The Presence of Hyperhomocysteinemia Does Not Aggravate the Cardiometabolic Risk Imposed by Hyperuricemia in Young Individuals: A Retrospective Analysis of a Cross-Sectional Study

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Abstract: Background: Little research has been conducted into the effects of the combined manifestation of hyperuricemia and hyperhomocysteinemia on cardiometabolic risk factors and markers in young subjects. Methods: 1298 males and 1402 females, 14-to-20-year-olds, were classified into four groups: 1/normouricemic/normohomocysteinemic, 2/normouricemic/hyperhomocysteinemic, 3/hyperuricemic/normohomocysteinemic, and 4/hyperuricemic/hyperhomocysteinemic. Anthropometric measures, blood pressure, plasma glucose, insulin, lipids, markers of renal function, C-reactive protein, asymmetric dimethylarginine, and blood counts were determined. Results: Hyperuricemic males (but not females) had higher odds for hyperhomocysteinemia than normouricemic ones (OR: 1.8; 95% CI: 1.4–2.3; \(p < 0.001\)). Homocysteine and uric acid levels correlated directly (males: \(r = 0.076\), females: \(r = 0.120\); \(p < 0.01\), both). Two-factor analysis of variance did not reveal a significant impact of hyperhomocysteinemia on any of the investigated cardiometabolic variables in females; in males, hyperuricemia and hyperhomocysteinemia showed a synergic effect on asymmetric dimethylarginine levels. Among four groups, subjects concurrently manifesting hyperuricemia and hyperhomocysteinemia did not present the highest continuous metabolic syndrome score—a proxy measure of cardiometabolic risk; neither the multivariate regression model indicated a concurrent significant effect of uric acid and homocysteine on continuous metabolic syndrome score in either sex. Conclusion: In young healthy subjects, hyperhomocysteinemia does not aggravate the negative health effects imposed by hyperuricemia.

Keywords: uric acid; homocysteine; adolescents; cardiometabolic risk factors; continuous metabolic syndrome score; ADMA

1. Introduction

Uric acid (UA) is a bioactive end-product of the metabolism of purines (adenine and guanine). Extracellular UA acts as an antioxidant; intracellularly, UA exerts pro-oxidant effects [1]. Experimental studies document that UA affects vascular cell functions via promotion of degradation of the vasodilator nitric oxide and boosting of activity of the renin-angiotensin axis [2]. Both UA and xanthine oxidoreductase (the enzyme that generates uric acid) may induce oxidative stress, promote inflammation, endothelial dysfunction, and atherosclerosis [2,3]. Hypertension, kidney, and cardiovascular diseases, fatty liver, dyslipidemia, obesity, insulin resistance, metabolic syndrome (MetSy), or diabetes are associated with elevated serum UA (SUA) levels already in adolescents [4–6].
Homocysteine (Hcy) is a sulfur-containing amino acid produced from the essential amino acid methionine as a byproduct of trans-methylation reactions. It derives from S-adenosyl-homocysteine hydrolase-catalyzed hydrolysis of S-adenosylhomocysteine to adenosine. Experimental studies show that at the molecular level, the toxicity of Hcy includes mechanisms involving the formation of reactive oxygen species, hypomethylation, induction of unfolded protein response, and protein homocysteinylatation. At the cellular level, Hcy is a pro-inflammatory, pro-thrombotic, pro-atherogenic factor, vasodilation impairing agent, and an inducer of endoplasmatic reticulum stress [7]. Even in children and adolescents, increased levels of Hcy are associated with a range of disorders, such as renal and cardiovascular diseases, obesity, diabetes, premature atherosclerosis, or impaired bone health [8–11].

Uric acid and Hcy are metabolically interrelated: adenosine produced during metabolic transit of Hcy might eventually be metabolized into UA. Most daily UA and Hcy disposal occur via kidneys. Both UA and Hcy may affect the oxidative status, exert proinflammatory and proatherogenic effects, and may alter vascular cell function via interfering with NO metabolism. Levels of SUA and Hcy rise in identical pathologies, and both variables display a positive direct relationship even in healthy adults [12–17]. A synergistic association of hyperuricemia and hyperhomocysteinemia (hyperHcy) with chronic kidney disease has been documented in middle-aged and elderly patients [18]; while combined hyperuricemia and hyperHcy additively increased the risk of manifestation of subclinical atrial fibrillation in patients with cardiac implantable electronic devices [19]. However, it is not fully clarified whether hyperuricemia and hyperHcy represent markers, or rather act as etiological agents in cardiovascular and other mentioned pathologies [20,21]. The current guidelines of professional societies do not consider SUA or Hcy as cardiovascular disease risk stratifiers.

The recent cross-sectional analysis indicated that in adolescents, Hcy levels were positively correlated with those of SUA, and the odds to present elevated SUA levels increased across the Hcy terciles [22]. Yet, it remains unclear whether the combined manifestation of elevated SUA levels and hyperHcy exerts additive effects on cardiometabolic risk factors and markers in young healthy subjects. This question is of particular importance, as there is robust evidence linking cardiovascular risk factors in childhood and adolescence (even in juveniles with mildly elevated risk factor scores) with clinical atherosclerotic cardiovascular disease events in adulthood [23].

We hypothesized that concurrent manifestation of elevated SUA levels and hyperHcy exerts an additive worsening effect on cardiometabolic risk factors or markers compared with the presence of isolated hyperuricemia or hyperHcy. To this point, we retrospectively analyzed data obtained from healthy young individuals.

2. Materials and Methods

2.1. Subjects

The cross-sectional “Respect for Health” study has been described previously [22]. Briefly, students of state secondary schools in the Bratislava Region participated voluntarily in the survey. Exclusion criteria were any acute or chronic illness, pregnancy, or lactation in females.

Anthropometric, blood chemistry, and hematology data were obtained from 2960 students aged 11-to-23 years. We excluded 260 subjects (9 non-Caucasians (4 Vietnamese, 3 Koreans, 2 others; due to unavailable reference values of blood chemistry variables for minorities), 6 potential diabetics (fasting plasma glucose (FPG) > 6.9 mmol/L), aged < 14 (n = 11) or >20 (n = 14) years, 220 with missing values), leaving 2700 individuals (51.9% females) aged 14-to-20 years for the present analysis.

The study was approved by The Ethics Committee of the Bratislava Self-governing Region and conformed to the Helsinki Declaration. In minors, participation was subject to the written informed consent of the legal representative and the verbal assent of the child. Written informed consent was obtained from full-aged participants.
2.2. Measurements

Anthropometric measurements were performed following standard guidelines, as described previously [24]. Briefly, height was measured using a portable extendable stadiometer, waist circumference using a flexible tape, and body weight employing digital scales (Omron BF510, Kyoto, Japan). BMI and waist-to-height ratio (WHtR) were calculated.

Blood pressure (BP) was measured on a dominant arm in a person relaxed for at least 5 min in the seated position, using a digital monitor (Omron M-6 Comfort, Kyoto, Japan). The mean of the last two measurements was recorded.

After overnight fasting, venous blood and spot urine were collected. In the central laboratory, serum chemistry (glucose, triacylglycerols (TAG), high-density lipoprotein cholesterol (HDL-C), UA, insulin, creatinine, high-sensitivity C-reactive protein (CRP)) and urine (creatinine, albumin) analyses (Advia 2400 analyzer, Siemens, Germany) and blood counts (Sysmex XE-2100 analyzer, Sysmex Corporation, Kobe, Japan) were performed using standard laboratory methods, as described previously [24]. Total plasma L-homocysteine was measured with a fluorescence polarization immuno-812 assay (IMX; Abbott Diagnostics, Maidenhead, Berkshire, UK). Asymmetric dimethylarginine (ADMA) was determined at the Institute of Molecular Biomedicine, using commercial ELISA kits (DLD Diagnostika GmbH, Hamburg, Germany) according to the manufacturer’s instructions. Low-density lipoprotein cholesterol (LDL-C) was calculated employing the Friedewald formula; insulin sensitivity using the Quantitative Insulin Sensitivity Check Index (QUICKI) [25]; the atherogenic index of plasma (AIP) as log(TAG)/HDL-C [26]; and estimated glomerular filtration rate (eGFR) employing the equation for the full-age spectrum with Q-height extension [27]. Cardiometabolic risk was estimated using the continuous metabolic syndrome score as WHtR/0.5 + fasting glycemia/5.6 + SBP/130 + TAG/1.7 − HDL-C/1.02 (males) or 1.28 (females) [28]. The urinary albumin-to-creatinine ratio was calculated.

2.3. Definition of Elevated Uric Acid Levels, Hyperuricemia, Hyperhomocysteinemia, Cardiometabolic Risk Factors, and Metabolic Syndrome

Employing reference ranges of the laboratory of the National Institute for Children’s Diseases in Bratislava, we classified hyperuricemia as SUA concentration >340 µmol/L in females; in males >360 µmol/L if aged < 17 years, and >420 µmol/L in those aged ≥ 17 years; individuals aged 15 and 16 years who presented with Hcy > 10.0 µmol/L, adolescents aged 16 and 17 years who displayed Hcy > 11.3 µmol/L, and those aged ≥ 18 years with Hcy concentrations >15.0 µmol/L were classified as hyperhomocysteinemic.

In 14-to-17-year-olds, general overweight/obesity was classified according to the international age- and sex-specific cutoff points for BMI [29], in individuals aged ≥ 18 years as BMI ≥ 25 kg/m². Central obesity was defined as WHtR ≥ 0.5 [30]. The increased cardiometabolic risk was classified according to guidelines for the classification of metabolic syndrome components: systolic BP ≥ 130 mmHg, DBP ≥ 85 mmHg, triacylglycerols ≥ 1.7 mmol/L, fasting glycemia ≥5.6 mmol/L, and HDL-C as <1.03 mmol/L in males and females aged < 16 years; and <1.29 mmol/L in females aged ≥ 16 years [31]. Subjects presenting at least three cardiometabolic risk factors, e.g., central obesity, elevated fasting glycemia, BP, TAG, or low HDL-C concentrations were considered as suffering from metabolic syndrome [31]. Moreover, fasting insulin ≥20 µIU/mL [32], CRP > 3 mg/L [33], atherogenic index >0.11 [26], and the presence of microalbuminuria/albuminuria (urinary albumin/creatinine ≥2.5 mg/mmol in males and ≥3.5 mg/mmol in females [24]) were considered as markers of increased cardiometabolic risk. The number of cardiometabolic risk factors (RF) was calculated as a sum of the presence of binary coded elevated BP, adiposity (presence of central obesity or general overweight/obesity), dyslipidemia (elevated TAG or AIP or low HDL-C), alteration of glucose metabolism (elevated fasting glycemia or insulinemia), and elevated CRP.
2.4. Statistical Analyses

Data not fitting the normal distribution (Shapiro–Wilk test) were log-transformed before statistical analyses. Males and females were compared using the two-sided independent samples Student’s t-test. According to the reference ranges of SUA and Hcy, subjects were classified into four groups: 1/concentrations of SUA and Hcy below the upper reference range (e.g., normal, n), 2/SUA levels below and Hcy above the upper reference range, 3/SUA above and Hcy concentration below, and 4/both SUA and Hcy concentrations above the reference ranges. Four groups were compared using the two-factor analysis of variance (ANOVA) with the presence/absence of hyperuricemia and presence/absence of hyperHcy as fixed factors. Normally distributed data are given as mean ± standard deviation (SD), those failing assumptions of normality are described with a back-transformed geometric mean (interval −1 SD, +1 SD). Categorical data were compared using the Fisher’s exact test or Chi-square test with Yates’ correction (Y) if appropriate, and are given as counts and frequencies. Pearson correlation coefficients and odds ratios (OR) were calculated. *p* value < 0.05 was considered significant. Statistical software SPSS version 16 (SPSS, Chicago, IL, USA) was used.

Multivariate regression of independent factors on continuous metabolic syndrome score was performed using the orthogonal projection to latent structures model (OPLS, Simca v.16 software, Sartorius Stedim Data Analytics AB, Umea, Sweden). In Model 1, age, insulin, CRP, eGFR, ACR, leukocyte (WBC) and erythrocyte (RBC) counts, and ADMA, were entered as independent variables; in Model 2, SUA was forced into the model; in Model 3 SUA was replaced by Hcy; in Model 4 both SUA and Hcy were entered. Before fitting the OPLS models, all variables with high skewness and a low min/max ratio were log-transformed and all data were mean-centered. Variables with a variable of importance for the projection (VIP) values ≥ 1.00 were considered significant.

3. Results

Cohort characteristics are given in Table 1. Males differed from females in all variables except for age, QUICKI, the prevalence of elevated fasting insulinemia, elevated TAG levels, or microalbuminuria/albuminuria.

3.1. Males

SUA and Hcy levels ranged 142–563 µmol/L, and 1.7–63.3 µmol/L, respectively. There was a significant direct relationship between lnHcy and SUA levels (r = 0.076, *p*= 0.006).

3.1.1. Correlations between Cardiometabolic Risk Factors and Markers with Uricemia or Homocysteinemia

Correlations between age or glycemia and SUA were insignificant; significant inverse correlations were revealed between SUA and HDL-C, QUICKI, ln urinary albumin/creatinine, and eGFR; all other variables showed a direct significant relationship with SUA (Table 2). Age, DBP, non-HDL-C, AIP, and lnTAG showed a positive significant relationship with lnHcy; while eGFR, ln urinary albumin/creatinine, and lnADMA correlated inversely. However, all significant associations were weak (Pearson r: SUA: −0.062-to −0.316, lnHcy: −0.056-to −0.094; Table 2).

3.1.2. The Effects of Uricemia and Homocysteinemia on Cardiometabolic Variables

30.9% of males suffered from hyperuricemia, 32.6% displayed hyperHcy; 12.8% manifested combined hyperuricemia and hyperHcy (Table 3). Among 423 hyperhomocysteinemic males, 34 displayed moderate hyperHcy (>30 µmol/L), and 9 out of 34 suffered from hyperuricemia. Compared with males displaying SUA levels within the reference range, those with hyperuricemia had increased odds for hyperHcy (OR: 1.76 (95% confidence interval [CI]: 1.38–2.49; *p* < 0.001).
### Table 1. Cohort characteristics.

|                   | Males          | Females        | p     |
|-------------------|----------------|----------------|-------|
| N (%)             | 1298 (48.1)    | 1402 (51.9)    |       |
| Age, years        | 17.2 ± 1.4     | 17.2 ± 1.4     | 0.274 |
| Uric acid, µmol/L | 354 ± 60       | 258 ± 51       |       |
| Homocysteine, µmol/mL | 11.2 (7.7; 16.2) | 9.4 (7.0; 12.7) | <0.001|
| Waist/height      | 0.44 ± 0.05    | 0.43 ± 0.05    | <0.001|
| Body mass index, kg/m² | 23.0 ± 3.9   | 21.9 ± 3.5     |       |
| Systolic blood pressure, mm Hg | 122 ± 12   | 107 ± 9        | <0.001|
| Diastolic blood pressure, mm Hg | 73 ± 8   | 70 ± 8         | <0.001|
| Glucose, mmol/L   | 4.9 ± 0.4      | 4.7 ± 0.4      | <0.001|
| Insulin, µIU/mL   | 9.6 (5.7; 16.1)| 10.0 (6.3; 16.0)| 0.013 |
| HDL-C, mmol/L     | 1.25 ± 0.23    | 1.52 ± 0.30    | <0.001|
| Non-HDL-C, mmol/L | 2.56 ± 0.68    | 2.74 ± 0.69    | <0.001|
| Triacylglycerols, mmol/L | 0.79 (0.51; 1.21) | 0.79 (0.52; 1.19) | 0.047 |
| cMSS              | −0.19 ± 0.23   | −0.26 ± 0.20   | <0.001|
| eGFR, mL/min/1.73 m² | 1.99 ± 0.48   | 1.83 ± 0.41    | <0.001|
| ACR, mg/mmol crea | 0.4 (0.2; 1.0) | 0.5 (0.2; 1.3) | <0.001|
| C-reactive protein, mg/L | 0.5 (0.2; 1.4) | 0.5 (0.2; 2.0) |       |
| ADMA, (µmol/L)    | 0.47 (0.36; 0.60) | 0.44 (0.34; 0.57) | <0.001|
| Erythrocytes, 10¹²/L | 5.14 ± 0.31  | 4.55 ± 0.29    | <0.001|
| Leukocytes, 10⁹/L | 6.35 ± 1.44    | 6.85 ± 1.78    | <0.001|

| Prevalence        | p       |
|-------------------|---------|
| Elevated:         |         |
| Uric acid, n (%)  | 401 (30.9) | 81 (5.8) | <0.001      |
| Homocysteine, n (%) | 391 (30.1) | 189 (13.5) | <0.001      |
| Waist/height, n (%) | 175 (13.5) | 138 (9.8) | 0.004       |
| Body mass index, n (%) | 369 (28.4) | 261 (18.6) | <0.001      |
| Systolic blood pressure, n (%) | 329 (25.3) | 20 (1.4) | <0.001      |
| Diastolic blood pressure, n (%) | 87 (6.7) | 56 (4.0) | 0.002       |
| Blood pressure, n (%) | 347 (26.7) | 65 (4.6) | <0.001      |
| Glucose, n (%)     | 84 (6.5) | 29 (2.1) | <0.001      |
| Insulin, n (%)     | 104 (8.0) | 89 (6.3) | 0.100       |
| Triacylglycerols, n (%) | 66 (5.1) | 73 (5.2) | 0.931       |
| Atherogenic index, n (%) | 111 (8.6) | 55 (3.9) | <0.001      |
| C-reactive protein, n (%) | 98 (7.6) | 156 (11.1) | 0.002      |
| ACR, n (%)         | 48 (3.7) | 45 (3.2) | 0.527       |
| Low HDL-C, n (%)   | 193 (14.9) | 273 (19.5) | 0.001       |
| MetSy, n (%)       | 53 (4.1) | 19 (1.4) | <0.001      |

SBP: systolic blood pressure; DBP: diastolic blood pressure; QUICKI, quantitative insulin sensitivity check index; HDL-C, high-density lipoprotein cholesterol; TAG, triacylglycerols; cMSS, continuous metabolic syndrome score; eGFR, estimated glomerular filtration rate; ACR, urinary albumin-to-creatinine ratio; ADMA, asymmetric dimethylarginine; data are given as mean ± standard deviation, those analyzed after log transformation as back-transformed geometric mean (interval −1 SD, +1 SD), categorical data as counts and frequencies; groups were compared using the two-sided Student’s t-test for independent samples or the Fisher’s exact test, p < 0.05 is given in bold.

To investigate whether the concurrent manifestation of hyperuricemia and hyperHcy is associated with worsening of cardiometabolic variables, 2-factor ANOVA was performed. Hyperuricemia was associated with higher BMI, WHtR, systolic and diastolic BP (SBP, DBP), fasting insulinemia, non-HDL-C concentrations, lnTAG, lnCRP, lnADMA, atherogenic index of plasma, continuous metabolic syndrome score, risk factors number, and erythrocyte counts; lower insulin sensitivity and HDL-C levels. HyperHcy independently affected 6 variables, and there was a concurrent independent opposite effect of hyperuricemia and hyperHcy on BMI, WHtR, SBP, number of cardiometabolic risk factors, or lnCRP, and synergic one on lnADMA (Table 3).
Table 2. Pearson correlations between selected cardiometabolic markers and uric acid or homocysteine in males and females.

|        | Males                         | Females                        |
|--------|-------------------------------|--------------------------------|
|        | Age  | BMI  | WHtR | SBP  | DBP  | Glucose | Insulin | QUICKI | HDL-C | Non-HDL-C | Age  | BMI  | WHtR | SBP  | DBP  | Glucose | Insulin | QUICKI | HDL-C | Non-HDL-C |
|        | r    | p    | p    | p    | p    | p      | p       | p      | p     | p        | r    | p    | p    | p    | p    | p      | p       | p      | p     | p        |
| UA     | r    | 0.316 | 0.286 | 0.152 | 0.120 | 0.099  | 0.121   | 0.103  | 0.156  | 0.176    | r    | 0.253 | 0.198 | 0.111 | 0.110 | 0.037   | 0.022   | 0.12   | 0.134  | 0.055    |
|        | p    | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.752  | <0.001 | <0.001 | <0.001  | r    | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001  | <0.001  | <0.001 | <0.001  | <0.001  |
| LnHcy  | r    | 0.004 | 0.021 | 0.073 | 0.023 | 0.001  | 0.005   | 0.005  | 0.005  | 0.005    | r    | 0.095 | 0.051 | 0.008 | 0.076 | 0.053   | 0.012   | 0.007  | 0.030  | 0.051    |
|        | p    | <0.001 | 0.497 | 0.440 | 0.008 | 0.401  | 0.967   | 0.856  | 0.156  | 0.019    | p    | <0.001 | 0.204 | <0.001 | <0.001 | <0.001 | <0.001  | <0.001  | <0.001 | <0.001  | <0.001  |
| LnTAG  | r    | 0.155 | 0.270 | 0.257 | 0.062 | 0.093  | 0.063   | 0.185  | 0.110  | 0.067    | r    | 0.081 | 0.257 | 0.181 | 0.152 | 0.043   | 0.113   | 0.111  | 0.126  | 0.107    |
| AIP    | r    | 0.303 | 0.040 | 0.077 | 0.047 | 0.756  | 0.653   | 0.799  | 0.258  | 0.058    | r    | 0.058 | 0.026 | 0.786 | 0.267 | 0.001  | 0.527   | 0.009   | 0.706  | 0.048  | 0.053    |
| cMSS   | r    | 0.002 | 0.009 | 0.030 | 0.131 | 0.018  | 0.071   | 0.010  | 0.053  | 0.052    | r    | 0.003 | 0.266 | 0.008 | 0.030 | 0.131 | 0.018  | 0.071   | 0.010  | 0.053  | 0.052    |
| RF No. | r    | 0.087 | 0.253 | 0.198 | 0.111 | 0.110  | 0.037   | 0.022  | 0.12   | 0.134    | r    | 0.058 | 0.026 | 0.786 | 0.267 | <0.001 | 0.527   | 0.009   | 0.706  | 0.048  | 0.053    |
| eGFR   | r    | 0.094 | 0.028 | 0.047 | 0.053 | 0.008  | 0.012   | 0.007  | 0.030  | 0.051    | r    | 0.078 | 0.059 | 0.008 | 0.030 | 0.131 | 0.018  | 0.071   | 0.010  | 0.053  | 0.052    |
| lnACR  | r    | 0.023 | 0.081 | 0.257 | 0.181 | 0.152  | 0.043   | 0.113  | 0.111  | 0.126    | r    | 0.388 | 0.002 | 0.009 | 0.030 | 0.131 | 0.018  | 0.071   | 0.010  | 0.053  | 0.052    |
| LnADMA | r    | 0.038 | 0.266 | 0.008 | 0.030 | 0.030  | 0.030   | 0.030  | 0.030  | 0.030    | r    | 0.003 | 0.266 | 0.008 | 0.030 | 0.131 | 0.018  | 0.071   | 0.010  | 0.053  | 0.052    |
| LnCRP  | r    | 0.067 | 0.051 | 0.076 | 0.053 | 0.008  | 0.012   | 0.007  | 0.030  | 0.051    | r    | 0.087 | 0.059 | 0.008 | 0.030 | 0.131 | 0.018  | 0.071   | 0.010  | 0.053  | 0.052    |
| Ery    | r    | 0.095 | 0.051 | 0.008 | 0.076 | 0.056  | 0.072   | 0.018  | 0.046  | 0.051    | r    | 0.095 | 0.051 | 0.008 | 0.076 | 0.056 | 0.072   | 0.018  | 0.046  | 0.051    |
| Leu    | r    | 0.001 | 0.069 | 0.786 | 0.006 | 0.044  | 0.010   | 0.521  | 0.059  | 0.068    | r    | 0.001 | 0.069 | 0.786 | 0.006 | 0.044  | 0.010   | 0.521  | 0.059  | 0.068    |

UA, uric acid; ln, logarithm; Hcy, homocysteine; BMI, body mass index; WHtR, weight-to-height ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; QUICKI, quantitative insulin sensitivity check index; HDL-C, high-density lipoprotein cholesterol; TAG, triacylglycerols; AIP, atherogenic index of plasma; cMSS, continuous metabolic syndrome score; RF No., number of cardiometabolic risk factors; eGFR, estimated glomerular filtration rate; ACR, urinary albumin-to-creatinine ratio; ADMA, asymmetric dimethylarginine; CRP, C-reactive protein; Ery, erythrocytes; Leu, leukocytes; p < 0.05 is given in bold.

The prevalence of MetSy was the highest in males manifesting isolated hyperuricemia (nSUA/nHcy: 2.5%, nSUA/hyperHcy: 1.6%, hyperuricemia/nHCY: 8.5%, hyperuricemia/hyperHcy: 7.8%; p < 0.001).

3.1.3. Multivariate Regression Models

The OPLS multivariate regression model was employed to elucidate whether and how SUA and/or Hcy affect the continuous metabolic syndrome score—a proxy measure of cardiometabolic risk. If neither SUA nor Hcy was considered, the model indicated that insulinemia and inflammatory markers independently affect the continuous metabolic syndrome score (Table 4, Model 1). After the inclusion of SUA, it became an additional significant predictor of cardiometabolic risk, regardless of the absence (Model 2) or presence (Model 4) of Hcy in the model. However, the variance of the continuous metabolic syndrome score explained by models 2 and 4 increased only slightly (by 3%) after the inclusion of SUA. After forcing Hcy into the model, erythrocyte counts but not Hcy became a significant predictor of continuous metabolic syndrome score (Models 3 and 4). The variability of the continuous metabolic syndrome score explained by the models was not affected.

3.2. Females

Serum uric acid levels ranged 123–578 µmol/L, those of homocysteine 2.0–37.7 µmol/L. SUA and lnHcy showed a direct significant correlation (r = 0.120, p < 0.001).
Table 3. Characteristics of males according to uricemia and homocysteinemia.

|                      | Normouricemia, n = 897 (69.1%) | Hyperuricemia, n = 401 (30.9%) | p       |
|----------------------|--------------------------------|--------------------------------|---------|
| Number               | NHcy (71.3%)                   | HHcy (28.7%)                   |         |
|                      | 640 (49.3%)                    | 257 (19.8%)                    |         |
| Age, years           | 17.6 ± 1.4                     | 16.9 ± 1.4                     |         |
| Uric acid, μmol/L    | 326 ± 43                       | 325 ± 39                       |         |
| Homocysteine, μmol/L | 9.6 (7.6, 12.1)                | 16.5 (11.2, 24.2)              | <0.001  |
| Body mass index, kg/m² | 22.7 ± 3.6                    | 21.9 ± 3.0                     | <0.001  |
| WHR                  | 0.44 ± 0.05                    | 0.43 ± 0.04                    | <0.001  |
| SBP, mmHg            | 122 ± 12                       | 120 ± 11                       | <0.001  |
| TAG, mmol/L          | 0.77 (0.51, 1.16)              | 0.78 (0.54, 1.14)              | <0.001  |
| Atherogenic index    | 1.95 ± 0.43                    | 1.91 ± 0.38                    | <0.001  |
| Risk factors number | 0.85 ± 0.98                    | 0.72 ± 0.89                    | <0.001  |
| eGFR, mL/min/1.73 m² | 111 ± 22                       | 109 ± 20                       | 0.354   |
| HDL-C, mmol/L        | 1.27 ± 0.22                    | 1.28 ± 0.24                    | 0.001   |
| Non-HDL-C, mmol/L    | 2.55 ± 0.66                    | 2.47 ± 0.60                    | 0.001   |
| Insulin, μU/mL       | 9.1 (5.5, 15.0)                | 9.5 (5.8, 15.6)                | 0.001   |
| HDL-C                | 1.27 ± 0.22                    | 1.28 ± 0.24                    | 0.001   |
| TAG                  | 5.11 ± 0.30                    | 5.16 ± 0.31                    | 0.001   |
| cMSS                 | 0.43 (0.33, 0.56)              | 0.47 (0.37, 0.60)              | <0.001  |
| Risk factors number | 0.5 (0.1, 1.5)                 | 0.4 (0.1, 1.2)                 | <0.001  |
| HDL-C                | 0.51 ± 0.30                    | 0.51 ± 0.31                    | 0.001   |
| Leukocytes, 10^9/L   | 6.32 ± 1.35                    | 6.34 ± 1.69                    | 0.001   |
| p<0.05 is given in bold. 

NHcy, normohomocysteinemia; HHcy, hyperhomocysteinemia; UA, uric acid; Hcy, homocysteine; WHR, weight-to-height ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; QUICKI, quantitative insulin sensitivity check index; HDL-C, high-density lipoprotein cholesterol; TAG, triacylglycerols; cMSS, continuous metabolic syndrome score; eGFR, estimated glomerular filtration rate; ACR, urinary albumin-to-creatinine ratio; ADMA, asymmetric dimethylarginine; SUA, systemic uric acid; cMSS, continuous metabolic syndrome score; eGFR, estimated glomerular filtration rate; Hcy, homocysteine.

Table 4. Multivariate regression of uric acid, homocysteine, and cardiometabolic risk factors and markers on continuous metabolic syndrome score using the orthogonal projections to latent structures model in males and females.

|                      | Males                  |          | Females                 |          |
|----------------------|------------------------|----------|-------------------------|----------|
|                      | Model 1                | Model 2  | Model 3                | Model 4  |          | Model 1                | Model 2  | Model 3                | Model 4  |          |
| Insulin              | 1.93                   | 1.89     | 2.06                    | 2.01     | 1.57     | 1.63                   | 1.66     | 1.71                   |          |
| lnCRP                | 1.19                   | 1.21     | 1.24                    | 1.25     | 1.50     | 1.57                   | 1.58     | 1.65                   |          |
| Leukocytes           | 1.17                   | 1.07     | 1.24                    | 1.13     | 1.04     | 1.10                   | 1.10     | 1.17                   |          |
| Erythrocytes         | 0.98                   | 0.97     | 1.04                    | 1.02     | 0.22     | 0.32                   | 0.24     | 0.34                   |          |
| lnACR                | 0.54                   | 0.56     | 0.62                    | 0.60     | 0.12     | 0.15                   | 0.13     | 0.15                   |          |
| Age                  | 0.44                   | 0.54     | 0.41                    | 0.48     | 0.88     | 0.87                   | 0.92     | 0.90                   |          |
| lnADMA               | 0.15                   | 0.33     | 0.10                    | 0.25     | 1.50     | 1.00                   | 1.10     | 1.14                   |          |
| eGFR                 | 0.08                   | 0.17     | 0.04                    | 0.24     | 0.40     | 0.59                   | 0.47     | 0.66                   |          |
| Uric acid            | –                      | 1.07     | –                       | 1.13     | –        | 0.61                   | –        | 0.64                   |          |
| lnHcy                | –                      | 0.29     | 0.35                    | –        | –        | 0.31                   | –        | 0.43                   |          |
| R²                   | 32%                    | 32%      | 35%                     | 22%      | 23%      | 22%                    | 22%      | 22%                    |          |

Variables with variable of importance for the projection values ≥1.00 were considered as important contributors (given in bold); ln, logarithm; CRP, C-reactive protein; ACR, urinary albumin-to-creatinine ratio; ADMA, asymmetric dimethylarginine; eGFR, estimated glomerular filtration rate; Hcy, homocysteine.

3.2.1. Correlations between Cardiometabolic Risk Factors and Markers with Uricemia or Homocysteinemia

BMI, WHR, continuous metabolic syndrome score, risk factors number, erythrocytes count, lnADMA, lnCRP, SBP, DBP, leukocytes count, atherogenic index of plasma, and non-HDL-C displayed a positive correlation, while eGFR, HDL-C, age, and ln urine albumin/creatinine ratio showed a negative significant relationship with SUA (Table 2). lnHcy positively correlated with age, lnTAG, continuous metabolic syndrome score, atherogenic index of plasma.
plasma, leukocyte counts, and non-HDL-C; and inversely with eGFR and lnADMA. Similar to males, all significant correlations were weak (Pearson r: SUA: −0.043 to −0.253, lnHcy: −0.053 to −0.131; Table 2).

3.2.2. The Effects of Uricemia and Homocysteinemia on Cardiometabolic Variables

The prevalence of hyperuricemia reached 5.8%, that of hyperHcy was 14.9%, and both markers were concurrently elevated in 1.1% of females (Table 5). Among 209 hyperhomocysteinemic females, 5 displayed moderate hyperHcy (>30 µmol/L); 1 of them suffered from hyperuricemia. Compared with the normouricemic females, those presenting with hyperuricemia did not have increased odds to manifest hyperHcy (OR: 1.32; 95% CI: 0.74–2.34; p = 0.349).

Table 5. Characteristics of females according to uricemia and homocysteinemia.

|                     | Normouricemia, n = 1321 (94.2%) | Hyperuricemia, n = 81 (5.8%) | p  |
|---------------------|---------------------------------|------------------------------|----|
|                     | NHcy (85.3%)                    | NHcy (81.5%)                 |    |
| Number              | 1127 (80.3%)                   | 194 (13.8%)                  |    |
| Age, years          | 17.4 ± 1.4                     | 16.5 ± 1.3                   |    |
| Uric acid, µmol/L   | 250 ± 44                        | 263 ± 42                     |    |
| Homocysteine, µmol/L| 8.8 (6.9, 11.1)                | 14.3 (11.3, 18.1)            |    |
| Body mass index, kg/m² | 21.8 ± 3.3                     | 21.7 ± 3.3                   |    |
| SBP, mmHg           | 107 ± 9                        | 107 ± 10                     |    |
| Glucose, mmol/L     | 4.7 ± 0.4                      | 4.7 ± 0.4                    |    |
| Insulin, µU/mL      | 9.9 (6.2, 15.8)                | 10.1 (6.5, 15.6)             |    |
| QUICKI              | 0.344 ± 0.025                  | 0.342 ± 0.024                |    |
| HDL-C, mmol/L       | 1.53 ± 0.30                    | 1.48 ± 0.32                  |    |
| Non-HDL-C, mmol/L   | 2.73 ± 0.69                    | 2.74 ± 0.70                  |    |
| Atherogenic index   | −0.27 ± 0.20                   | −0.25 ± 0.20                 |    |
| eGFR, mL/min/1.73 m²| 108 ± 16                       | 106 ± 15                     |    |
| ACR, mg/mmol        | 0.5 (0.2, 1.3)                 | 0.5 (0.2, 1.5)               |    |
| ADMA, µmol/L        | 0.43 (0.34, 0.56)              | 0.47 (0.38, 0.59)            |    |
| C-reactive protein, mg/L | 0.5 (0.1, 2.0)               | 0.4 (0.1, 1.4)               |    |
| Leukocytes, 10³/L   | 6.82 ± 1.76                    | 6.79 ± 1.74                  |    |
| NHy, normohomocysteine; NHcy, hyperhomocysteine; UA, uric acid; Hcy, homocysteine; WHR, weight-to-height ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; QUICKI, quantitative insulin sensitivity check index; HDL-C, high-density lipoprotein cholesterol; TAG, triacylglycerols; cMSS, continuous metabolic syndrome score; eGFR, estimated glomerular filtration rate; ACR, urinary albumin-to-creatinine ratio; ADMA, asymmetric dimethylarginine; data are given as mean ± standard deviation, those analyzed after log transformation as back-transformed geometric mean (interval −1 SD, +1 SD), groups were compared using the two-factor Analysis of variance (ANOVA).

Two-factor ANOVA indicated that hyperuricemia was associated with higher BMI, WHR, TBF, SBP, DBP, AIP, continuous metabolic syndrome score, risk factor number, lnCRP, and leukocyte count; and lower HDL-C and eGFR (Table 5). The model neither indicated a significant impact of hyperHcy on either variable nor a significant SUA/hyperHcy interaction. No female displaying concurrently hyperuricemia and hyperHcy manifested MetSy (nSUA/nHcy: 1.2%, nSUA/hyperHcy: 1.0%, hyperuricemia/nHcy: 6.1%, hyperuricemia/hyperHcy: 0%; p = 0.039⁹).  

3.2.3. Multivariate Regression Models

The multiple regression model not adjusted for SUA and Hcy selected insulinemia, inflammatory markers, and ADMA as significant independent predictors of continuous metabolic syndrome score (Model 1; Table 4). Forcing SUA (Model 2), Hcy (Model 3), or their combination (Model 4) into the model neither affected the selection of independent variables modulating the continuous metabolic syndrome score, nor its variability explained by the OPLS model, which was generally low.
4. Discussion

Retrospectively, we tested the hypothesis that in healthy young individuals, the concurrent presence of hyperuricemia and hyperHcy is associated with less favorable cardiometabolic status in comparison with the manifestation of only one of them. We did not confirm our hypothesis. In males, two-factor ANOVA indicated that out of nineteen investigated risk factors and markers, hyperuricemia significantly affected fifteen; hyperHcy only five. Paradoxically, hyperHcy was associated with lower measures of obesity, lower SBP, number of manifested risk factors, and CPR concentration regardless of the absence or presence of hyperuricemia. The synergic effect of hyperuricemia and hyperHcy was observed only for lnADMA. In females, hyperuricemia was associated with worsening of eleven cardiometabolic risk factors and markers; while none of the endpoints was affected significantly by hyperHcy. No significant interaction between hyperuricemia and hyperHcy was observed in either sex.

Numerous studies in the general population of adults indicate that SUA and Hcy levels show a linear positive correlation [12–15,17]. In line with the recent study on teenagers [22], we show that this direct relationship is manifested already in young healthy subjects—a population not affected by age-associated comorbidities. Similar to other studies [14,19,34], this correlation was tighter in females compared with males, despite that females generally present with lower levels of SUA and Hcy, and a lower prevalence of cardiometabolic risk factors and markers compared with males. As in the aforementioned studies, correlations between SUA and Hcy were weak. This evokes a question of whether such weak statistical correlations might be of clinical impact.

Associations between uricemia or homocysteinemia and variables characterizing cardiometabolic risk are widely studied in different populations. In the general population of adolescents, rising SUA concentrations go hand in hand with worsening of the components of MetSy, other cardiovascular disease indicators, such as inflammatory markers or glomerular filtration rate, as well as increased cardiometabolic risk [35–38]. With some minor sex differences, several cardiometabolic risk factors and markers worsened, and the number of cardiometabolic risk factors and cardiometabolic risk (evaluated as continuous metabolic syndrome score) increased significantly with increasing SUA levels also in our study.

The reports on whether variables characterizing cardiometabolic status worsen with increasing Hcy levels in adults are inconsistent [12–17]. Large studies in adolescents show that neither MetSy nor the rising number of its components is associated with increased Hcy levels [39,40]. In our study, all significant simple correlations indicated a less favorable cardiometabolic status with increasing lnHcy in both sexes, albeit significant correlations were less frequent compared with those observed for SUA. However, two-factor ANOVA indicated a concurrent significant impact of hyperuricemia and hyperHcy only in males; and in five out of six cases—BMI, WHtR, SBP, risk factors number, and lnCRP—the presence of hyperHcy paradoxically associated with a partial amelioration of the negative effect of hyperuricemia. The cross-sectional nature of our study does not allow for commenting on potential mechanisms. We are not aware of similar reports in the literature; thus, our findings open the field for further research.

Although the combination of hyperuricemia and hyperHcy was associated with the highest ADMA levels among the four groups, the effect was significant only in males; and was synergic, not additive. Reports on the association of SUA and ADMA in the general population are scarce. The Polish study reported elevated ADMA levels in adolescents with hyperuricemia [41]. The hyperhomocysteinemia-associated rise in ADMA might reflect the interconnection of their metabolism. S-adenosylmethionine methyltransferases and protein-arginine methyl transferases participate simultaneously in Hcy and ADMA synthesis and hyperHcy may increase ADMA levels by reducing the activity of dimethylarginine dimethylaminohydrolase—an enzyme that metabolizes ADMA [42,43]. Moreover, ADMA is eliminated also by renal excretion. Thus, some of the deleterious effects of hyperHcy may involve ADMA-related cardiovascular effects. ADMA acts as a competitive inhibitor.
of NO synthase and may cause a further decrease in the bioavailability of NO by increasing the production of reactive oxygen species [44]. Elevated serum ADMA is associated with MetSy, endothelial dysfunction, and cardiovascular diseases such as hypertension and atherosclerosis [45].

In our adolescents, the prevalence of combined hyperuricemia and hyperHcy was low, particularly in females. Thus, the study could be underpowered concerning the ability of two-factor ANOVA to detect an additive effect of both factors. To this point, we used multivariate regression to test whether and how uricemia and/or homocysteinemia affect the continuous metabolic syndrome score. However, only SUA appeared as a significant independent predictor, and only in males; and the addition of both biomarkers into baseline prediction models did not improve their prediction abilities for the continuous metabolic syndrome score in either sex.

There are several limitations associated with this study. This is a retrospective analysis of a cross-sectional study; thus, a causal relationship cannot be inferred. The measurements were taken at a one-time point. Our results cannot be generalized to different populations. Information on circulating levels of vitamins essential for Hcy metabolism, genetics, lifestyle factors, or dietary habits that could potentially affect SUA or Hcy levels were not available. However, the study in Slovak adolescents indicated that 677 C → T mutation of the methylenetetrahydrofolate reductase gene, one of the most frequent genetic causes of moderate hyperHcy, was not associated with increased Hcy levels [46]. Regarding diets, daily intake of vitamin B12 and folate in these adolescents exceeded the recommended daily allowance, while that of vitamin B6 reached only 60–66%, thus could contribute to hyperHcy. On the other hand, to our knowledge, this is the largest study exploring the combined effects of hyperuricemia and hyperHcy on several cardiometabolic risk factors and markers in apparently healthy young individuals. The number of participants allowed for a separate evaluation of both sexes thus pointing out physiological sex disparities which may remain undetected if the sexes are not analyzed apart.

5. Conclusions

In our young healthy subjects, presence of combined hyperuricemia and hyperHcy was not associated with worse cardiometabolic status compared with that imposed by isolated hyperuricemia. While speculative, there might be several potential explanations. First, the relationship of SUA and Hcy with cardiometabolic risk variables rather reflects their metabolic interconnection than the pathophysiological link. It is also possible that in young healthy individuals SUA or Hcy may not be as specific as the conventional cardiometabolic risk factors concerning cardiovascular risk prediction. Our data do not rule out that there are (even non-clinical) populations where the combined hyperuricemia and hyperHcy associate with an increased cardiometabolic risk—thus, it requires validation in diverse cohorts. If combined risk is confirmed in certain populations, it remains to be elucidated whether successful intervention restoring SUA and Hcy to normal levels concomitantly reduces cardiometabolic risk. Moreover, potential sex-specific disease risk in later life imposed by combined hyperuricemia and hyperHcy should be evaluated.

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Informed Consent Statement: Written informed consent was obtained from all full-aged participants, in all minors from their parents/guardians after the study purpose and procedures had been explained.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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References

1. Ames, B.N.; Cathcart, R.; Schwiers, E.; Hochstein, P. Uric acid provides an antioxidant defense in humans against oxidant- and radical-caused aging and cancer: A hypothesis. Proc. Natl. Acad. Sci. USA 1981, 78, 6858–6862. [CrossRef] [PubMed]
2. Neogi, T.; George, J.; Rekhraj, S.; Struthers, A.D.; Choi, H.; Terkeltaub, R.A. Are either or both hyperuricemia and xanthine oxidase directly toxic to the vasculature? A critical appraisal. Arthritis Rheum. 2012, 64, 327–338. [CrossRef] [PubMed]
3. Maruhashi, T.; Hisatome, I.; Kihara, Y.; Higashi, Y. Hyperuricemia and endothelial function: From molecular background to clinical perspectives. Atherosclerosis 2018, 278, 226–231. [CrossRef] [PubMed]
4. Kubota, M. Hyperuricemia in Children and Adolescents: Present Knowledge and Future Directions. J. Nutr. Metab. 2019, 2019, 3480718. [CrossRef]
5. Schiel, R.; Heinrichs, M.; Stein, G.; Bambauer, R.; Steveling, A. Non-Alcoholic Fatty Liver Disease (NAFLD) in overweight and obese children and adolescents. Arch. Clin. Gastroenterol. 2020, 6, 082–087. [CrossRef]
6. Lu, J.; Sun, W.; Cui, L.; Li, X.; He, Y.; Liu, Z.; Li, H.; Han, L.; Ji, A.; Wang, C.; et al. A cross-sectional study on uric acid levels among Chinese adolescents. Pediatr. Nephrol. 2020, 35, 441–446. [CrossRef] [PubMed]
7. Perla-Kajan, J.; Twardowski, T.; Jakubowski, H. Mechanisms of homocysteine toxicity in humans. Amino Acids 2007, 32, 561–572. [CrossRef]
8. Azzini, E.; Ruggeri, S.; Polito, A. Homocysteine: Its Possible Emerging Role in At-Risk Population Groups. Int. J. Mol. Sci. 2020, 21. [CrossRef]
9. Rehackova, P.; Skalova, S.; Kutilek, S. Serum homocysteine levels in children and adolescents with impaired bone health. Rev. Bras. Reumatol. 2013, 53, 464–468. [CrossRef]
10. Dineleyici, E.C.; Kirel, B.; Alatas, O.; Muslumanoglu, H.; Kilic, Z.; Dogrue, N. Plasma total homocysteine levels in children with type 1 diabetes: Relationship with vitamin status, methylene tetrahydrofolate reductase genotype, disease parameters and coronary risk factors. J. Trop. Pediatr. 2006, 52, 260–266. [CrossRef] [PubMed]
11. Dvořáková, H.M.; Sztányi, P.; Dvořák, P.; Janda, J.; Seeman, T.; Zieg, J.; Lánská, V.; Kotala, K.; Pit'ha, J. Determinants of premature atherosclerosis in children with end-stage renal disease. Physiol. Res. 2012, 61, 53–61. [CrossRef] [PubMed]
12. Zhao, J.; Li, Z.; Hou, C.; Sun, F.; Dong, J.; Chu, X.; Guo, Y. Gender differences in risk factors for high plasma homocysteine levels based on a retrospective checkup cohort using a generalized estimating equation analysis. Lipids Health Dis. 2021, 20, 31. [CrossRef] [PubMed]
13. Bao, F.; Cui, M.; Shi, X.; Ju, S.; Cong, H. Distribution characteristics and influencing factors of homocysteine in an apparently healthy examined population. BMC Cardiovasc. Disord. 2021, 21, 429. [CrossRef] [PubMed]
14. Lussier-Cacan, S.; Xhignesse, M.; Piolot, A.; Sehub, J.; Davignon, J.; Genest, J., Jr. Plasma total homocysteine in healthy subjects: Sex-specific relation with biological traits. Am. J. Clin. Nutr. 1996, 64, 587–593. [CrossRef] [PubMed]
15. Chen, P.; Lu, Y.C.; Wang, P.M.; Huang, C.F.; Loke, S.S. Factors associated with hyperhomocysteinemia in relatively healthy Taiwanese adults: A retrospective medical record study. Medicine 2021, 100, e23829. [CrossRef] [PubMed]
16. Cohen, E.; Levi, A.; Vecht-Lifshitz, S.E.; Goldberg, E.; Garty, M.; Krause, I. Assessment of a possible link between hyperhomocysteinemia and hyperuricemia. J. Investig. Med. 2015, 63, 534–538. [CrossRef] [PubMed]
17. Fu, S.; Yao, Y.; Zhao, Y.; Luan, F. Relationships of Hyperhomocysteinemia and Hyperuricemia With Metabolic Syndrome and Renal Function in Chinese Centenarians. Front. Endocrinol. 2018, 9, 502. [CrossRef]
18. Liu, P.-T.; Chen, J.-D. Synergistic association of hyperuricemia and hyperhomocysteinemia with chronic kidney disease in middle-aged adults and the elderly population. Medicine 2021, 100, e27202. [CrossRef] [PubMed]
19. Wang, S.A.; Wei, Y.S.; Hidru, T.H.; Li, D.B.; Wang, N.; Yang, Y.H.; Wang, Y.S.; Yang, X.L.; Xia, Y.L. Combined Effect of Homocysteine and Uric Acid to Identify Patients With High Risk for Subclinical Atrial Fibrillation. J. Am. Heart Assoc. 2022, 11, e021997. [CrossRef] [PubMed]
20. El Din, U.; Salem, M.M.; Abdulazim, D.O. Uric acid in the pathogenesis of metabolic, renal, and cardiovascular diseases: A review. J. Adv. Res. 2017, 8, 537–548. [CrossRef]
21. Kumar, A.; Palfrey, H.A.; Pathak, R.; Kadowitz, P.J.; Gettys, T.W.; Murthy, S.N. The metabolism and significance of homocysteine in nutrition and health. Nutr. Metab. 2017, 14, 78. [CrossRef]
