IDS-iSYS Multi-Discipline Automated System. The study was conducted in accordance with the Helsinki Declaration of Human Rights, the Council of Europe Convention on Human Rights and Biomedicine, and Ukrainian laws governing research on human subjects [26].

*Statistical analysis*

The auxological parameters (body weight, height, body mass index (BMI)) in the surveyed children were obtained by routine anthropometry. Electrocardiography (ECG) and echocardiography were performed on all subjects according to standard protocols to evaluate their cardiac function and structure.

The KINDL® questionnaire [3] and the Child/Youth Physical Activity Questionnaire (C(Y)PAQ) [4] were used to establish quality-of-life and physical activity levels, respectively.

The KINDL® is a comprehensive tool for assessing health-related quality of life in children and young people aged 3 years and over. The KINDL® consists of 24 Likert scale items related to six modules: physical well-being, emotional well-being, self-esteem, family, friends and daily activities (school or kindergarten). The subscales of these six modules were combined to produce an overall score. Participants answered questions on a 5-point Likert scale (0 – never, 1 – rarely, 2 – sometimes, 3 – often and 4 – always). All subscales were then converted into scores from 0 to 100, where higher scores corresponded to a better quality-of-life index. Age-specific versions consider the changes in the quality-of-life dimensions in the course of child development [26].

The Child Physical Activity Questionnaire (CPAQ) was administered to the youngest group (ages 5–9) and completed with partial parental help. The CPAQ questionnaire assesses the type, frequency and duration of physical activity and sedentary behaviour over the past 7 days. The Youth Physical Activity Questionnaire (YPAQ) was used among older children (10–14 years and 15–18 years). This tool allows to determine the frequency and duration of 47 different activities on both weekdays and weekends during the past week. As such, the YPAQ assesses the mode, frequency and duration of physical activity and sedentary behaviour across all parameters, including school hours and free time over the past 7 days. Estimates of energy expenditure for physical activity were derived from the CPAQ and YPAQ questionnaires. The calculation was based on the formula [4] used to estimate daily PAEEq, according to accepted metabolic equivalent of task (MET) values [5]. PAEEq levels were assessed according to the Sesso classification [6] as follows:

- Low: <2,100 kilojoules per week (kJ/wk)
- Low intermediate: 2,100–4,199 kJ/wk
- Intermediate: 4,200–8,399 kJ/wk
- Upper intermediate: 8,400–12,599 kJ/wk
- High: ≥12,600 kJ/wk [26]

Children with familial hypercholesterolemia included in the study were interviewed using an adapted Food Frequency Questionnaire (FETA, FFQ EPIC Tool for Analysis® University of Cambridge) [7]. The interview was conducted with parents present as it was requested by all patients.

The FFQ EPIC Tool for Analysis® University of Cambridge food frequency questionnaire is designed to measure the participant's usual food intake during the previous year. The main part of the questionnaire contains a list of the 130 most frequently and infrequently consumed food items. For each item on the list, participants are asked to indicate their usual frequency of consumption by selecting one of nine frequency categories. Categories range from "never" or "less than once a month" to "6+ times a day". Portions are reported in units or usual portions (e.g., one apple, one slice of bread) or in household measures (e.g., glass, cup, spoon). Each item in the questionnaire was assigned an average portion size (this portion size is the same for all participants, regardless of their gender or age). The input data were processed in FETA® University of Cambridge [7, 27].

Extended lipid profile data (TC, LDL-C, HDL-C, VLDL-C, triglycerides, rC, non-LDL-C, apoA1, apoB, lipoprotein (a)) and dp-uc matrix Gla protein level were analyzed with SAS® OnDemand for Academics (SAS Institute Inc, North Carolina, USA). Data were assumed to be normally distributed (verified analytically by Shapiro-Wilk, Kolmogorov-Smirnov, and graphically by Q-Q plot). Statistical significance was set at $p \leq 0.05$.

The interpretation of the results was based on the strength of the association, derived from the obtained Pearson correlation coefficient [8]. After analyzing the correlation matrix, all possible combinations of variables were considered to identify potential patterns and interactions. Based on the correlation matrix and the analysis of all variable combinations, a thorough selection of variables for further analysis was conducted. The variables were chosen based on their correlation strength, statistical significance, and relevance to the study's objectives. Using logistic regression analysis, the relationship between mGla protein levels and the presence of a familial hypercholesterolemia diagnosis was investigated. The model's effectiveness was evaluated using the receiver operating characteristic (ROC) curve.

A stepwise multiple linear regression analysis was conducted to determine which variables significantly predict the mGla protein variable in both the FH and comparison groups, followed by an evaluation of the model's effectiveness.

## RESULTS AND DISCUSSION

In children from the Ukrainian Familial Hypercholesterolemia Registry, there is a clear association between the presence of FH and elevated blood plasma levels of mGla protein. This marker of arterial media microcalcification is significantly higher in pediatric patients with familial hypercholesterolemia across all age groups compared to the control group. Complete data on the lipid profile and dp-uc MGP levels of children in both the patient and control groups can be found in our previous research paper (Marushko et al., 2022) [9]. Therefore, the measurement of mGla protein may be used as a marker of vascular microcalcification [10], regardless of etiology.

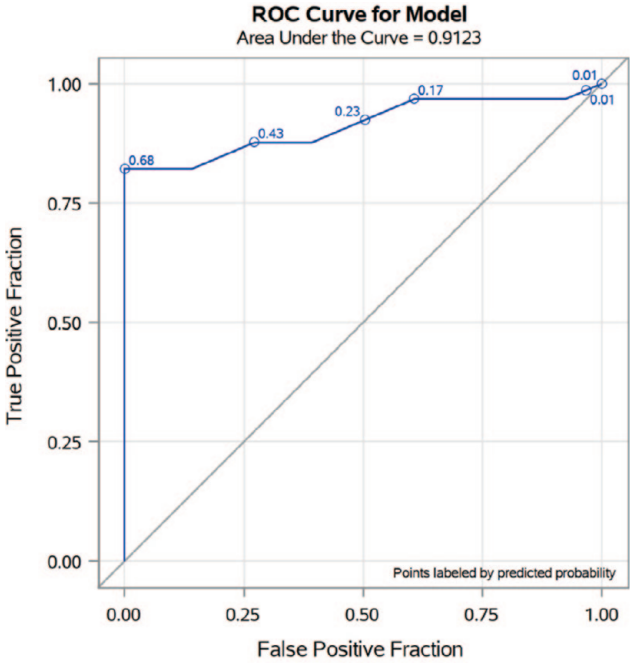


**Figure 1. ROC Curve of the Model. Area Under the Curve (AUC) = 0.912**

The association between mGla protein levels and the diagnosis of familial hypercholesterolemia was investigated using logistic regression analysis. The performance of the model was assessed using the ROC curve. The area under the curve (AUC) was calculated to be 0.912, which indicates a high level of discriminative ability (Figure 1).

The optimal cut-off point for the mGla protein level, determined by maximizing the Youden index (Youden J = 0.680), was 751.49 pmol/L, which provided the best balance between sensitivity (82.17%) and specificity (85.87%) (Figure 2). These results suggest that the mGla protein biomarker may be a useful predictor of intimal and medial calcification in patients with familial hypercholesterolemia.

In the present study, as in the study by Shroff [25], no association was found between the level of mGla protein and the Doppler sonographic measurements of major blood vessels. In all the studied children with FH, blood pressure indicators were also within the 50$^{th}$–70$^{th}$ percentiles, further confirming the subclinical nature of vascular damage in our patients with FH and the importance of laboratory diagnostics for identifying such patients [9].

In the analysis of the correlation matrix in children with FH, partial Pearson correlation controlling for weight revealed a moderate negative association between age and systolic blood pressure (r = -0.67; p = 0.04), and a strong positive association between age and mGla protein levels (r = 0.76; p = 0.01). It is important to note that this correlation is partial, with weight control, which enhances the reliability of the result. After controlling for age, a moderate positive correlation was found between body mass and systolic blood pressure (r = 0.69; p = 0.03), and a strong positive correlation was found between body mass and carotid intima-media thickness (r = 0.72; p = 0.02). The correlations between the variables after controlling for age and body mass are presented in Table 3.

A multiple linear regression analysis was conducted to determine whether age and cholesterol intake according to FFQ® data significantly predict the mGla protein variable in children with FH.

The fitted regression model was as follows: mGla protein level = 593.65 + 19.16*(age) + 0.70*(cholesterol intake). The regression model indicated that the predictors

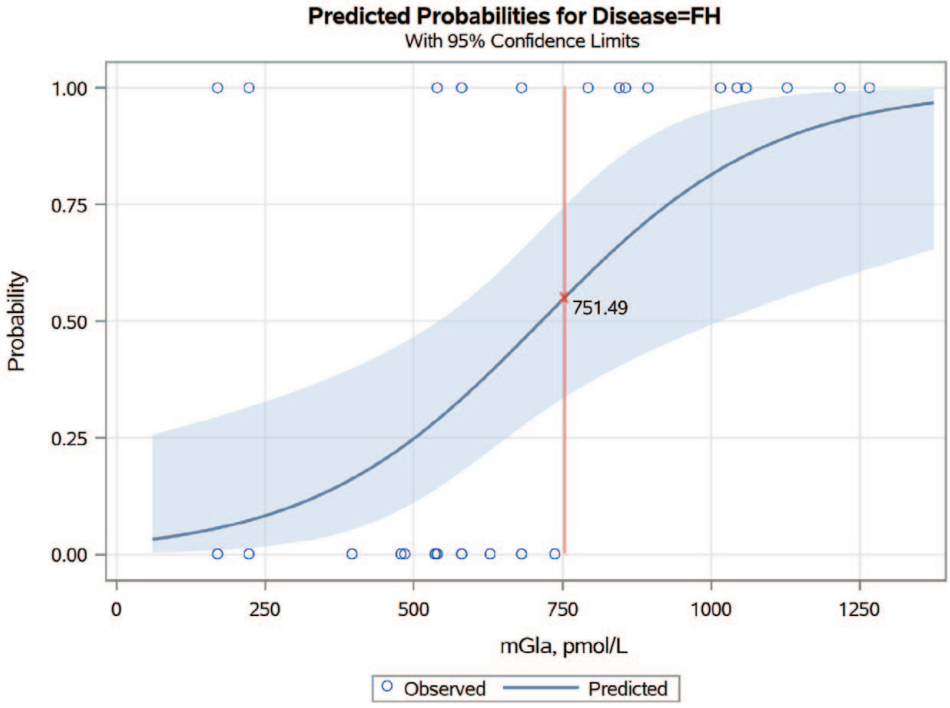


**Figure 2. Graph of predicted probability of FH diagnosis based on logistic regression analysis and ROC analysis using mGla protein level (pmol/L) as a predictor**

*Table 3*

**Correlations between clinical variables and health or dietary outcomes after controlling for age and body mass in children with FH from Ukrainian FH registry**

| Variable A | Variable B | Pearson correlation (r) and significance (p) |
|---|---|---|
| apoB level | KINDL® questionnaire segment "Physical Well-being" | r = 0.92; p < 0.01 |
| matrix Gla protein levels | FFQ® cholesterol intake | r = 0.94; p < 0.01 |
| Ejection fraction | Average daily energy intake (kcal) | r = 0.83; p = 0.01 |
| Ejection fraction | KINDL® questionnaire segment "Self-esteem" | r = -0.89; p < 0.01 |
| Left atrial volume indexed to BSA (LAVI) | HDL levels | r = -0.76; p = 0.02 |
| Average daily energy intake (kcal) | Fractional shortening (%) | r = 0.78; p = 0.02 |
| Average daily energy intake (kcal) | Total cholesterol levels | r = -0.77; p = 0.02 |
| rC | KINDL® questionnaire segment "Physical Well-being" | r = -0.86; p < 0.01 |
| Plasma triglycerides | KINDL® questionnaire segment "Physical Well-being" | r = -0.83; p = 0.01 |
| Mitral E/A ratio | KINDL® overall health-related quality of life score | r = 0.82; p = 0.01 |

explained 91.01% of the variance, and a significant collective effect was found, $F = 46.56$; $p < 0.0001$; $R^2 = 0.91$. The individual predictors resulted in age ($\beta = 19.16$; $t = 4.23$; $p = 0.0039$) and cholesterol intake ($\beta = 0.70$; $t = 5.13$; $p = 0.0013$). No similar dependency was observed in the control group. It can be asserted that in our sample of children with FH, exposure to elevated cholesterol levels over a longer period is significantly associated with higher levels of the vascular calcification marker, mGla protein (Figure 3). Therefore, with age, in children from the Ukrainian familial hypercholesterolemia registry, prolonged cholesterol exposure may be linked to a greater risk of vascular calcification.

The regression model also showed that the predictor of FFQ® cholesterol intake significantly predicted the variable KINDL® "Self-Esteem" in our sample of children with FH. The model explained 49.55% of the variance, and a significant collective effect was found, $F = 9.84$; $p = 0.01$; $R^2 = 0.49$. This suggests that nearly half of the variation in self-esteem levels can be attributed to cholesterol intake. No such relationship was observed in the control group, which may indicate a unique effect of cholesterol intake on the psychosocial well-being of children with FH.

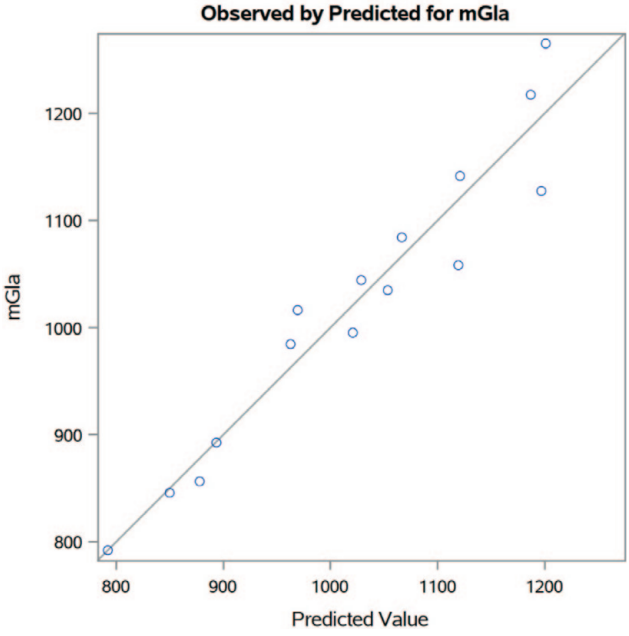


**Figure 3. Regression model with predictors significantly predicting dp-uc MGP in children with FH**

## CONCLUSIONS

This study confirmed that the vascular microcalcification marker mGla protein is correlated with the presence of FH, highlighting its important role in diagnosing arterial stiffness and managing these patients.

At the level of 751.49 pmol/L, dp-uc MGP stratifies FH patients from healthy peers with a sensitivity of 82.17% and a specificity of 85.87%. The effectiveness of the developed regression model ($R^2 = 0.91$; $p < 0.0001$) emphasizes the significance of age and cholesterol intake as predictors of elevated mGla protein levels.

Furthermore, the study results suggest the potential use of mGla protein for risk stratification and the development of preventive strategies to avoid vascular wall microcalcification.

These findings indicate the need for additional research to further explore and validate the predictors of cardiovascular lesions and vascular microcalcification in pediatric patients with FH. Further studies are essential to deepen our understanding and refine the statistical models in this area.

Additionally, the study results highlight the necessity of a comprehensive approach to treating patients with FH, which involves not only controlling biochemical parameters but also paying attention to their psychosocial state. Given the complexity of the disease's pathogenesis, it is essential to integrate medical treatment with psychosocial support, including dietary counseling, psychological care, and social adaptation. Thus, monitoring mGla protein levels, alongside a comprehensive approach, could become a vital tool in reducing cardiovascular morbidity and mortality among children with FH.

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



FAMILY MEDICINE. EUROPEAN PRACTICES / СІМЕЙНА МЕДИЦИНА. ЄВРОПЕЙСЬКІ ПРАКТИКИ • ISSN 2786-7218 (Online) | ISSN 2786-720X (Print) №4 (110)/2024

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*Стаття надійшла до редакції 23.08.2024. – Дата першого рішення 28.08.2024. – Стаття подана до друку 04.10.2024*