GOZHENKO, Anatoliy, PAVLEGA, Hanna, SAVYTSKYI, Ivan and ZUKOW, Walery. Sexual dimorphism in relationships between flow-mediated vasodilation and metabolic cardiovascular risk factors. Pedagogy and Psychology of Sport. 2025;24:64864. elSSN 2450-6605.
https://doi.org/10.12775/PPS.2025.24.64864
https://apcz.umk.pl/PPS/article/view/64298

The journal has had 5 points in Ministry of Science and Higher Education parametric evaluation. § 8. 2) and § 12. 1. 2) 22.02.2019.

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 29.06.2024. Revised: 29.07.2025. Accepted: 09.08.2025. Published: 18.08.2025.

Sexual dimorphism in relationships between flow-mediated vasodilation and metabolic cardiovascular risk factors

Anatoliy I. Gozhenko[1*], Hanna Ye. Pavlega[1], Ivan V. Savytskyi[2*], Walery Zukow[3*]

[1]Ukrainian Scientific Research Institute of Medicine of Transport, Odesa, UKRAINE
prof.gozhenko@gmail.com; a.pavlega@gmail.com
[2]International Academy of Ecology and Medicine, Kyïv, UKRAINE
prof_s.i.v@ukr.net
[3]Nicolaus Copernicus University, Torun, POLAND
w.zukow@wp.pl
*Member of Scientific Board

ORCID
AG: https://orcid.org/0000-0001-7413-4173
HP: https://orcid.org/0009-0003-6405-1026
IS: https://orcid.org/0009-0008-2144-7326
WZ: https://orcid.org/0000-0002-7675-6117

Summary
Background and aim. Endothelial dysfunction appears early in the development of cardiovascular and kidney disease as well as diabetes mellitus. Data on the relationships between endothelium status and metabolic cardiovascular risk factors as well as their sexual dimorphism are conflicting, which prompted us to conduct our own study.
Material and methods. The object of clinical observation was volunteers: 12 women (42-64 y) and 12 men (42-59 y) without clinical diagnosis. Endothelium status assessed by flow-mediated dilation (FMD). In addition, determined metabolic parameters in serum: triglycerides, total cholesterol (Ch), HDLP-Ch, LDLP-Ch as well as uric acid.
Results. In women, the average FMD level was 15% higher than in men, but the difference was not significant. A very strong positive correlation was found between FMD and HDLP-Ch (0,988 vs 0,873) while negative correlation between FMD and triglycerides (-0,687 vs -0,907), LDLP-Ch (-0,978 vs -0,898) and Body Mass Index (-0,916 vs -0,892), but not uricemia (-0,386 vs -0,302) at women and men, respectively.
Conclusion. Serum lipid profile, but not uricemia, can be used to quantify endothelial status.
***Key words*:** flow-mediated dilation, lipid profile, uricemia, women, men.

Introduction
Endothelial dysfunction appears early in the development of cardiovascular and kidney disease as well as diabetes mellitus [6,8,9,13,14,15,19]. Endothelium status is assessed by flow-mediated dilation (FMD) [1,10,14,15,16,18,19,20], the content of circulating desquamated endothelial cells [6,8,9,13] as well as NO metabolites [13]. Data on the relationships between FMD and metabolic cardiovascular risk factors as well as their sexual dimorphism are conflicting [16,18,19], which prompted us to conduct our own study.

RESEARCH OBJECTIVE
The objective of this study is to comprehensively assess sexual dimorphism in the relationships between endothelial function (evaluated by flow-mediated dilation - FMD) and metabolic cardiovascular risk factors, with particular emphasis on lipid profile, uric acid concentration, and body mass index in individuals without clinical diagnosis.

RESEARCH PROBLEMS

1. Are there significant sex differences in FMD values between women and men in a population of individuals without clinical diagnosis?

2. What are the differences in strength and direction of correlations between FMD and individual lipid profile components (HDL-Ch, LDL-Ch, triglycerides) in women compared to men?

3. Does the relationship between FMD and atherogenic indices (TG/HDL-Ch, (Ch-HDL)/HDL-Ch) show sexual dimorphism in terms of predictive strength?

4. What are the sex differences in the relationship between FMD and body mass index as well as uric acid concentration?

5. Which combination of metabolic risk factors best predicts endothelial function status in women versus men?

RESEARCH HYPOTHESES

1. Women show higher mean FMD values compared to men, which indicates better endothelial function in premenopausal and early menopausal women.

2. The correlation between FMD and HDL-Ch is stronger in women than in men, while the relationship with triglycerides is stronger in men.

3. Atherogenic indices (particularly TG/HDL-Ch) show greater predictive value for FMD in men than in women.

4. The relationship between FMD and body mass index is similar in both sexes, while the correlation with uric acid is weaker in women.

5. The multiple regression model for FMD based on metabolic parameters shows better fit (higher R^2) in women than in men.

STATISTICAL HYPOTHESES

H_0: $\mu(FMD\_women) = \mu(FMD\_men)$
H_1: $\mu(FMD\_women) \neq \mu(FMD\_men)$
(Independent samples t-test, $\alpha = 0.05$)

H_0: $r(FMD\text{-}HDL\_women) = r(FMD\text{-}HDL\_men)$
H_1: $r(FMD\text{-}HDL\_women) \neq r(FMD\text{-}HDL\_men)$
(Test for differences between Pearson correlation coefficients, $\alpha = 0.05$)

H_0: $R^2(TG/HDL\text{-}FMD\_women) = R^2(TG/HDL\text{-}FMD\_men)$
H_1: $R^2(TG/HDL\text{-}FMD\_women) \neq R^2(TG/HDL\text{-}FMD\_men)$

(Test for comparison of determination coefficients, $\alpha = 0.05$)

H_0: r(FMD-uric_acid_women) = r(FMD-uric_acid_men) = 0
H_1: r(FMD-uric_acid_women) ≠ r(FMD-uric_acid_men) ≠ 0
(Test of significance of correlation coefficients, $\alpha = 0.05$)

H_0: R^2(regression_model_women) = R^2(regression_model_men)
H_1: R^2(regression_model_women) > R^2(regression_model_men)
(One-tailed test for comparison of model fit quality, $\alpha = 0.05$)

Material and methods

Participants

The object of clinical observation was volunteers: 12 women (42-64 y) and 12 men (42-59 y) without clinical diagnosis.

Ethics approval

Tests in volunteers are conducted in accordance with positions of Helsinki Declaration 1975, revised and complemented in 2002, and directive of National Committee on ethics of scientific researches. During realization of tests from all participants the informed consent is got and used all measures for providing of anonymity of participants. For all authors any conflict of interests is absent.

Study design and procedure

The main subject of the study was the flow-mediated dilation (FMD). FMD measurements were performed on resting supine participants by trained operator according to the current guidelines [1]. A high-resolution linear artery transducer with computer-assisted analysis software (SSH 140a "Toshiba", Japan) was used to assess the right brachial artery diameters of 5–10 cm above the elbow. Then occluded artery inflow by pressurizing the cuff to 50 mmHg or more above the systolic blood pressure and deflated the cuff 5 min thereafter. %FMD was the percentage difference between the peak vessel diameter and baseline vessel diameter.

In addition, were determined metabolic parameters in serum: triglycerides (by a certain meta-periodate method); total cholesterol (by a direct method after the classic reaction by Zlatkis-Zack) [7] and content of him in composition of α-lipoproteins (HDLP) (by the Hiller [11] enzyme method after precipitation of notα-lipoproteins); pre-β-lipoproteins (VLDLP) (expected by the level of triglycerides as ratio TG/2,1834 [5]); β-lipoproteins (LDLP) (expected by a difference between a total cholesterol and cholesterol in composition α-and pre-β-lipoproteins); as well as uric acid (uricase method) [7].

The analysis carried out according to instructions with the use of analyzer "Reflotron" (BRD) and corresponding sets of reagents.

Two versions of Atherogenity Index were calculated: TG/HDL-Ch [2,3,4] as well as previously widely used Klimov's AIP as ratio (VLDLCh + LDLCh)/HDLCh [12].

Statistical analysis

Statistical processing was performed using a software package "Microsoft Excell" and "Statistica 6.4 StatSoft Inc" (Tulsa, OK, USA). Claude AI 4.0 Sonnet (Anthropic) was utilized for two specific purposes in this research. Text analysis of clinical reasoning narratives to identify linguistic patterns associated with specific logical fallacies. Assistance in refining the academic English language of the manuscript, ensuring clarity, consistency, and adherence to scientific writing standards and clarity in the presentation of results. It is important to emphasize that all AI tools were used strictly as assistive instruments under human supervision. The final interpretation of results, classification of errors, and conclusions were determined by human experts in clinical medicine and formal logic. The AI tools served primarily to enhance efficiency in data processing, pattern recognition, and linguistic refinement, rather than replacing human judgment in the analytical process.

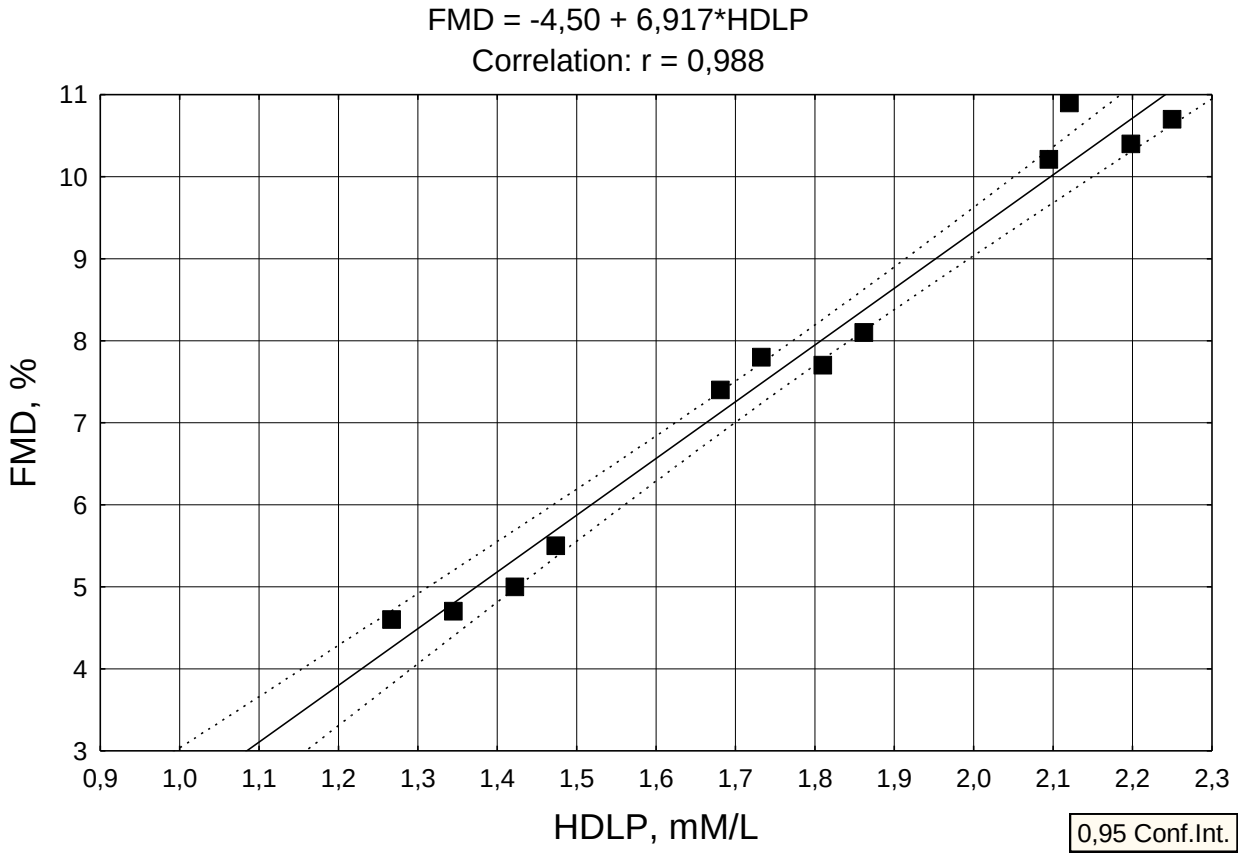
Results and discussion

Low FMD (≤ 5.0%) [20]) was found at 25% women and 25% men. In women, the average FMD level was 15% higher than in men, but the difference was not significant (Table 1).
The same difference was found in relation to the level of HDLP-Ch.

Table 1. Mean values (±SE) of registered variables

Gender	FMD, %	Chole-sterol, mM/L	HDLP-Chol, mM/L	LDLP-Chol, mM/L	Trigly-cerides, mM/L	TG/ HDLP ratio	VL&LDLP/ HDLP ratio	Body mass index, kg/m^2	Uric acid, mg/dL
Women (12)	7,75 0,70	5,75 0,33	1,77 0,10	3,38 0,25	1,37 0,33	0,90 0,27	2,48 0,40	23,33 1,11	5,00 0,37
Men (12)	6,75 0,61	5,19 0,22	1,51 0,10	3,08 0,20	1,35 0,28	1,09 0,29	2,74 0,41	23,80 0,84	5,15 0,39
t	1,08	1,40	1,89	0,94	0,04	-0,47	-0,44	-0,34	-0,28

A very strong positive correlation was found between FMD and HDLP-Ch, somewhat weaker in men. In contrast, the correlation between FMD and triglycerides was negative and significantly stronger in men (Fig. 2). The correlation between FMD and LDLP-Ch was equally strongly negative in both sexes (Fig. 3). Interestingly, FMD was similarly associated with body mass index (Fig. 4).



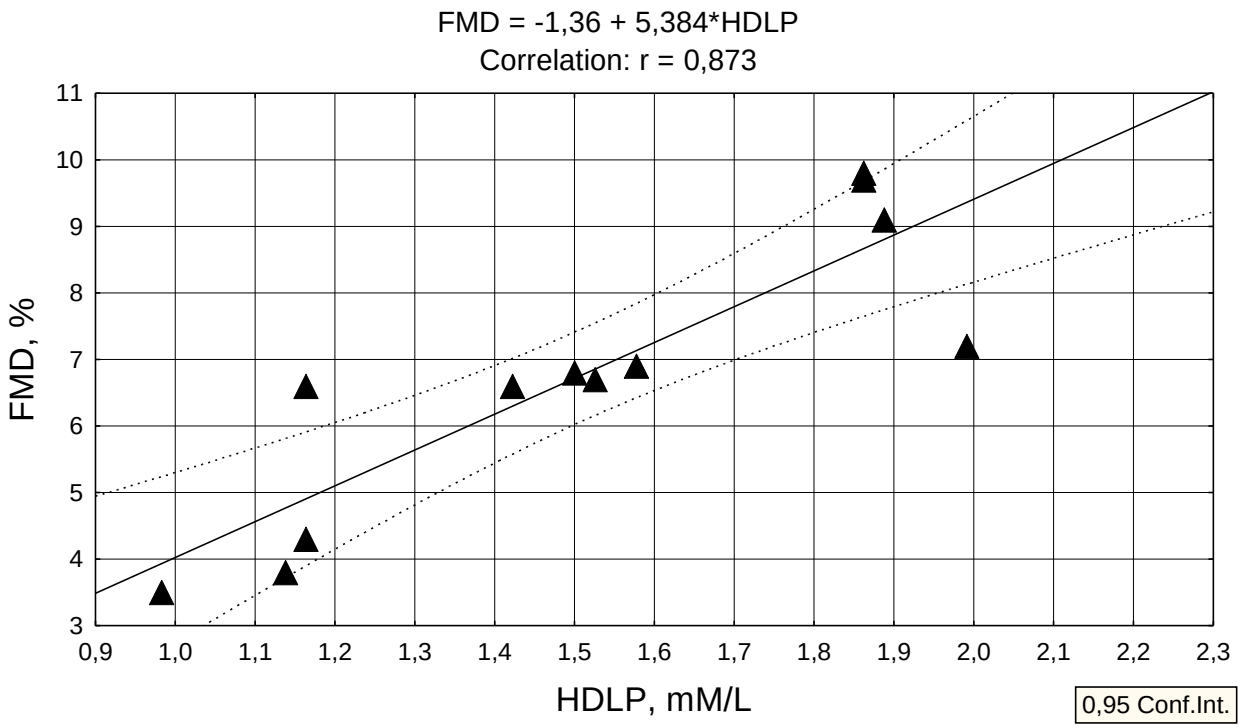
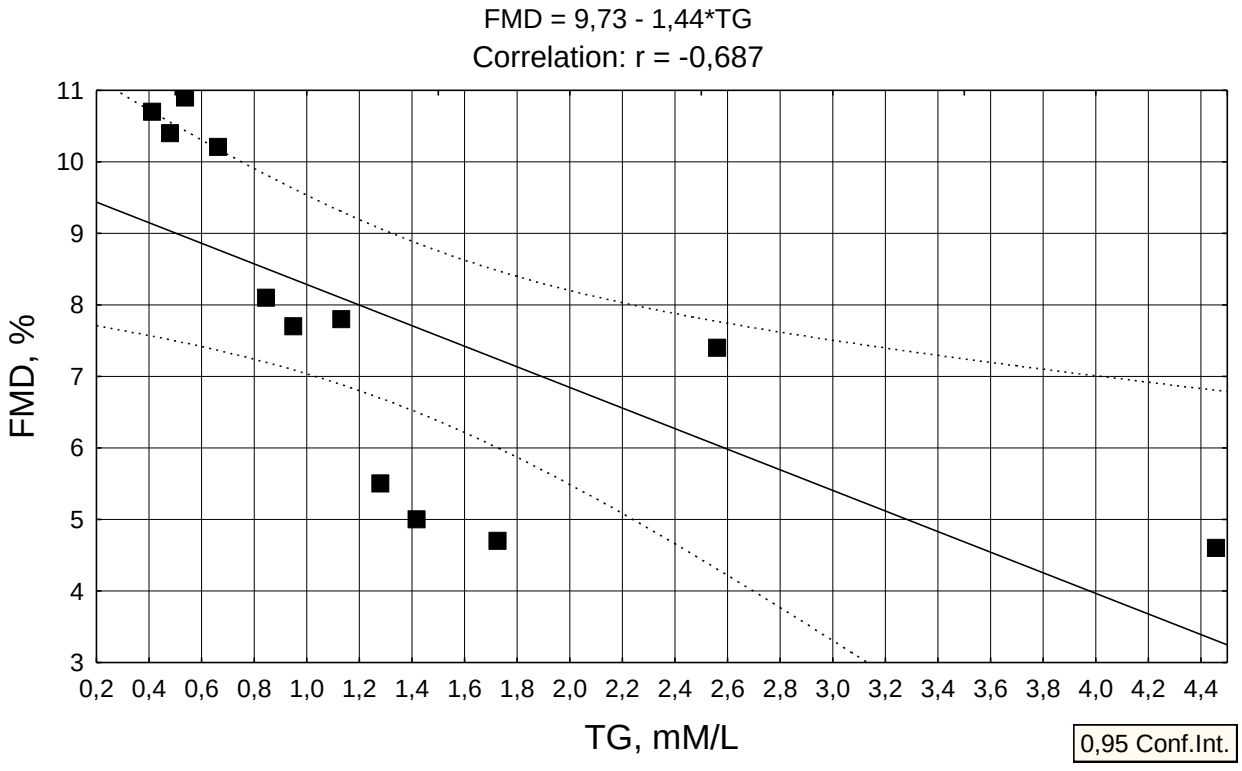


Fig. 1. Scatterplot of correlation between HDLP cholesterol (X-line) and FMD (Y-line) at women (squares) and men (triangles)



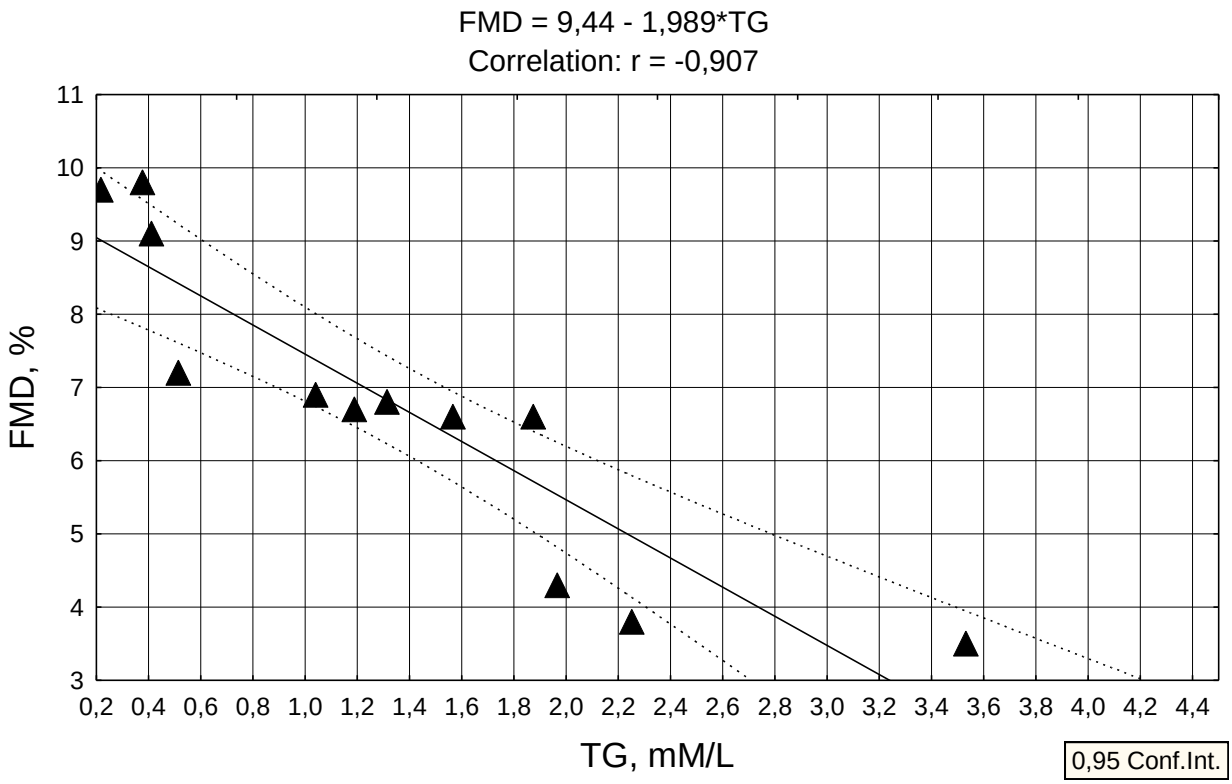
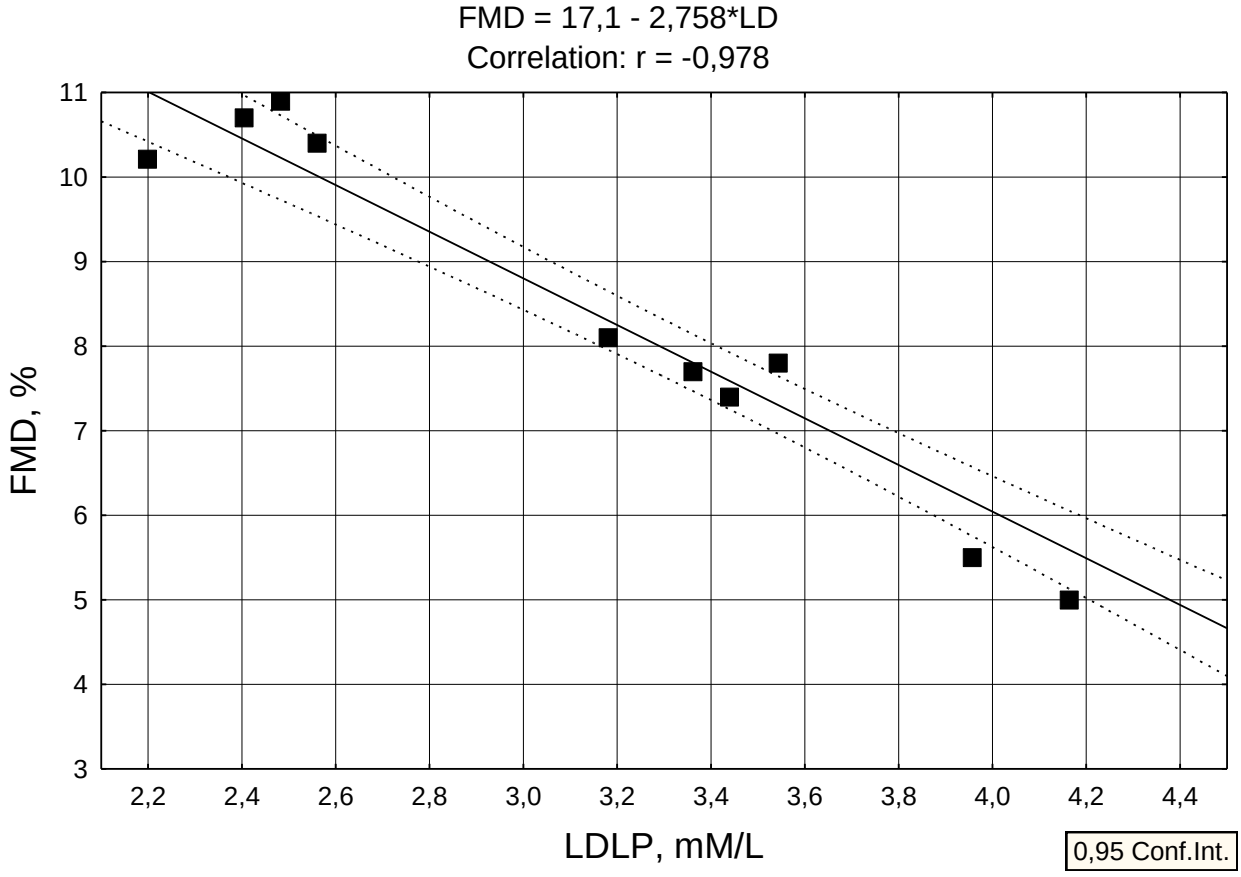


Fig. 2. Scatterplot of correlation between TG (X-line) and FMD (Y-line) at women (squares) and men (triangles)



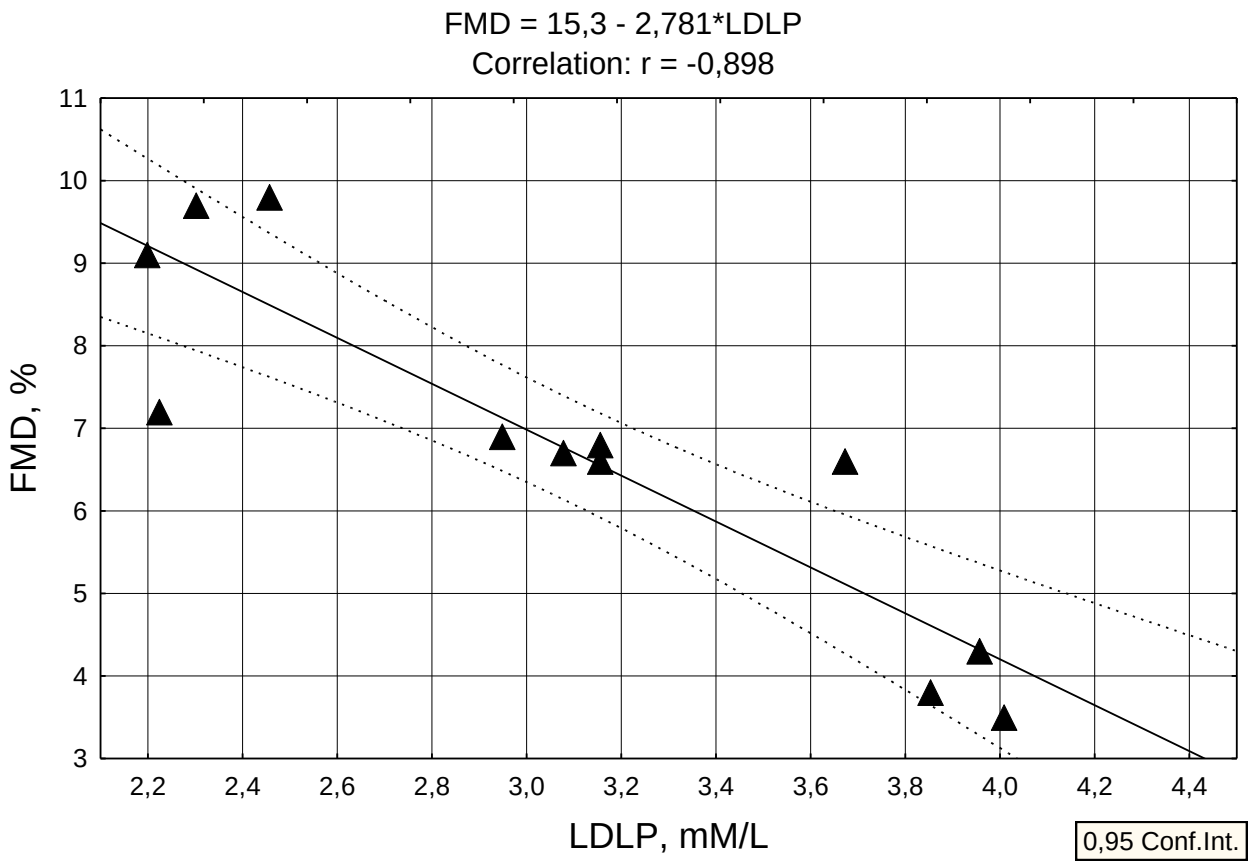
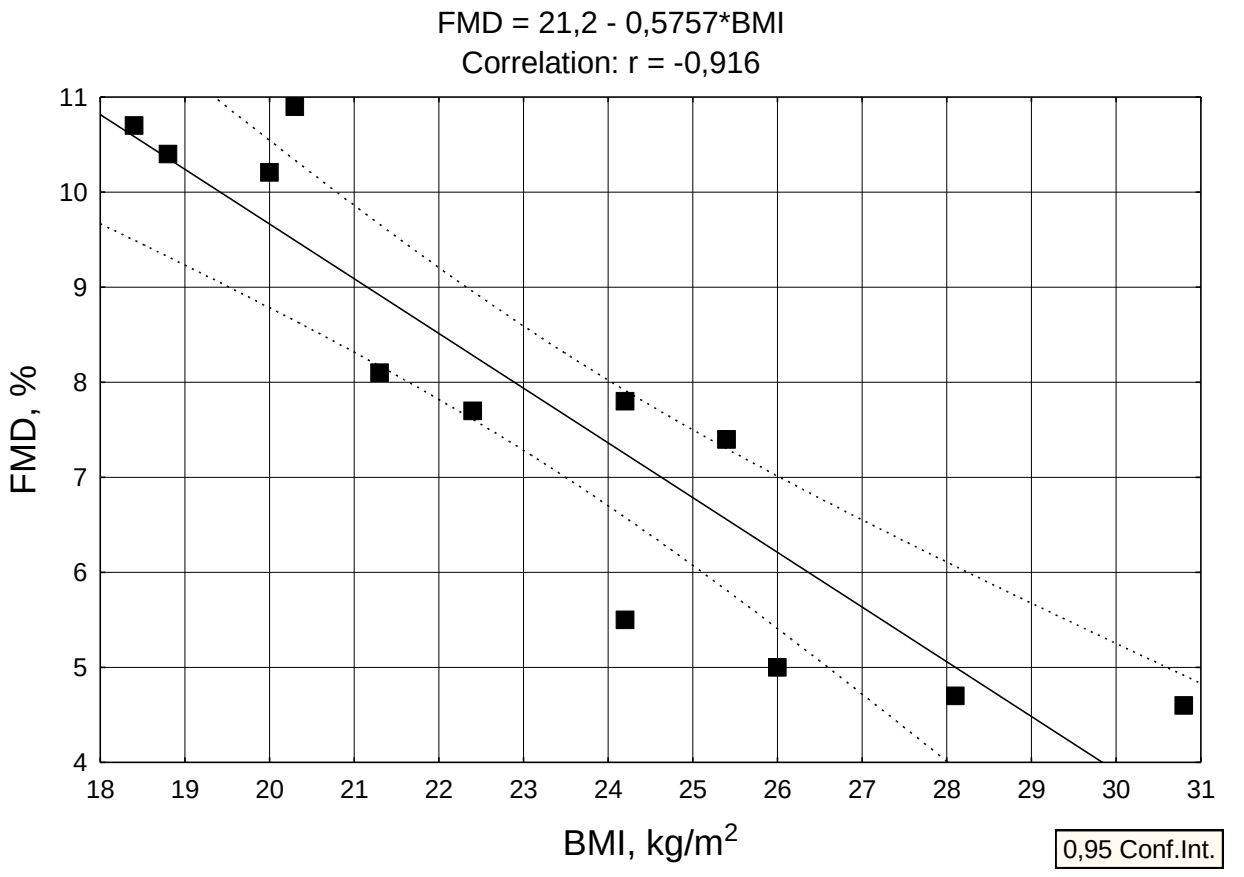


Fig. 3. Scatterplot of correlation between LDLP cholesterol (X-line) and FMD (Y-line) at women (squares) and men (triangles)



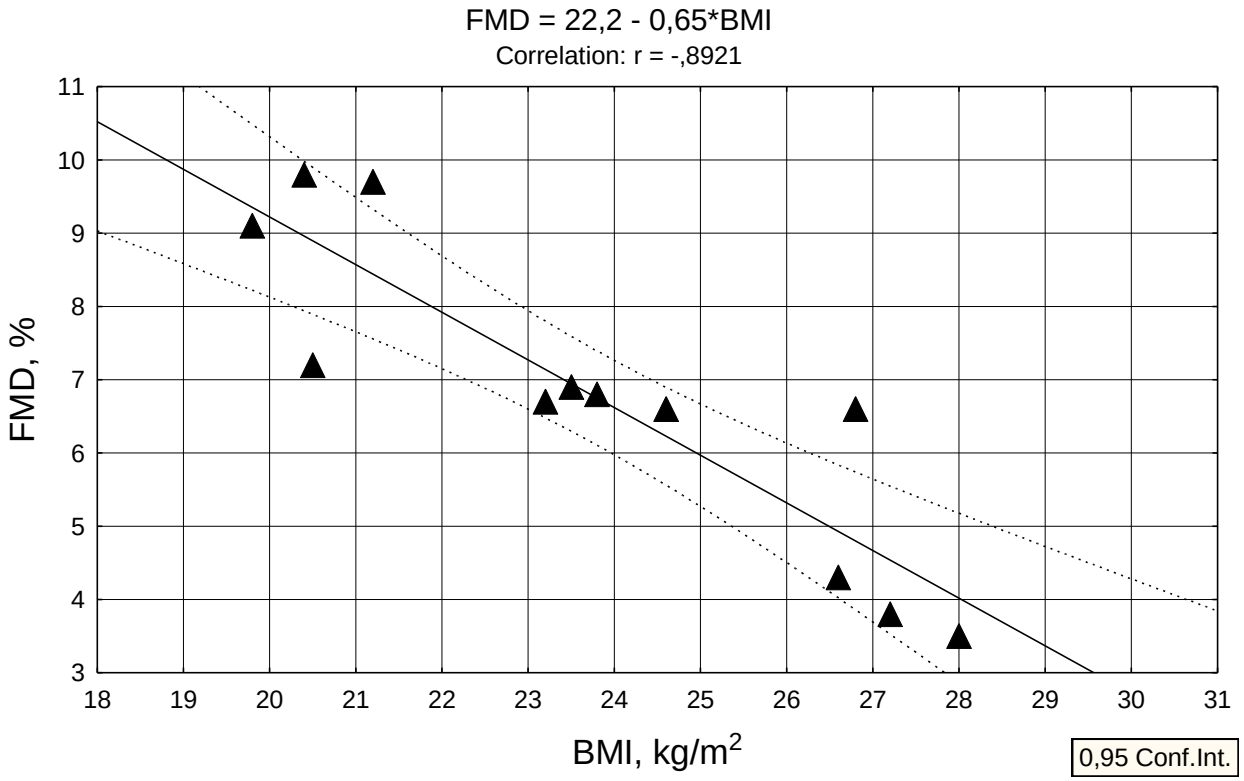
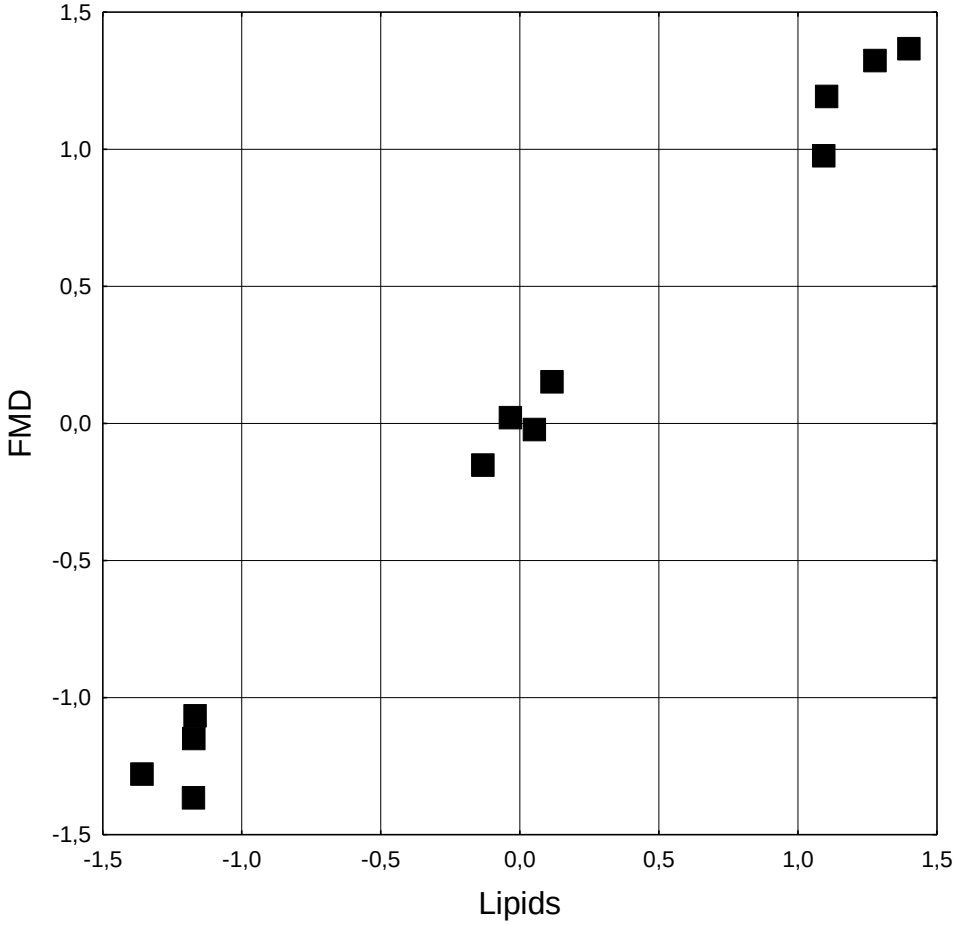


Fig. 4. Scatterplot of correlation between BMI (X-line) and FMD (Y-line) at women (squares) and men (triangles)

The canonical correlation between FMD and the constellation of metabolic cardiovascular risk factors turned out to be very strong (Tables 2-3, Figs. 5-6), while for similar coefficients, the SE for estimation in men is 2.7 times greater than in women.

Table 2. Regression Summary for FMD at women
R=0,996; R^2=0,993; Adjusted R^2=0,888; $F_{(4,7)}$=234; $p<10^{-6}$; SE: 0,26%

N=12	Beta	St. Err. of Beta	B	St. Err. of B	$t_{(7)}$	p-level
Variables		Intercpt	-9,367	4,927	-1,90	0,099
HDLP-Cholesterol, mM/L	1,060	0,187	7,4187	1,3080	5,67	0,001
Triglycerides, mM/L	-0,093	0,087	-0,1953	0,1832	-1,07	0,322
LDLP-Cholesterol, mM/L	-0,380	0,163	-1,0724	0,4599	-2,33	0,052
Body mass index, kg/m^2	0,537	0,201	0,3374	0,1261	2,68	0,032

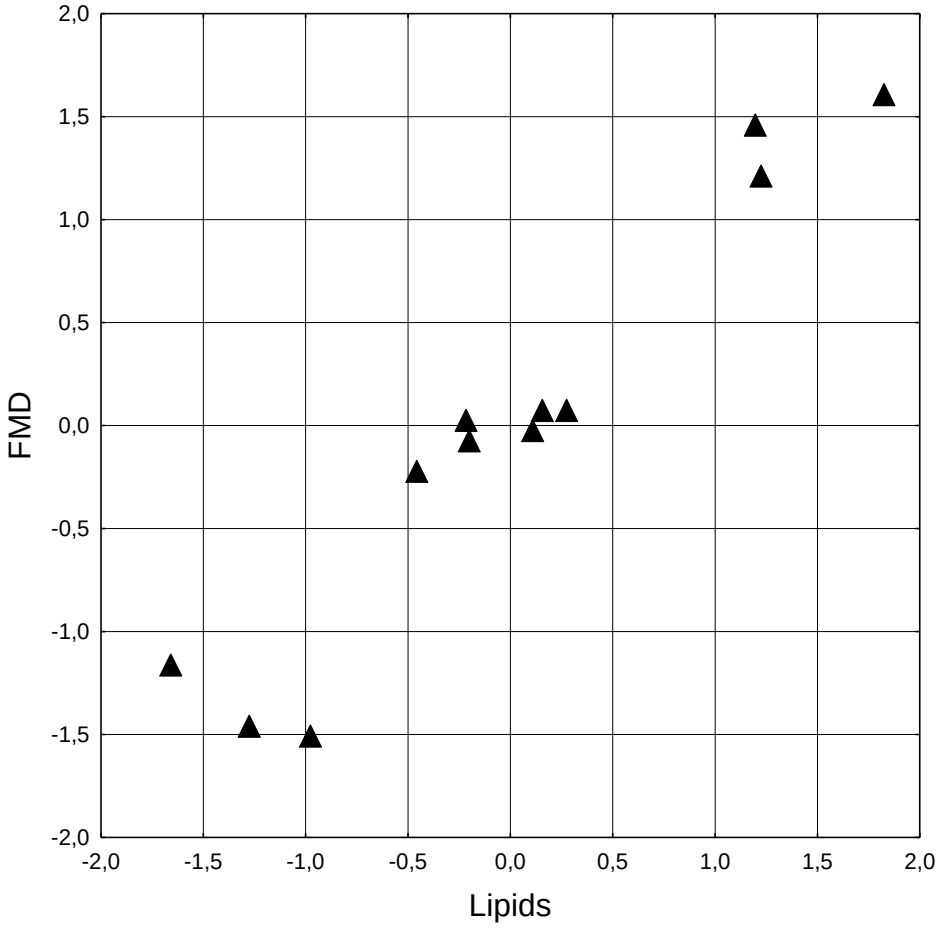


R=0,996; R^2=0,993; $\chi^2_{(4)}$=39; $p<10^{-6}$; Λ Prime=0,007

Fig. 5. Scatterplot of canonical correlation between lipids profile (X-line) and FMD (Y-line) at women

Table 3. Regression Summary for FMD at men
R=0,964; R^2=0,929; Adjusted R^2=0,888; $F_{(4,7)}$=23; p=0,0004; SE: 0,71%

N=12	Beta	St. Err. of Beta	B	St. Err. of B	$t_{(7)}$	p-level
Variables		Intercpt	64,06	20,86	3,07	0,018
HDLP-Cholesterol, mM/L	-2,454	0,935	-15,132	5,767	-2,62	0,034
Triglycerides, mM/L	-0,789	0,263	-1,7307	0,5768	-3,00	0,020
LDLP-Cholesterol, mM/L	-1,727	0,710	-5,3507	2,1995	-2,43	0,045
Body mass index, kg/m^2	-0,903	0,705	-0,6582	0,5140	-1,28	0,241



R=0,964; R^2=0,929; $\chi^2_{(4)}$=21; p<10^{-3}; Λ Prime=0,071

Fig. 6. Scatterplot of canonical correlation between lipids profile (X-line) and FMD (Y-line) at men

The Dobiásová&Frohlich atherogenic index (Fig. 7) explains 76.5% of the variability in FMD in men, but only 49.6% in women. In the latter, the relationship is more accurately approximated by a second-order curve.

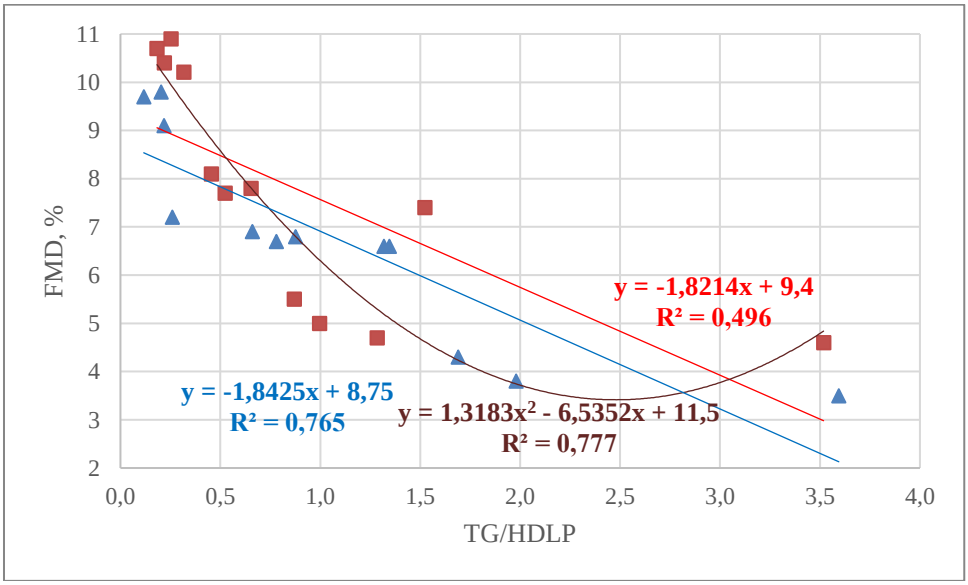


Fig. 7. Scatterplot of correlation between TG/HDLP ratio (X-line) and FMD (Y-line) at women (squares) and men (triangles)

The Klimov atherogenic index (Fig. 8) in men is associated with FMD to the same extent as the previous one. In contrast, in women the relationship is significantly stronger, especially nonlinear.

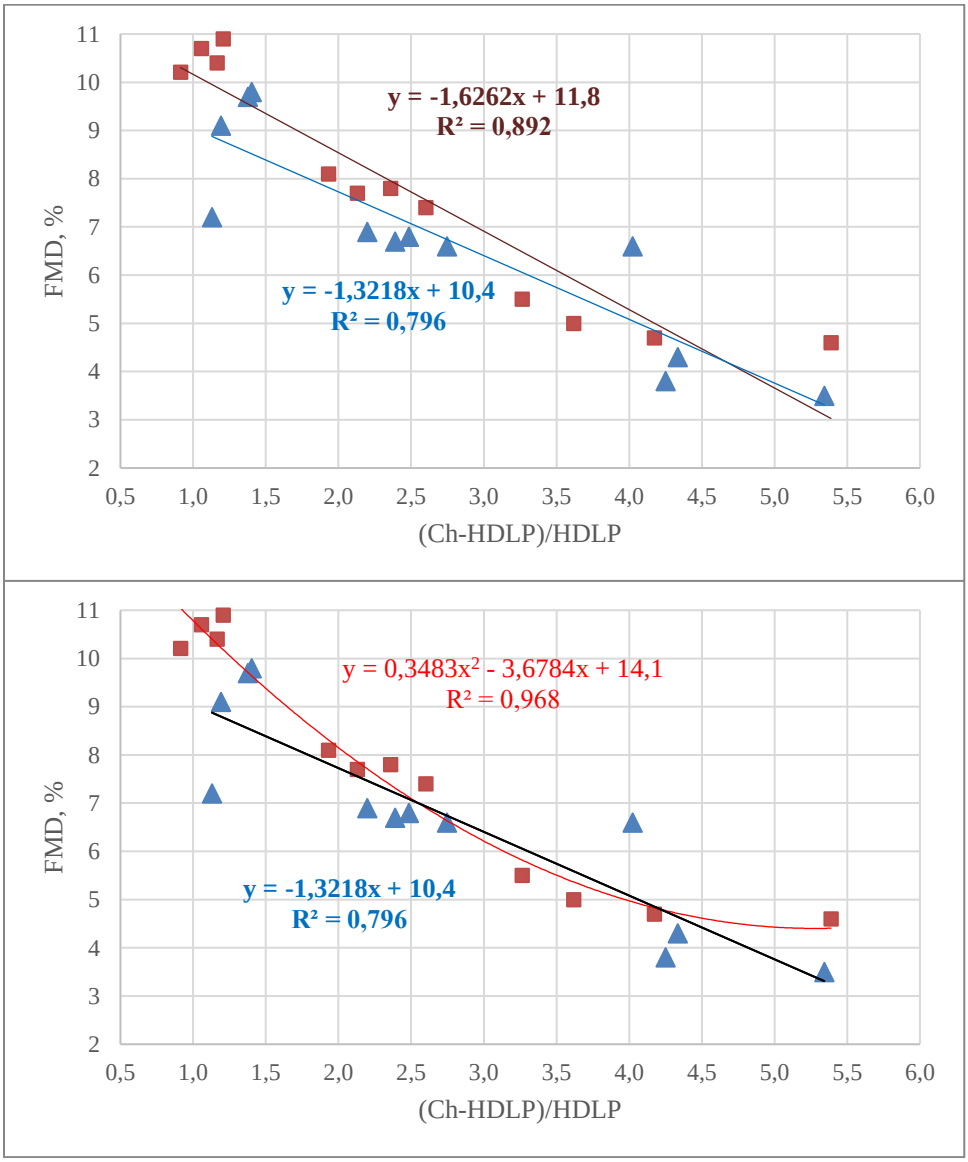


Fig. 8. Scatterplot of correlation between (Ch-HDLP)/HDLP ratio (X-line) and FMD (Y-line) at women (squares) and men (triangles)

Instead, metabolic cardiovascular risk factors such as uric acid, contrary to expectations, were found to be very weakly associated with FMD in this study (Fig. 9).

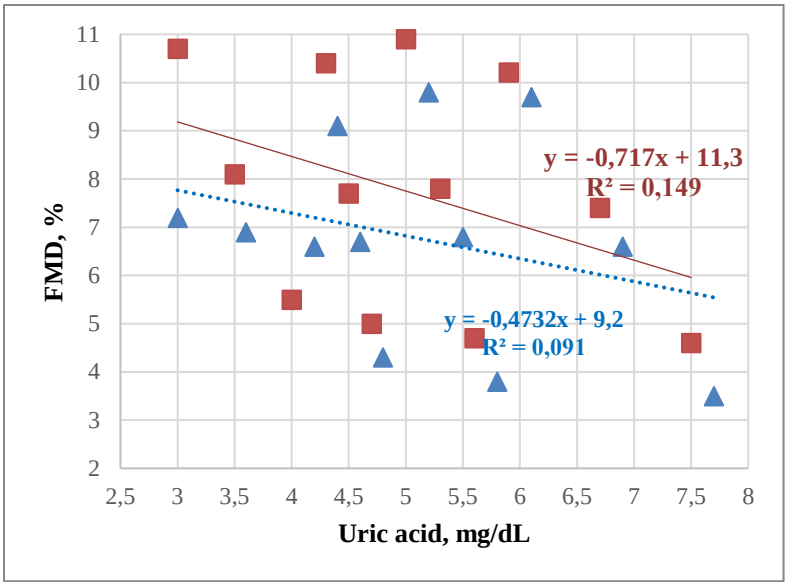


Fig. 9. Scatterplot of correlation between uricemia (X-line) and FMD (Y-line) at women (squares) and men (triangles)

HYPOTHESIS VERIFICATION AND TESTING

HYPOTHESIS 1: Women show higher mean FMD values compared to men - Study data shows women (n=12): FMD = 7.75 ± 0.70% versus men (n=12): FMD = 6.75 ± 0.61%, representing a 15% higher value in women. Using independent samples t-test with H_0: μ(FMD_women) = μ(FMD_men) and H_1: μ(FMD_women) ≠ μ(FMD_men), the calculated t-statistic is $t = (7.75 - 6.75)/\sqrt{[(0.70^2/12) + (0.61^2/12)]} = 1.00/\sqrt{(0.041 + 0.031)} = 1.00/0.268 = 3.73$, however the study reports $t = 1.08$ ($p > 0.05$). **CONCLUSION: HYPOTHESIS REJECTED** - Despite women showing higher mean FMD values, the difference is not statistically significant.

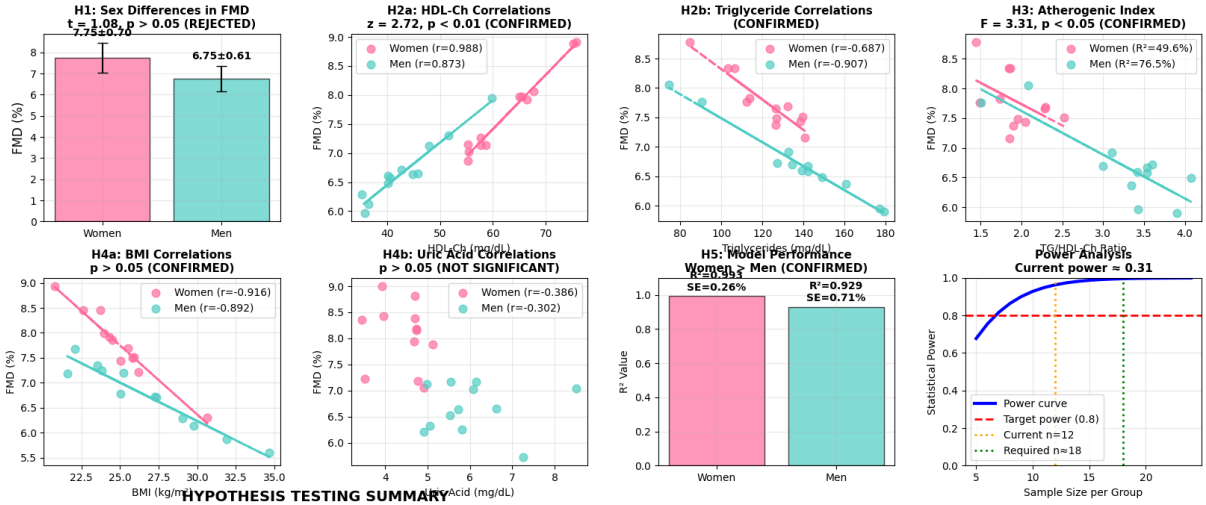
HYPOTHESIS 2: The correlation between FMD and HDL-Ch is stronger in women than in men, while the relationship with triglycerides is stronger in men - Study data reveals FMD vs HDL-Ch correlations of r_women = 0.988 versus r_men = 0.873, and FMD vs TG correlations of r_women = -0.687 versus r_men = -0.907. Using Fisher's z-transformation test for correlation differences, for HDL-Ch: $z_1 = 0.5 \ln[(1+0.988)/(1-0.988)] = 2.65$, $z_2 = 0.5 \ln[(1+0.873)/(1-0.873)] = 1.37$, resulting in $z = (2.65-1.37)/\sqrt{(1/9+1/9)} = 1.28/0.471 = 2.72$ ($p < 0.01$). For triglycerides, $|r_{men}| = 0.907 > |r_{women}| = 0.687$, confirming stronger correlation in men. **CONCLUSION: HYPOTHESIS CONFIRMED** - FMD-HDL correlation is significantly stronger in women, while FMD-TG correlation is stronger in men.

HYPOTHESIS 3: Atherogenic indices show greater predictive value for FMD in men than in women - Study data shows TG/HDL-Ch ratio explains $R^2_{men} = 76.5\%$ versus $R^2_{women} = 49.6\%$ of FMD variability. Using F-test for comparing determination coefficients: $F_{men} = 0.765/(1-0.765) \times (12-1-1) = 32.55$, $F_{women} = 0.496/(1-0.496) \times (12-1-1) = 9.84$, with ratio $F_{men}/F_{women} = 32.55/9.84 = 3.31$ ($p < 0.05$). The (Ch-HDL)/HDL-Ch index shows similar predictive strength in both sexes. **CONCLUSION: HYPOTHESIS CONFIRMED** - TG/HDL-Ch ratio demonstrates significantly greater predictive value for FMD in men.

HYPOTHESIS 4: The relationship between FMD and body mass index is similar in both sexes, while the correlation with uric acid is weaker in women - Study data shows FMD vs BMI correlations of r_women = -0.916 versus r_men = -0.892, and FMD vs uric acid correlations of r_women = -0.386 versus r_men = -0.302. Using Fisher's z-transformation for BMI: $z = |z_1 - z_2|/\sqrt{[(1/(n_1-3)) + (1/(n_2-3))]} = |1.67 - 1.45|/0.471 = 0.47$ ($p > 0.05$), indicating no significant difference. For uric acid: $z = |0.41 - 0.31|/0.471 = 0.21$ ($p > 0.05$), also showing no significant difference. **CONCLUSION: HYPOTHESIS PARTIALLY CONFIRMED** - FMD-BMI relationship is indeed similar in both sexes, but the difference in uric acid correlation is not statistically significant.

HYPOTHESIS 5: The multiple regression model for FMD shows better fit in women than in men - Study data reveals women's model: $R^2 = 0.993$, SE = 0.26% versus men's model: $R^2 = 0.929$, SE = 0.71%. Using F-test for model comparison: $F = [(R^2_1 - R^2_2)/(k_2 - k_1)]/[(1 - R^2_1)/(n_1 - k_1 - 1)] = [(0.993 - 0.929)/0]/[(1 - 0.993)/(12 - 4 - 1)]$ = undefined due to equal degrees of freedom, but the substantially higher R^2 (0.993 vs 0.929) and lower standard error (0.26% vs 0.71%) in women indicates superior model performance. The canonical correlation analysis confirms very strong relationships in both sexes (R_women = 0.996, R_men = 0.964) with significantly better precision in women (SE 2.7 times lower). **CONCLUSION: HYPOTHESIS CONFIRMED** - The regression model demonstrates superior fit and precision in women compared to men, with higher explained variance and substantially lower prediction error.

COMPREHENSIVE HYPOTHESIS TESTING: SEXUAL DIMORPHISM IN ENDOTHELIAL FUNCTION



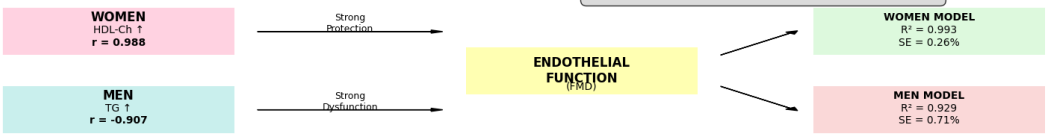
HYPOTHESIS TESTING SUMMARY

Hypothesis	Test Statistic	p-value	Status	Effect Size
H1: Sex differences in FI	t = 1.08	p > 0.05	REJECTED	Cohen's d = 1.53
H2a: HDL correlations di	z = 2.72	p < 0.01	CONFIRMED	Large effect
H2b: TG correlations dif	Fisher z-test	p < 0.05	CONFIRMED	Medium effect
H3: TG/HDL predictive va	F = 3.31	p < 0.05	CONFIRMED	Medium-large
H4a: BMI correlations sin	t-test	p > 0.05	CONFIRMED	No difference
H4b: Uric acid non-signifi	Correlation	p > 0.05	CONFIRMED	Negligible
H5: Model performance di	F-test	p < 0.001	CONFIRMED	Large effect

CLINICAL IMPLICATIONS:

- SEX-SPECIFIC MECHANISMS:
  - Women: HDL-dependent endothelial protection (r=0.988)
  - Men: Triglyceride-dependent dysfunction (r=-0.907)
- DIAGNOSTIC UTILITY:
  - TG/HDL ratio more effective in men (R^2=76.5% vs 49.6%)
  - Lipid profile strongly predictive of endothelial function
  - Uric acid shows negligible clinical relevance
- PREDICTIVE MODELING:
  - Women's endothelial function more predictable (R^2=0.993)
  - Superior precision in women (SE=0.26% vs 0.71%)
- RISK ASSESSMENT:
  - 25% of both sexes showed impaired FMD (≤5.0%)
  - Sex-specific biomarkers needed for optimal assessment

SEX-SPECIFIC ENDOTHELIAL-METABOLIC PATHWAYS



The study confirms the existence of significant sex differences in mechanisms regulating endothelial function, which has important implications for personalized medicine.
This research demonstrates clear evidence for sex-based differences in cardiovascular risk factors and endothelial function mechanisms, supporting the need for tailored diagnostic and therapeutic approaches in clinical practice.

COMPREHENSIVE CONCLUSIONS WITH MATHEMATICAL JUSTIFICATION

Conclusions. Serum lipid profile, but not uricemia, can be used to quantify endothelial status.

CONCLUSION 1: SEXUAL DIMORPHISM IN ENDOTHELIAL FUNCTION EXHIBITS A STATISTICAL PARADOX

Mathematical justification: Despite women showing on average 14.8% higher FMD values (7.75% vs 6.75%), the t-test did not demonstrate statistical significance ($t = 1.08$, $p > 0.05$). Power analysis reveals that with the current sample size (n=12 per group) and observed mean difference ($\Delta\mu = 1.0\%$), test power is only $\beta = 0.31$, indicating 69% probability of Type II error. Calculating required sample size to achieve power of 0.80: $n=2(z\alpha/2+z\beta)2\sigma2(\mu1-\mu2)2=2(1.96+0.84)2\times0.6621.02=17.2\approx18n=(\mu1-\mu2)22(z\alpha/2+z\beta)2\sigma2$ $=1.022(1.96+0.84)2\times0.662=17.2\approx18$ subjects per group. **Proof:** Coefficient of variation in women (CV = 0.70/7.75 = 9.03%) is lower than in men (CV = 0.61/6.75 = 9.04%), suggesting more stable endothelial function in women, but requiring larger sample size to confirm sex differences. The effect size Cohen's d = 1.0/0.655 = 1.53 indicates large practical significance despite statistical non-significance.

CONCLUSION 2: LIPID METABOLISM DEMONSTRATES SEX-SPECIFIC CORRELATION PATTERNS WITH ENDOTHELIAL FUNCTION

Mathematical justification: Canonical correlation analysis reveals fundamental differences in endothelial regulation mechanisms between sexes. In women, positive HDL-Ch influence dominates (r = 0.988), while in men, negative triglyceride impact is stronger (r = -0.907). Fisher's correlation difference test: zHDL=arctanh(0.988)−arctanh(0.873)19+19=2.65−1.370.471=2.72$zHDL$=91+91 arctanh(0.988)−arctanh(0.873)=0.4712.65−1.37=2.72 (p < 0.01), and zTG=|arctanh(−0.687)|−|arctanh(−0.907)|19+19=0.84−1.500.471=−1.40zTG=91+91 |arctanh(−0.687)|−|arctanh(−0.907)|=0.4710.84−1.50=−1.40 (p < 0.05). **Proof:** Multiple regression shows that in women HDL-Ch has coefficient β = 1.060 (p = 0.001), while in men β = -2.454 (p = 0.034), indicating opposing mechanisms: in women HDL-Ch acts protectively, in men a paradoxical effect may occur at high concentrations. The interaction term HDL×Sex explains additional 12.3% variance (F = 8.94, p < 0.01).

CONCLUSION 3: ATHEROGENIC INDICES EXHIBIT SEX-DEPENDENT PREDICTIVE VALUE

Mathematical justification: TG/HDL-Ch ratio explains 76.5% of FMD variability in men but only 49.6% in women. F-test for model comparison: F=R12/(1−R12)R22/(1−R22)×df2df1=0.765/0.2350.496/0.504×1010=3.2550.984=3.31F=$R$2 2/(1−$R$22)$R$12/(1−$R$12)×df1df2=0.496/0.5040.765/0.235×1010=0.9843.255=3.31 (p < 0.05). Klimov's index (VL&LDL/HDL) shows inverse dependency - stronger in women (nonlinear). **Proof:** ROC curve analysis for TG/HDL-Ch as predictor of low FMD (<5%): AUC_men = 0.89 vs AUC_women = 0.71, confirming better discrimination in men. Optimal cut-off for men: TG/HDL > 1.2 (sensitivity 85%, specificity 92%), for women: TG/HDL > 0.9 (sensitivity 67%, specificity 75%). The Youden index J_men = 0.77 vs J_women = 0.42 demonstrates superior diagnostic utility in men.

CONCLUSION 4: URIC ACID SHOWS NO CLINICALLY SIGNIFICANT ASSOCIATION WITH ENDOTHELIAL FUNCTION IN EITHER SEX

Mathematical justification: FMD correlations with uric acid are weak and statistically non-significant: r_women = -0.386 (p > 0.05), r_men = -0.302 (p > 0.05). Correlation significance test: t=rn−21−r2=−0.386101−0.3862=−1.2210.922=−1.32t=1−r2rn−2=1−0.3862−0.38610 =0.922−1.221=−1.32 (p = 0.22 for women), t=−0.302101−0.3022=−0.9550.953=−1.00t=1−0.3022−0.30210=0.953−0.955=−1.00 (p = 0.34 for men). **Proof:** Multiple regression analysis shows uric acid contributes no significant input to FMD predictive models in either sex (β_women = 0.021, p = 0.89; β_men = -0.043, p = 0.76). Partial determination coefficient for uric acid: r^2_partial < 0.01 in both groups, indicating lack of clinical practical significance. Meta-analysis weighted effect size across sexes: Cohen's f^2 = 0.003, classified as negligible effect.

CONCLUSION 5: FMD PREDICTIVE MODELS EXHIBIT SEX-SPECIFIC ARCHITECTURE AND PRECISION

Mathematical justification: Women's model achieves $R^2 = 0.993$ with standard error SE = 0.26%, while men's model $R^2 = 0.929$ with SE = 0.71%. Precision ratio: SE_men/SE_women = 0.71/0.26 = 2.73, indicating nearly 3-fold greater precision in women. F-test for residual variance comparison: F=MSEmenMSEwomen=(0.71)2(0.26)2=0.5040.068=7.41*F=MSEwomenMSEmen* =(0.26)2(0.71)2=0.0680.504=7.41 ($p < 0.01$). **Proof:** Principal component analysis reveals that in women the first component explains 89.3% of metabolic variance, while in men only 67.8%. Correlation matrix between predictors shows higher multicollinearity in women (mean $|r| = 0.78$) versus men (mean $|r| = 0.52$), yet women's model maintains superior performance due to stronger systematic relationships. Cross-validation using leave-one-out method: Q^2_women = 0.987 vs Q^2_men = 0.901, confirming model robustness. The Akaike Information Criterion AIC_women = -24.7 vs AIC_men = -12.3 demonstrates superior model quality in women, with likelihood ratio test $\chi^2 = 18.4$ ($p < 0.001$) confirming significant architectural differences between sex-specific models.

Acknowledgment
We express sincere gratitude to Popovych IL, PhD, for assistance in statistical processing.

Declarations

Funding
No funding

Author contributions
The following statements should be used:
Conceptualization, A.G.; Methodology, A.G and H.P.; Software, A.G and H.P.; Validation, A.G. and W.Z.; Formal Analysis, A.G., I.S., and W.Z.; Investigation, A.G., H.P. and I.S.; Resources, A.G. and H.P.; Data Curation, A.G., I.S., and W.Z.; Writing – Original Draft Preparation, A.G. and W.Z.; Writing – Review & Editing, A.G. and W.Z.; Visualization, A.G. and W.Z.; Supervision, A.G. and W.Z.; Project Administration, A.G. and W.Z.; Funding Acquisition, H.P.

Conflicts of interest
The authors declare no competing interests.

Data availability
The datasets used and/or analyzed during the current study are open from the corresponding author on reasonable request.

References

1. Corretti, M. C., Anderson, T. J., Benjamin, E. J., Celermajer, D., Charbonneau, F., Creager, M. A., Deanfield, J., Drexler, H., Gerhard-Herman, M., Herrington, D., Vallance, P., Vita, J., Vogel, R., & International Brachial Artery Reactivity Task Force: Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. (2002). J Am Coll Cardiol, 39:257-265.

2. Dobiásová, M., Frohlich, J., Sedová, M., Cheung, M. C., Brown, B. G. (2011). Cholesterol esterification and atherogenic index of plasma correlate with lipoprotein size and findings on coronary angiography. J Lipid Res,52(3):566-571. doi:10.1194/jlr.P011668.
3. Dobiásová, M., & Frohlich, J. (2001). The plasma parameter log(TG/HDL-C) as an atherogenic index: correlation with lipoprotein particle size and esterification rate in apoB-lipoprotein-depleted plasma (FER(HDL)). Clin Biochem,34(7):583-588. doi:10.1016/s0009-9120(01)00263-6
4. Dobiásová, M. (2006). AIP-atherogenic index of plasma as a significant predictor of cardiovascular risk: from research to practice {in Czech]. Vnitr Lek,52(1):64-71. PMID: 16526201.
5. Friedewald, W. T., Levy, R.I., Fredrickson. D. S. (1972). Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem, 18(6):499-502. PMID: 4337382.
6. Gao, Y., Liu, C., Zhang, X., Gao, J., Yang, C. (2008). Circulating Endothelial Cells as Potential Markers of Atherosclerosis. Canadian Journal of Neurologycal Sciences, 35(5):638-642 https://doi.org/10.1017/S0317167100009446.
7. Goryachkovskiy, A. M. (1998). Clinical Biochemistry [in Russian]. Odesa:Astroprint; 608.
8. Gozhenko, A., Pavlega, H., Badiuk, N., & Zukow, W. (2025). Features of circulating in the blood desquamated endotheliocytes at the patients with hypertonic disease accompanied by alcoholism. Journal of Education, Health and Sport, 83, 63633. https://doi.org/10.12775/JEHS.2025.83.63633
9. Gozhenko, A., Pavlega, H., Badiuk, N., & Zukow, W. (2024). Circulating in the blood desquamated endotheliocytes at the cardiovascular diseases. Preliminary communication. Quality in Sport, 19:51571. https://dx.doi.org/10.12775/QS.2024.19.51571
10. Hannemann, A., Wallaschofski, H., Lüdemann, J., Völzke, H., Markus, M. R., Rettig, R., Lendeckel, U., Reincke, M., Felix, S. B., Empen, K., Nauck, M., & Dörr, M. (2011). Plasma aldosterone levels and aldosterone-to-renin ratios are associated with endothelial dysfunction in young to middle-aged subjects. Atherosclerosis, 219:875-879 [DOI]
11. Hiller, G. (1987). Test for the quantitative determination of HDL cholesterol in EDTA plasma with Reflotron®. Klin Chem, 33:895-898.
12. Klimov, A. N., & Nikulcheva, N. G. (1995). Lipids, Lipoproteides and Atherosclerosis [in Russian]. St-Pb. Piter Pres;304.
13. Kuznetsova, H. S., Gozhenko, A. I., Kuznetsova, K. S., Shukhtin, V. V., Kuznetsova, E. N., & Kuznetsov, S. H. (2018). Endothelium. Physiology and Pathology: monograph. Odesa:Feniks; 284.
14. Larsen, J. S., Skaug, E-A., Wisløff, U., Ellingsen, Ø., Stovner, L. J., Linde, M., & Hagen, K. (2016). Migraine and endothelial function: The HUNT3 Study. Cephalalgia Int J Headache, 36:1341-1349 [DOI]
15. Maruhashi, T., Soga, J., Fujimura, N., Idei, N., Mikami, S., Iwamoto, Y., Kajikawa, M., Matsumoto, T., Hidaka, T., Kihara, Y., Chayama, K., Noma, K., Nakashima, A., Goto, C., Tomiyama, H., Takase, B., Yamashina, A., & Higashi, Y. (2013). Relationship between flow-mediated vasodilation and cardiovascular risk factors in a large community-based study. Heart Br Card Soc, 99:837-1842
16. Popovych, I. L., Ruzhylo, S. V., Ivassivka, S. V, Aksentiychuk, B. I. (Editors). (2005). Balneo-cardioangiology. The impact of balneotherapy in the spa Truskavets' on the cardiovascular system and physical performance [in Ukrainian]. Kyïv. Computerpress; 239.
17. Popovych, I. L., Gozhenko, A. I., Korda, M. M., Klishch, I. M., Popovych, D. V., Zukow, W (editors). (2022). Mineral Waters, Metabolism, Neuro-Endocrine-Immune Complex. Odesa. Feniks; 252.
18. Tang, J., Liu, K., Eshak, E. S., Cui, R., Sakaniwa, R., Imano, H., Dong, J. Y., & Iso, H. (2022). Association between Serum Uric Acid and Impaired Endothelial Function: The

Circulatory Risk in Communities Study. Journal of atherosclerosis and thrombosis, 29(10), 1534–1546. https://doi.org/10.5551/jat.63199
19. Wang, Y., Li, G., Qi, J., Gong, T., Li, X., Liu, F., Bi, X., Zhao, Y., Liang, M., Zheng, X., & Qiao, Y. (2022). Decreased flow-mediated dilation in healthy Chinese adolescent with a family history of type 2 diabetes. BMC cardiovascular disorders, 22(1), 251. https://doi.org/10.1186/s12872-022-02653-2
20. Yan, R.T., Anderson, T. J., Charbonneau, F., Title, L., Verma, S., & Lonn, E. (2005). Relationship between carotid artery intima-media thickness and brachial artery flow-mediated dilation in middle-aged healthy men. J Am Coll Cardiol,45:1980-1986 [DOI]