ORIGINAL RESEARCH

Asymptomatic Hyperuricemia Associates with Cardiometabolic Risk Indicators in Overweight/Obese but Not in Lean Adolescents

Katarina Sebekova [ID] [1]
Radana Gurecka [ID] [1,2]
Ludmila Podracka [ID] [3,4]

[1]Institute of Molecular BioMedicine, Faculty of Medicine, Comenius University, Bratislava, Slovakia; [2]Institute of Medical Physics, Biophysics, Informatics and Telemedicine, Faculty of Medicine, Comenius University, Bratislava, Slovakia; [3]Department of Pediatrics, Faculty of Medicine, Comenius University, Bratislava, Slovakia; [4]The National Institute of Children's Health, Bratislava, Slovakia

Purpose: In overweight/obese adolescents, asymptomatic hyperuricemia is associated with increased prevalence of metabolic syndrome, its components, and a higher cardiometabolic risk. Whether similar associations exist in lean hyperuricemic adolescents is unknown.

Subjects and Methods: In 2424 adolescents (51.9% females) aged 16–19 years, anthropometric variables, blood pressure, uric acid, glucose, insulin, lipid profile, inflammatory markers, and renal function were determined. Continuous cardiometabolic score was calculated. Normouricemic vs hyperuricemic subjects were compared among lean and overweight/obese individuals of both sexes.

Results: Females (5.4%) and males (13.3%) presented with hyperuricemia; among them 63% of females and 53% of males were lean. In both sexes, hyperuricemic lean and hyperuricemic overweight/obese adolescents displayed similar uric acid concentrations (eg, males: 455±30 vs 461±32 µmol/L, respectively, p=0.933). Lean normouricemic adolescents manifested significantly lower uric acid levels than their overweight/obese peers (eg, males: 333±46 vs 357±41 µmol/L, respectively, p<0.001). Lean normouricemic and hyperuricemic subjects presented similar cardiometabolic score (eg, males: 2.60±0.67 vs 2.64±0.60, respectively, p=0.998); among overweight/obese adolescents those with hyperuricemia displayed higher scores compared with their normouricemic counterparts (eg, males: 3.36±1.04 vs 4.21±1.65, respectively, p<0.001). A decision-tree model revealed phenotypes associated with higher uricemia, however, distribution of individuals with hyperuricemia among phenotypes was random.

Conclusion: In lean adolescents, hyperuricemia is not associated with cardiometabolic profile indicating an increased risk. Existence of this rather prevalent phenotype remains undetected unless lean and overweight/obese subjects are analyzed separately. Longitudinal studies are needed to elucidate the potential clinical consequences of asymptomatic hyperuricemia in lean subjects in later life.

Keywords: uric acid, continuous cardiometabolic score, sex-difference, obesity, lean phenotype

Introduction

In humans, uric acid is a bioactive end-product of purine metabolism and is excreted mainly via urine. Although uric acid is not part of any definition of metabolic syndrome (MetS), studies in adolescents document a significant correlation between uricemia and components of MetS, and other cardiovascular disease indicators, eg, inflammatory markers or glomerular filtration rate.[1–5] Serum uric acid (SUA) levels rise with increasing number of manifested MetS components, the

Correspondence: Katarina Sebekova
Institute of Molecular BioMedicine, Medical Faculty, Comenius University, Sasinkova 4, 811 08 Bratislava, Slovakia
Tel +421-2-9011-9429
Fax +421-2-9011-9631
Email kata.sebekova@gmail.com

prevalence of MetS rises across quartiles of SUA, and clustering of cardiometabolic risk factors with rising SUA levels imposes increased cardiometabolic risk.[3,4,6] High baseline SUA levels during adolescence are associated with higher risk of later development of hypertension, and in males also of MetS.[7]

Body mass index (BMI) and waist circumference generally display the highest correlation with SUA,[2–4] suggesting that obesity and central fat distribution play a major role linking hyperuricemia with cardiometabolic risk factors clustering in MetS. However, the 12-year trend in Japanese adolescent males showed a significant decrease in mean BMI, associated with an increase of mean SUA levels and the prevalence of hyperuricemia.[1] Data from the US adolescents also suggest that a proportion of hyperuricemic adolescents are nonobese.[8] The world-wide rocketing incidence of obesity in youth prompted several studies on the association of hyperuricemia with MetS, its components, and other cardiometabolic risk markers in obese children and adolescents.[9–13] In contrast, the prevalence of hyperuricemia, and whether hyperuricemia is associated with cardiometabolic profile indicating an increased risk in nonobese adolescents, remains largely unknown.

We assumed that a higher proportion of hyperuricemic adolescents are overweight/obese rather than lean; and that both lean and overweight/obese hyperuricemic adolescents present worse cardiometabolic characteristics and a worse continuous cardiometabolic score (a proxy measure of cardiometabolic risk) compared with their normouricemic peers. Due to sex-differences in the pathophysiology of MetS and in the prevalence of MetS components,[14,15] we anticipated sex-differences in association of metabolic factors with SUA and in their clustering patterns. To verify our hypothesis, we analyzed data obtained from 2424 apparently healthy 16–19-year-old adolescents.

Methods
Study Design and Subjects
We performed a secondary analysis of data obtained in the cross-sectional study "Respect for Health" which aimed to assess the health status of secondary school students in the Bratislava region. Information on study objectives and procedures was provided to parents and students at school meetings. Participation was voluntary; a signed informed consent to participate was required from full-aged participants, in minors from their parents or legal guardians. The survey was carried out in accordance with the Declaration of Helsinki, after approval of the protocol by The Ethics Board of the Health Department of the Bratislava Self-governing Region.

Study design had been described in detail previously.[16] Briefly, any acute or chronic illness, in females pregnancy or lactation were exclusion criteria. Anthropometric, blood chemistry and hematology data were obtained from 2960 students aged 11–23 years. After exclusion of non-Caucasians, potential diabetics, adolescents presenting C-reactive protein (CRP) concentration >10 mg/L, estimated glomerular filtration rate <1 mL/s/1.73 m^2, and those aged ≤15 or ≥20 years, data from 2424 White Caucasians of Central European descent (51.9% females) aged 16–19 years were analyzed.

Measurements
Anthropometric measurements were performed by trained personnel in accordance with standard anthropometric guidelines, on barefoot students wearing light clothing. Height was measured using a potable extendable stadiometer, waist circumference using a flexible tape, body weight employing digital scales (Omron BF510, Kyoto, Japan). BMI and waist-to-height ratio (WHtR) were calculated.

Blood pressure (BP) was measured in seated subjects on a dominant arm after 10 min rest, three times in five-minute intervals, using a digital monitor (Omron M-6 Comfort, Kyoto, Japan). The mean of the last two measurements was recorded.

Blood was collected from antecubital vein after overnight fasting. In the central laboratory, plasma glucose, insulin, total cholesterol, high-density lipoprotein cholesterol (HDL-C), triacylglycerols, creatinine, uric acid, and high sensitive CRP were analyzed using standard laboratory methods (Advia 2400 analyzer, Siemens, Germany). Blood count was performed (Sysmex XE-2100 analyzer, Sysmex Corporation, Kobe, Japan). Insulin resistance was estimated using the Homeostasis Model Assessment for Insulin Resistance (HOMA-IR),[17] low-density lipoprotein cholesterol (LDL-C) was calculated using Friedewald formula, atherogenic index of plasma as log (triacylglycerols/HDL-C),[18] estimated glomerular filtration rate employing the equation for the full age spectrum,[19] and continuous cardiometabolic score according to the modified formula of Soldatovic et al,[20] eg, WHtR/0.5+fasting glycemia/5.6 +triacylglycerols/1.7+SBP/130−HDL-C/1.02 (males) or 1.28 (females)+fasting insulinemia/20+CRP/3. To clarify

whether the increase in the score is conditional only on the presence of obesity, alternatively we calculated the score after omitting the WHtR component.

Definition of Hyperuricemia, Cardiometabolic Risk Factors and Metabolic Syndrome

Hyperuricemia was classified as SUA concentration ≥340 µmol/L in females, and ≥420 µmol/L in males, according to the age- and sex-specific reference ranges of the laboratory.

Presence of general overweight/obesity was classified using the international age- and sex-specific cutoff points for BMI in 16–18-year olds,[21] and as BMI ≥25 kg/m² in individuals aged ≥18 years. Centrally obese were considered as individuals displaying WHtR ≥0.5. Adolescents presenting either with general overweight/obesity or central obesity were classified as overweight/obese, those not meeting either criteria, as lean.

MetS was defined as a presence of at least three cardiometabolic risk factors: elevated BP, eg SBP ≥130 mmHg and/or DBP ≥85 mmHg; elevated triacylglycerols (≥1.7 mmol/L), low HDL-C (males: <1.03 mmol/L, females: <1.29 mmol/L); elevated fasting glycemia (≥5.6 mmol/L), central obesity (WHtR ≥0.5). Moreover, the concentration of fasting insulin ≥20 µIU/mL,[22] CRP >3 mg/L,[23] or atherogenic index ≥0.11[18] were also considered as markers of increased cardiometabolic risk.

Statistical Analysis

Data distribution was checked by using the D'Agostino's test. Skewed data were logarithmically transformed. Two sets of continuous variables were compared by using the two-sided unpaired Student's *t*-test. Proportions were compared employing the two-sided Fisher's exact test. In both sexes, individuals were classified according to the presence/absence of hyperuricemia, and presence/absence of overweight/obesity. Between-group comparison of SUA and proxy measures of obesity was performed employing analysis of variance (ANOVA) with post hoc Bonferroni test to correct for multiple comparisons. In all other variables, four groups were compared using the two-factor ANOVA, with categorized SUA status and that of overweight/obesity entered as fixed factors, and their interaction. Binary logistic regression analyses with each single cardiometabolic risk factor or maker, or MetS as dependent variables and SUA and overweight/obesity status as

covariates were performed. Odds were adjusted for the first category, ie, lean normouricemic subjects. Pearson's or Spearman's correlation coefficients were calculated. Whereas the number of subjects in the groups differed, we used the Fisher's r-to-z transformation (two-sided) to assess the significance of the difference between two correlation coefficients. Results of normally distributed data are presented as the mean ±SD, of data analyzed after log transformation as back-transformed geometric mean (interval −1SD, +1SD), as odds and 95%CI or as counts and percentages. To detect and visualize interaction patterns of independent variables affecting SUA, and to predict outcomes, a decision-tree model employing a chi-square d automatic interaction detection was employed. Independent categorized variables, (eg, elevated/nonelevated BP, glycemia, insulinemia, triacylglycerols, atherogenic index, CRP; low/not decreased HDL-C; estimated glomerular filtration rate ≥/< the median; and in overweight/obese groups also presence/absence of central obesity, and general overweight/obesity), and age as an influence variable were entered into the model. A *p*-value of <0.05 was considered as statistically significant. Analyses were performed by using GraphPad Prism v. 6.0 software (GraphPad Software, San Diego, CA, USA), and SPSS v.16 for Windows software (SPSS Inc., Chicago, IL, USA).

Results

Males differed from females in all variables except for age, HOMA-IR, triacylglycerolemia, and the prevalence of hypertriacylglycerolemia (SuppIementary Table S1). In the whole cohort, 9.2% of adolescents were hyperuricemic, 76.3% were lean.

Females

Among 1259 females, 79% were lean, and 5.3% presented hyperuricemia (Table 1). Twenty normouricemic females presented isolated central obesity, 118 displayed only general overweight/obesity, and 82 displayed both types of obesity. Their SUA levels averaged 259±34 µmol/L, 268 ±43 µmol/L, and 269±44 µmol/L, respectively (*p*=0.620). Four hyperuricemic females were centrally obese, eight presented isolated general overweight/obesity, and 14 were concurrently overweight/obese and centrally obese, presenting SUA concentrations of 394±84 µmol/L, 379±36 µmol/L, and 367±21 µmol/L, respectively (*p*=0.469). As the type of obesity did not affect uricemia significantly, females presenting either type of obesity were combined into

Table 1 Characteristics of Females

	Lean		Overweight/Obese		p			Interaction UA*Oweight/Obese
	Normouricemic	Hyperuricemic	Normouricemic	Hyperuricemic	ANOVA	UA Class	Overweight/Obese Class	
n (%)	971 (77.1)	42 (3.3)	220 (17.5)	26 (2.1)		–	–	–
Age, years	17.4±1.0	17.2±1.0	17.5±1.1	16.9±1.0	0.038[a]	–	–	0.503
SBP, mmHg	106±9	109±7	111±9	115±10	<0.001	0.003	<0.001	0.109
DBP, mmHg	70±7	72±6	72±8	78±7	<0.001	<0.001	<0.001	–
Height, cm	165.9±6.1	166.1±5.7	165.1±6.5	165.4±7.4	0.289	–	–	–
Weight, kg	58.8±6.8	58.4±7.0	73.2±10.4[+++]	78.7±16.0[**,+++]	<0.001	–	–	–
Waist, cm	69.0±5.0	70.0±5.1	81.9±7.8[+++]	85.5±10.6[*,+++]	<0.001	–	–	–
BMI, kg/m^2	20.6±2.0	21.2±1.9	26.8±3.0[+++]	28.7±4.9[**,+++]	<0.001	–	–	–
WHtR	0.42±0.03	0.42±0.03	0.50±0.05[+++]	0.52±0.06[*,+++]	<0.001	–	–	–
Glycemia, mmol/L	4.7±0.4	4.7±0.4	4.7±0.4	4.8±0.4	0.015	0.573	0.054	0.797
Insulinemia, μIU/mL	9.3 (6.0, 14.3)	8.2 (5.1, 13.4)	12.8 (8.2, 20.0)	16.9 (9.7, 29.7)	<0.001	0.164	<0.001	<0.001
HOMA-IR	1.92 (1.21, 3.04)	1.67 (0.98, 2.84)	2.68 (1.64, 4.36)	3.58 (1.97, 6.51)	<0.001	0.164	<0.001	0.001
Cholesterol, mmol/L	4.23±0.77	4.21±0.75	4.25±0.69	4.32±0.59	0.927	–	–	–
HDL-C, mmol/L	1.55±0.30	1.51±0.32	1.40±0.29	1.34±0.27	<0.001	0.240	<0.001	0.819
LDL-C, mmol/L	2.29±0.61	2.31±0.59	2.44±0.59	2.51±0.50	0.005	0.586	0.028	0.723
TAG, mmol/L	0.79 (0.53, 1.20)	0.81 (0.57, 1.15)	0.85 (0.59, 1.23)	0.93 (0.60, 1.45)	0.032[a]	0.303	0.042	0.480
Atherogenic index	−0.28±0.20	−0.26±0.18	−0.21±0.19	−0.15±0.23	<0.001	0.146	<0.001	0.456
eGFR, mL/s/1.73m^2	1.83±0.23	1.71±0.21	1.84±0.23	1.73±0.25	<0.001	<0.001	0.816	0.997
CRP, mg/L	0.4 (0.1, 1.5)	0.7 (0.2, 2.3)	0.9 (0.3, 2.9)	1.5 (0.6, 3.8)	<0.001	0.002	<0.001	0.959
Leukocytes, 10^9/L	6.7±1.7	6.9±2.0	7.2±1.7	8.4±2.1	<0.001	0.006	<0.001	0.025
CCM score without the WHtR component	1.8±0.7	1.9±1.0	2.4±0.9	3.0±1.3	<0.001	<0.001	<0.001	0.023

Notes: Data are presented as counts (percentage), mean ±SD (normally distributed data) or as geometric mean (−1SD, +1SD) of back-transformed log data (data not fitting to normal distribution were logarithmically transformed prior to analysis). Measures of obesity were compared using ANOVA with post hoc Bonferroni test. *p<0.05 vs normouricemic overweight/obese subjects; **p<0.01 vs normouricemic overweight/obese subjects; ***p<0.001 vs normouricemic overweight/obese subjects; +++ p <0.001 vs lean subjects in the corresponding serum uric acid category. The two-factor ANOVA, with categorized SUA status and that of overweight/obesity entered as fixed factors, and their interaction was employed to all other variables. Significant p are highlighted in bold. Hyperuricemia, serum uric acid ≥340 μmol/L; overweight/obesity was classified as presence of central obesity (waist-to-height ratio (WHtR) ≥0.5) or general overweight/obesity (BMI ≥25 kg/m^2 in subjects aged ≥18 years or using the international age- and sex-specific cutoff points for BMI in 16–18-year olds)

Abbreviations: UA, uric acid; HOMA-IR, homeostasis model assessment for insulin resistance; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TAG, triacylglycerols; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; CCM, continuous cardiometabolic; BMI, body mass index.

overweight/obese (normouricemic or hyperuricemic) groups. Mean SUA levels (252±49 µmol/L), as well as the prevalence of hyperuricemia (4.1%) were lower in lean, compared with overweight/obese, females (279±53 µmol/L and 10.6%, respectively; $p<0.001$, both) and 61.8% of hyperuricemic females were lean. Lean hyperuricemic females presented about 49% higher mean SUA levels compared with their normouricemic peers; while in overweight/ obese hyperuricemic vs normouricemic females the difference reached about 40% (Figure 1A). Normouricemic lean females presented lower mean SUA levels compared with their overweight/obese counterparts ($p<0.001$); hyperuricemic lean and overweight/obese females displayed similar uricemia ($p=0.994$), (Figure 1A).

While lean normouricemic and hyperuricemic females presented similar proxy measures of obesity, overweight/ obese hyperuricemic females displayed higher body weight, waist circumference, BMI, as well as WHtR compared with their normouricemic peers (Table 1). Body weight, waist circumference, and BMI showed positive association with SUA levels both in lean and overweight/obese females (Table 2). Although that with WHtR showed significance only in overweight/obese females, comparison of two correlation coefficients showed no significant difference (Table 2).

Only glomerular filtration rate was independently impacted solely by uricemia (Table 1). This was reflected by a significant inverse relationship between these variables, regardless of overweight/obesity status (Table 2). In comparison with the reference group of lean normouricemic females, only lean hyperuricemic females had higher odds to present glomerular filtration rate less than the median value (Table 3).

Two-factor ANOVA indicated an independent impact of both, uricemia and overweight/obesity, on SBP, DBP, and CRP; while in the case of leukocyte counts their interaction was also significant (Table 1). SBP showed a direct relationship with SUA in lean females, DBP and leukocyte counts in overweight/obese females, and CRP showed a significant association in both categories (Table
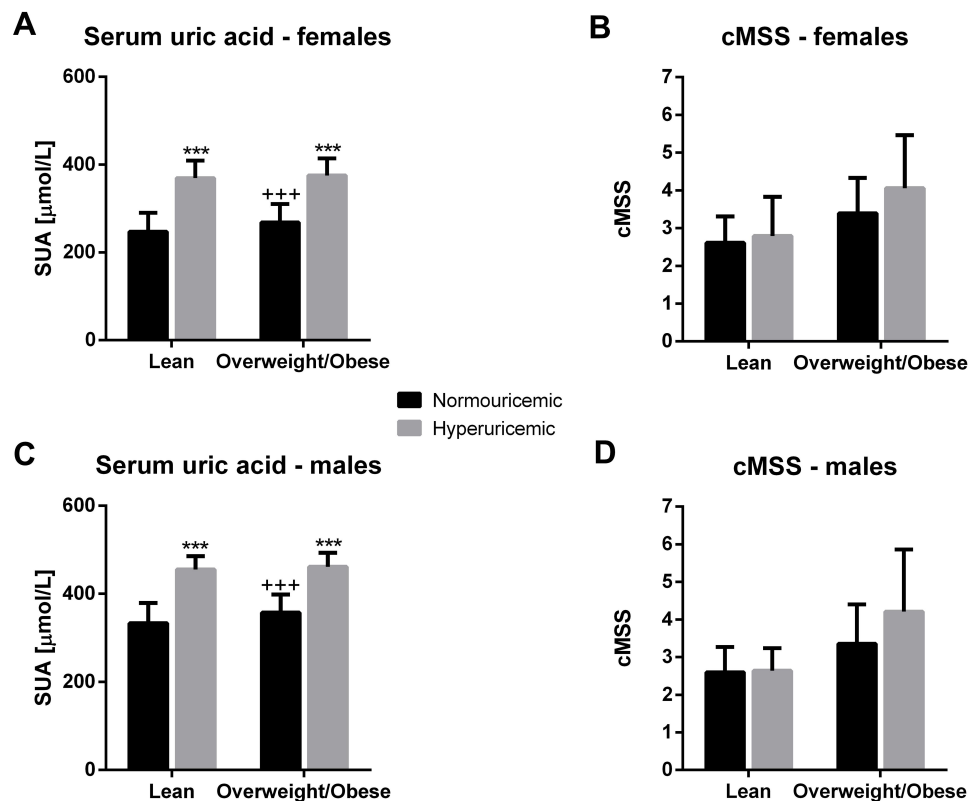

Figure 1 Serum uric acid concentrations and continuous cardiometabolic score according to the presence or absence of overweight/obesity in normouricemic and hyperuricemic females and males (**A**) serum uric acid concentrations in females; (**B**) continuous cardiometabolic score in females; (**C**) serum uric acid concentrations in males; (**D**) continuous cardiometabolic score in males SUA levels were compared using ANOVA with post hoc Bonferroni test to correct for multiple comparisons. ***$p<0.001$ vs normouricemic subjects of the same body frame. +++$p<0.001$ vs lean subjects in the corresponding serum uric acid category. cMSS in four groups was compared using the two-factor ANOVA, with categorized SUA status and that of overweight/obesity entered as fixed factors, and their interaction. ANOVA ($p<0.001$) indicated that both independent factors ($p<0.001$, both) affect the continuous cardiometabolic score in females, and that the score depends on the interaction of two factors (interaction: $p=0.017$). In males, both independent factors, as well as their interaction affected the continuous cardiometabolic score ($p<0.001$, all).
Abbreviations: SUA, serum uric acid; cMSS, continuous cardiometabolic score.

Table 2 Pearson's or Spearman's Correlations Between Serum Uric Acid and Cardiometabolic Risk Factors and Markers in Females and Males

	Females			Males		
	Lean r/rho; p	Overweight/ Obese r/rho; p	Correl. Coeff. Comparison z; p	Lean r/rho; p	Overweight/ Obese r/rho; p	Correl. Coeff. Comparison z; p
SBP	0.062; **0.047**	0.071; 0.271	-0.13; 0.897	0.094; **0.006**	0.095; 0.089	-0.02; 0.984
DBP	0.061; 0.051	0.176; **0.006**	-1.63; 0.103	0.050; 0.145	0.170; **0.002**	-1.84; 0.066
Weight	0.150; **<0.001**	0.176; **0.006**	-0.37; 0.711	0.197; **<0.001**	0.249; **<0.001**	-0.83; 0.407
Waist	0.088; **0.005**	0.151; **0.018**	-0.89; 0.238	0.156; **<0.001**	0.284; **<0.001**	-2.04; **0.041**
BMI	0.115; **<0.001**	0.179; **0.006**	-0.92; 0.358	0.185; **<0.001**	0.215; **<0.001**	-0.47; 0.638
WHtR	0.041; 0.196	0.132; **0.038**	-1.28; 0.201	0.105; **0.002**	0.223; **<0.001**	-1.84; 0.066
Glycemia	0.011; 0.737	0.023; 0.731	-0.17; 0.865	-0.050; 0.150	0.096; 0.086	-2.22; **0.026**
Insulinemia	-0.052; 0.098	0.160; **0.012**	-2.99; **0.003**	-0.002; 0.949	0.179; **0.001**	-2.77; **0.006**
HOMA-IR	-0.047; 0.132	0.150; **0.019**	-2.77; **0.006**	-0.005; 0.892	0.181; **0.001**	-2.85; **0.004**
Cholesterol	-0.048; 0.129	0.113; 0.077	-2.26; **0.024**	0.083; **0.016**	0.106; 0.058	-0.35; 0.726
HDL-C	-0.087; **0.006**	-0.120; 0.060	0.47; 0.638	-0.070; **0.043**	-0.250; **<0.001**	2.81; **0.005**
LDL-C	-0.009; 0.771	0.146; **0.022**	-2.18; **0.029**	0.114; **0.001**	0.113; **0.043**	0.02; 0.984
TAG	0.009; 0.776	0.058; 0.368	0.69; 0.490	-0.027; 0.428	0.174; **0.002**	-3.07; **0.002**
Atherogenic index	0.016; 0.602	0.176; **0.001**	-2.27; **0.023**	0.063; 0.066	0.258; **<0.001**	-3.05; **0.002**
eGFR	-0.201; **0.001**	-0.264; **<0.001**	0.93; 0.352	-0.258; **<0.001**	-0.093; 0.097	-2.59; **0.010**
CRP	0.098; **0.013**	0.129; **0.044**	-0.44; 0.660	0.084; **0.014**	0.103; 0.067	-0.29; 0.772
Leukocytes	0.044; 0.168	0.253; **<0.001**	-3.00; **0.003**	0.041; 0.232	0.093; 0.099	-0.79; 0.430
CCM score	0.011; 0.715	0.229; **<0.001**	-3.11; **0.002**	0.058; 0.093	0.259; **<0.001**	-3.14; **0.002**
CCM score without the WHtR component	0.008; 0.795	0.226; **<0.001**	-3.11; **0.002**	0.050; 0.146	0.252; **<0.001**	-3.15; **0.002**

Notes: Overweight/obesity was classified as presence of central obesity WHtR ≥0.5) or general overweight/obesity BMI ≥25 kg/m^2 in subjects aged ≥18 years or using the international age- and sex-specific cutoff points for BMI in 16–18-year olds. Significant p are highlighted in bold.

Abbreviations: r, Pearson's correlation coefficient; *rho*, Spearman's rank correlation coefficient; CCM, continuous cardiometabolic; HOMA-IR, homeostasis model assessment for insulin resistance; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TAG, triacylglycerols; eGFR, estimated glomerular filtration; CRP, C-reactive protein; CCM, continuous cardiometabolic; WHtR, waist-to-height ratio.

Table 3 Odds Ratios of Cardiometabolic Risk Factors by Serum Uric Acid and Overweight/Obesity Categories in Females[a]

	Lean		Overweight/Obese	
	Normouricemic	Hyperuricemic	Normouricemic	Hyperuricemic
SBP ≥130 mmHg, n (%)	12 (1.2)	1 (2.4)	3 (1.4)	3 (11.5)
OR (95%CI), p	1	1.95 (0.25–15.4), 0.526	1.11 (0.31–3.95), 0.878	10.4 (2.75–39.5), **0.001**
DBP ≥85 mmHg, n (%)	31 (3.2)	1 (2.4)	14 (6.4)	6 (23.1)
OR (95%CI), p	1	0.74 (0.10–5.55, 0.769	2.06 (1.08–3.94), **0.029**	9.10 (3.41–24.2), **<0.001**
Elevated SBP or DBP, n (%)	38 (3.9)	1 (2.4)	15 (6.8)	6 (23.1)
OR (95%CI), p	1	0.60 (0.08–4.47), 0.617	1.80 (0.97–3.33), 0.063	7.37 (2.80–19.4), **<0.001**
Glucose ≥5.6 mmol/L, n (%)	15 (1.5)	1 (2.4)	7 (3.2)	1 (3.8)
OR (95%CI), p	1	1.56 (0.20–12.1), 0.673	2.05 (0.84–5.20), 0.111	2.55 (0.32–20.1), 0.374
Insulin ≥20 μIU/mL, n (%)	34 (3.5)	3 (7.1)	30 (13.6)	7 (26.9)
OR (95%CI), p	1	2.12 (0.62–7.20), 0.229	4.35 (2.60–7.28), **<0.001**	10.2 (4.00–25.8), **<0.001**
TAG ≥1.7 mmol/L, n (%)	45 (4.6)	2 (4.8)	8 (3.6)	3 (11.5)
OR (95%CI), p	1	0.97 (0.24–4.39), 0.969	0.78 (0.36–1.67), 0.518	2.68 (0.78–9.27), 0.119
Atherogenic index ≥0.11, n (%)	26 (2.7)	1 (2.4)	12 (5.5)	5 (19.2)
OR (95%CI), p	1	0.89 (0.12–6.69), 0.907	2.10 (1.04–4.22), **0.038**	8.65 (3.03–24.7), **<0.001**
CRP ≥3 mg/L, n (%)	75 (7.7)	7 (16.7)	41 (18.6)	7 (26.9)
OR (95%CI), p	1	2.39 (1.03–5.56), **0.043**	2.74 (1.81–4.14), **<0.001**	4.40 (1.79–10.8), **0.001**
HDL-C <1.29 mmol/L, n (%)	187 (19.3)	9 (21.4)	85 (38.6)	13 (50.0)
OR (95%CI), p	1	1.14 (0.54–2.43), 0.728	2.64 (1.93–3.62), **<0.001**	4.19 (1.91–9.19), **<0.001**
eGFR <1.81 mL/s/1.73 m², n (%)	477 (49.1)	30 (71.4)	103 (46.8)	17 (65.4)
OR (95%CI), p	1	2.59 (1.31–5.12), **0.006**	0.91 (0.68–1.22), 0.537	1.96 (0.86–4.43), 0.108
MetS, n (%)	1 (0.1)	0 (0)	10 (4.5)	4 (15.4)
OR (95%CI), p	1		46.2 (5.9–362.8), **<0.001**	176.4 (18.9–1643), **<0.001**

Notes: [a]Hyperuricemia was classified as SUA concentration ≥340 μmol/L, overweight/obesity was classified as presence of central obesity, WHtR ≥0.5) or general overweight/obesity BMI ≥25 kg/m² in subjects aged ≥18 years or using the international age- and sex-specific cutoff points for BMI in 16–18-year olds. Significant p is highlighted in bold.
Abbreviations: p, multiple logistic regression analysis; TAG, triacylglycerols; CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; MetS, metabolic syndrome; WHtR, waist-to-height ratio; BMI, body mass index.

Table 4 Characteristics of Males

	Lean		Overweight/Obese		p			
	Normouricemic	Hyperuricemic	Normouricemic	Hyperuricemic	ANOVA	UA Class	Overweight/Obese Class	Interaction UA*Overweight/Obese
n (%)	763 (65.5)	83 (7.1)	246 (21.1)	73 (6.2)				
Age, years	17.3±1.0	17.3±1.1	17.3±1.1	17.4±1.0	0.971	–	–	–
SBP, mmHg	120±11	122±10	127±13	130±13	**<0.001**	0.072	**<0.001**	0.588
DBP, mmHg	72±7	72±7	74±8	77±10	**0.010**	**0.012**	**<0.001**	**0.009**
Height, cm	179.6±6.7	179.7±6.7	178.6±7.1	180.0±6.8	0.344	–	–	–
Weight, kg	67.8±8.3	70.6±7.7**	87.5±12.7**	95.4±15.5*·**	**<0.001**	–	–	–
Waist, cm	75.3±5.1	76.9±4.8	88.0±8.7**	94.0±10.3*·**	**<0.001**	–	–	–
BMI, kg/m²	21.1±2.0	21.8±1.7	27.4±3.1**	29.3±3.7*·**	**<0.001**	–	–	–
WHtR	0.42±0.03	0.43±0.03	0.49±0.05**	0.52±0.05*·**	**<0.001**	–	–	–
Glycemia, mmol/L	4.9±0.4	4.9±0.4	4.9±0.4	5.0±0.4	0.255	–	–	–
Insulinemia, μIU/mL	8.5 (5.4, 13.4)	8.3 (5.3, 12.9)	12.2 (7.1, 20.9)	15.7 (8.2, 29.8)	**<0.001**	**0.009**	**<0.001**	**0.001**
HOMA-IR	1.86 (1.15, 3.00)	1.80 (1.11, 2.91)	2.67 (1.50, 4.76)	3.47 (1.76, 6.84)	**<0.001**	**0.012**	**<0.001**	**0.001**
Cholesterol, mmol/L	3.72±0.64	3.78±0.72	4.00±0.74	4.14±0.87	**<0.001**	0.095	**<0.001**	0.457
HDL-C, mmol/L	1.27±0.22	1.24±0.23	1.23±0.22	1.09±0.24	**<0.001**	**<0.001**	**<0.001**	**0.003**
LDL-C, mmol/L	2.09±0.54	2.18±0.59	2.33±0.64	2.44±0.64	**<0.001**	0.051	**<0.001**	0.802
TAG, mmol/L	0.75 (0.51, 1.08)	0.72 (0.45, 1.16)	0.88 (0.54, 1.42)	1.13 (0.62, 2.07)	**<0.001**	**0.002**	**<0.001**	**<0.001**
Atherogenic index	−0.22±0.19	−0.23±0.21	−0.14±0.24	0.03±0.33	**<0.001**	**<0.001**	**<0.001**	**<0.001**
eGFR, mL/s/1.73m²	1.75±0.23	1.66±0.19	1.74±0.21	1.69±0.20	**0.003**	**0.001**	0.575	0.280
CRP, mg/L	0.4 (0.1, 1.1)	0.5 (0.2, 1.4)	0.7 (0.3, 2.0)	1.0 (0.3, 3.0)	**<0.001**	**0.003**	**<0.001**	0.991
Leukocytes, 10⁹/L	6.2±1.4	6.5±1.5	6.5±1.3	6.9±1.4	**<0.001**	**0.006**	**0.003**	0.531
CCM score without the WHtR component	1.8±0.7	1.8±0.6	2.4±1.0	3.2±1.6	**<0.001**	**<0.001**	**<0.001**	**<0.001**

Notes: Hyperuricemia: serum uric acid ≥420 μmol/L; overweight/obesity was classified as presence of central obesity (WHtR ≥0.5) or general overweight/obesity was classified as presence of central obesity (WHtR ≥0.5) or general overweight/obesity (BMI ≥25 kg/m²) in subjects aged ≥18 years or using the international age- and sex-specific cutoff points for BMI in 16–18-year olds. Data are presented as counts (percentage), mean ±SD (normally distributed data) or as geometric mean (−1SD, +1SD) of back-transformed log data (data not fitting to normal distribution were logarithmically transformed prior analysis). Measures of obesity were compared using ANOVA with post hoc Bonferroni test, *p<0.001 vs normouricemic subjects of the same body frame; **p<0.001 vs lean subjects in the corresponding serum uric acid category. The two-factor ANOVA, with categorized SUA status and that of overweight/obesity entered as fixed factors, and their interaction was employed to all other variables. Significant p is highlighted in bold.

Abbreviations: UA, uric acid; HOMA-IR, homeostasis model assessment for insulin resistance; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; CCM, continuous cardiometabolic; WHtR, waist-to-height ratio; BMI, body mass index.

Table 5 Odds Ratios of Cardiometabolic Risk Factors by Serum Uric Acid and Overweight/Obesity Categories in Males[a]

	Lean		Overweight/Obese	
	Normouricemic	Hyperuricemic	Normouricemic	Hyperuricemic
SBP ≥130 mmHg, n (%)	144 (18.9)	15 (18.1)	96 (39.0)	40 (54.8)
OR (95%CI), p	1	0.95 (0.53–1.78), 0.859	2.75 (2.01–3.77), **<0.001**	5.21 (3.18–8.15), **<0.001**
DBP ≥85 mmHg, n (%)	36 (4.7)	2 (2.4)	21 (8.5)	18 (24.7)
OR (95%CI), p	1	0.50 (0.12–2.11), 0.344	1.89 (1.08–3.30), **0.026**	6.61 (3.53–12.4), **<0.001**
Elevated SBP or DBP, n (%)	158 (20.7)	15 (18.1)	99 (40.2)	40 (54.8)
OR (95%CI), p	1	0.85 (0.47–1.52), 0.572	2.58 (1.89–3.51), **<0.001**	4.64 (2.84–7.60), **<0.001**
Glucose ≥5.6 mmol/L, n (%)	47 (6.2)	8 (9.6)	17 (6.9)	4 (5.5)
OR (95%CI), p	1	1.63 (0.74–3.57), 0.226	1.13 (0.64–2.01), 0.675	0.88 (0.31–2.52), 0.817
Insulin ≥20 μIU/mL, n (%)	27 (3.5)	1 (1.2)	40 (16.2)	25 (34.2)
OR (95%CI), p	1	0.33 (0.05–2.48), 0.283	5.29 (3.17–8.83), **<0.001**	14.2 (7.66–26.3), **<0.001**
TAG ≥1.7 mmol/L, n (%)	21 (2.7)	2 (2.4)	20 (8.1)	19 (26.0)
OR (95%CI), p	1	0.87 (0.20–3.79), 0.872	3.13 (1.67–5.87), **<0.001**	12.4 (6.30–24.5), **<0.001**
Atherogenic index ≥0.11, n (%)	32 (4.2)	5 (6.0)	33 (13.4)	30 (41.1)
OR (95%CI), p	1	1.46 (0.56–3.87), 0.441	3.54 (2.13–5.89), **<0.001**	15.9 (8.88–28.6), **<0.001**
CRP ≥3 mg/L, n (%)	43 (5.6)	5 (6.0)	24 (9.7)	10 (13.7)
OR (95%CI), p	1	1.07 (0.41–2.79), 0.885	1.81 (1.08–3.05), **0.026**	2.26 (1.28–5.54), **0.009**
HDL-C <1.03 mmol/L, n (%)	90 (11.7)	14 (16.9)	40 (16.3)	26 (35.6)
OR (95%CI), p	1	1.54 (0.83–2.84), 0.171	1.47 (0.98–2.20), 0.062	4.19 (2.47–7.10), **<0.001**
eGFR <1.71 mL/s/1.73 m², n (%)	369 (48.4)	50 (60.2)	118 (48.0)	45 (61.6)
OR (95%CI), p	1	1.77 (1.11–2.83), **0.016**	0.96 (0.72–1.28), 0.772	1.43 (0.88–2.33), 0.447
MetS, n (%)	4 (0.5)	1 (1.2)	17 (6.9)	23 (31.5)
OR (95%CI), p	1	2.31 (0.26–20.9), 0.455	14.1 (4.69–42.3), **<0.001**	87.3 (29.1–262.1), **<0.001**

Notes: [a]Hyperuricemia was classified as SUA concentration ≥420 μmol/L, overweight/obesity was classified as presence of central obesity (WHtR ≥0.5) or general overweight/obesity (BMI) ≥25 kg/m²) in subjects aged ≥18 years or using the international age- and sex-specific cutoff points for BMI in 16–18-year olds. Significant *p* is highlighted in bold.

Abbreviations: *p*, multiple logistic regression analysis; TAG, triacylglycerols; CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; MetS, metabolic syndrome; WHtR, waist-to-height ratio; BMI, body mass index.

2). Correlation coefficient differed significantly only for leukocyte counts. Hyperuricemic overweight/obese females had about a 10-fold higher odds for elevated SBP than lean normouricemic subjects; while the odds for elevated DBP were higher in both groups of overweight/obese females (Table 3). CRP was the only variable for which all three groups showed higher odds to present values >3 mg/L in comparison with the reference group (Table 3).

Although ANOVA indicated significant difference in glycemia between the groups, it did not identify either the independent factors, or their interaction as significant (Table 1); and the odds for hyperglycemia were similar across four groups (Table 3). Insulinemia and insulin resistance were significantly impacted by the presence of overweight/obesity, and the interaction of two independent factors (Table 1). Both variables showed a significant positive correlation with SUA levels (Table 2). Regardless of uricemia, overweight/obese females had higher odds to present elevated fasting plasma insulin compared with lean normouricemic females (Table 3).

Presence of overweight/obesity significantly impacted lipid profile (except for total cholesterol levels), and atherogenic index of plasma (Table 1). However, only odds for low HDL-C and increased atherogenic index were higher in overweight/obese groups (Table 3). Neither total cholesterol, nor triacylglycerols showed a significant correlation with SUA; HDL-C correlated inversely in lean females, and LDL-C and atherogenic index showed a positive relationship with SUA in overweight/obese females (Table 2).

ANOVA ($p<0.001$) indicated that both independent factors ($p<0.001$, both) affect the continuous cardiometabolic score in females, and that the score depends on the interaction of two factors (interaction: $p=0.017$), (Figure 1B). Almost identical results were obtained if WHtR was omitted from the equation (Table 1). Correlation between the scores and SUA were significant only in overweight/obese females (Table 2).

Males
Among 1165 males, 72.6% were lean, 13.4% presented hyperuricemia (Table 4). Normouricemic centrally obese (n=9), overweight/obese (n=144) males, and those presenting combined obesity (n=93) displayed similar SUA levels (366 ±40 μmol/L, 356±41 μmol/L, and 357±41 μmol/L, respectively ($p=0.765$). Among hyperuricemic males, 26 presented isolated general overweight/obesity, and 47 displayed

concurrently central obesity and general overweight/obesity. Their mean SUA concentrations were similar (464±29 μmol/L, and 460±34 μmol/L, respectively, $p=0.620$). Thus, regardless of the type of obesity, males were classified as overweight/obese and grouped according to SUA concentrations. SUA levels were lower in lean (345±57 μmol/L) compared with overweight/obese males (380±59 μmol/L, $p<0.001$). The prevalence of hyperuricemia was higher among overweight/obese (22.9%) compared with lean males (9.8%, $p<0.001$). 53.2% of hyperuricemic males were lean. Lean hyperuricemic males presented about 37% higher mean SUA levels compared with their normouricemic peers, in overweight/obese males the difference reached about 29% (Figure 1C). Lean normouricemic males displayed lower mean SUA levels compared with normouricemic overweight/obese peers ($p<0.001$), while the difference among hyperuricemic males was insignificant ($p=0.933$), (Figure 1C).

As in females, proxy measures of obesity did not differ significantly between lean normouricemic and hyperuricemic subjects, while overweight/obese hyperuricemic males presented higher body weight, waist circumference, BMI, and WHtR compared with their normouircemic peers (Table 4). Proxy measures of obesity showed significant correlation with SUA both in lean and overweight/obese males (Table 2).

As in females, estimated glomerular filtration rate was the single variable impacted solely by presence of hyperuricemia (Table 4). It showed a significant (inverse) relationship with SUA only in lean males (Table 2), and lean hyperuricemic subjects had higher odds to present glomerular filtration rate less than median (Table 5).

Among independent factors, overweight/obesity significantly affected SBP; while presence or absence of hyperuricemia as well as that of overweight/obesity showed significant impact on DBP, with a significant interaction (Table 4). SBP showed significant correlation with SUA in lean males, DBP correlated with uricemia in overweight/obese males but Fisher's r-to-z transformation did not indicate significant differences (Table 2). Normouricemic and hyperuricemic overweight/obese males had higher odds to present elevated SBP, as well as DBP, compared with lean normouricemic subjects (Table 5).

Neither fasting plasma glucose concentration (Table 4), nor the odds for presenting elevated glycemia (Table 5) differed significantly among the four groups. Glycemia did not correlate with SUA significantly (Table 2). The ANOVA indicated a significant independent effect of both factors, including their interaction, on insulinemia and HOMA-IR (Table 4), indicating that overweight/
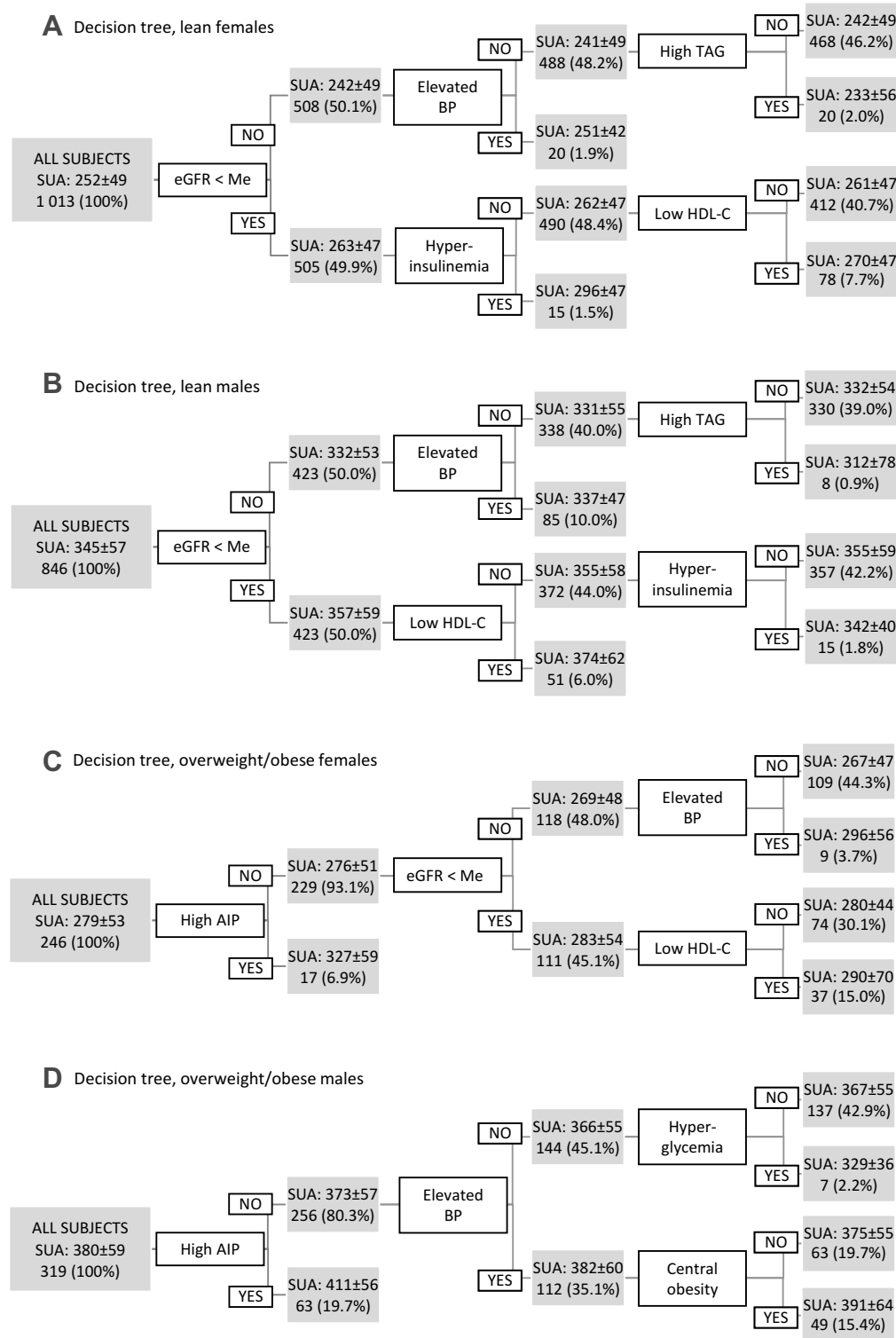
A Decision tree, lean females

```
ALL SUBJECTS
SUA: 252±49
1 013 (100%)
```
eGFR < Me

NO → SUA: 242±49 508 (50.1%) → Elevated BP
  - NO → SUA: 241±49 488 (48.2%) → High TAG
    - NO → SUA: 242±49 468 (46.2%)
    - YES → SUA: 233±56 20 (2.0%)
  - YES → SUA: 251±42 20 (1.9%)

YES → SUA: 263±47 505 (49.9%) → Hyper-insulinemia
  - NO → SUA: 262±47 490 (48.4%) → Low HDL-C
    - NO → SUA: 261±47 412 (40.7%)
    - YES → SUA: 270±47 78 (7.7%)
  - YES → SUA: 296±47 15 (1.5%)

B Decision tree, lean males

```
ALL SUBJECTS
SUA: 345±57
846 (100%)
```
eGFR < Me

NO → SUA: 332±53 423 (50.0%) → Elevated BP
  - NO → SUA: 331±55 338 (40.0%) → High TAG
    - NO → SUA: 332±54 330 (39.0%)
    - YES → SUA: 312±78 8 (0.9%)
  - YES → SUA: 337±47 85 (10.0%)

YES → SUA: 357±59 423 (50.0%) → Low HDL-C
  - NO → SUA: 355±58 372 (44.0%) → Hyper-insulinemia
    - NO → SUA: 355±59 357 (42.2%)
    - YES → SUA: 342±40 15 (1.8%)
  - YES → SUA: 374±62 51 (6.0%)

C Decision tree, overweight/obese females

```
ALL SUBJECTS
SUA: 279±53
246 (100%)
```
High AIP

NO → SUA: 276±51 229 (93.1%) → eGFR < Me
  - NO → SUA: 269±48 118 (48.0%) → Elevated BP
    - NO → SUA: 267±47 109 (44.3%)
    - YES → SUA: 296±56 9 (3.7%)
  - YES → SUA: 283±54 111 (45.1%) → Low HDL-C
    - NO → SUA: 280±44 74 (30.1%)
    - YES → SUA: 290±70 37 (15.0%)

YES → SUA: 327±59 17 (6.9%)

D Decision tree, overweight/obese males

```
ALL SUBJECTS
SUA: 380±59
319 (100%)
```
High AIP

NO → SUA: 373±57 256 (80.3%) → Elevated BP
  - NO → SUA: 366±55 144 (45.1%) → Hyper-glycemia
    - NO → SUA: 367±55 137 (42.9%)
    - YES → SUA: 329±36 7 (2.2%)
  - YES → SUA: 382±60 112 (35.1%) → Central obesity
    - NO → SUA: 375±55 63 (19.7%)
    - YES → SUA: 391±64 49 (15.4%)

YES → SUA: 411±56 63 (19.7%)

Figure 2 Decision tree visualizing patterns how presence or absence of independent categorical variables impact serum uric acid concentration in (**A**) lean females; (**B**) lean males; (**C**) overweight/obese females; (**D**) overweight/obese males. In each node, SUA concentration given as mean ±SD, second row: number of subjects in node (percentage of all subjects).
Notes: Me, median (females: 1.81 mL/s/1.73 m2, males: 1.71 mL/s/1.73 m2); BP, blood pressure; elevated, SBP ≥130 mmHg and/or DBP ≥85 mmHg; TAG, triacylglycerols, elevated: ≥1.7 mmol/L; hyperinsulinemia, fasting insulinemia ≥20 μIU/mL; HDL-C, high-density lipoprotein cholesterol; low, <1.29 mmol/L (females) or <1.03 mmol/L (males); AIP, atherogenic index of plasma; high, ≥0.11; hyperglycemia, fasting glycemia ≥5.6 mmol/L; central obesity, waist/height ≥0.5.
Abbreviations: SUA, serum uric acid; eGFR, estimated glomerular filtration rate; Me, median in corresponding sex; BP, blood pressure; TAG, triacylglycerols; HDL-C, high-density lipoprotein cholesterol; AIP, atherogenic index of plasma.

obese males maintained glycemia with higher insulin levels, and were more insulin resistant, particularly if they were also obese. Thus, correlations between insulin concentrations or insulin resistance index and SUA were significant only in overweight/obese males (Table 2).

Total cholesterol and LDL-C levels appeared to be significantly higher in presence of obesity; while HDL-C, triacylglycerols, and atherogenic index were significantly affected by both independent factors but their interaction was significant (Table 4). Cholesterolemia significantly associated with SUA levels in lean males, triacylglycero-lemia and atherogenic index correlated with uricemia in overweight/obese subjects, and HDL-C and LDL-C in both categories (Table 2). Odds for manifestation of ele-vated triacylglycerols and that of atherogenic index were increased in both groups of overweight/obese males, while only hyperuricemic overweight/obese males had higher odds to present low HDL-C (Table 5).

Inflammatory markers, CRP and leukocyte counts were independently affected by both classification factors (Table 4). Although CRP showed significant correlation with SUA only in lean males (Table 2), correlation coefficients did not differ significantly. Normouricemic as well as hyperuricemic overweight/obese males had higher odds for elevated CRP compared with the reference group (Table 5).

Two-factor ANOVA ($p<0.001$) indicated that both independent factors ($p<0.001$, both) affect the continuous cardiometabolic score in males, and that the score depends on the interaction of two factors (interaction: $p<0.001$), (Figure 1D). Identical results were obtained if WHtR was omitted from the equation (Table 4). Correlations between the scores and SUA were significant only in overweight/obese males (Table 2). The odds to present MetS were increased in both normouricemic and hyperuricemic over-weight/obese males (Table 5).

Decision-tree Models

The decision-tree model selected glomerular filtration rate as the predictor variable of SUA in the primary split both in females (Figure 2A; detailed classification tree given in the Supplemental Figure S1), and in males (Figure 2B; Supplemental Figure S2). In both sexes, in subjects with glomerular filtration rate less than median (females: <1.81 mL/s/1.73 m², males: <1.71 mL/s/1.73 m²), HDL-C and insulinemia predicted SUA levels in the next nodes; while in individuals with glomerular filtration rate greater than or equal to median, BP and triacylglycerols were subsequent determinants of SUA levels. Phenotypes with

a higher risk did not unequivocally display higher mean SUA levels, as visible in the terminal nodes predicted by triacylglycerols in both sexes and by insulin in males. Females presenting a rare phenotype, ie, glomerular filtra-tion rate less than median and elevated fasting insulin levels, displayed the highest mean SUA concentration and the highest prevalence of hyperuricemia (20%). In males, those with lower glomerular filtration rate and low HDL-C presented the highest SUA levels as well as the highest prevalence of hyperuricemia (23.5%). 52% of hyperurice-mic females clustered among those presenting glomerular filtration rate less than median, low HDL-C, and normal fasting insulinemia (Supplementary Figure S1). The highest prevalence of hyperuricemic males (48%) was in the phe-notype with glomerular filtration rate less than median, not presenting low HDL-C and elevated fasting insulinemia (Supplementary Figure S2).

The top-level node of the decision tree in overweight/ obese females (Figure 2C, Supplementary Figure S3) and males (Figure 2D, Supplementary Figure S4) showed that about 7% of females and 20% of males presented increased atherogenic index. In both sexes, this phenotype associated with the highest mean SUA levels. The prevalence of hyper-uricemic subjects reached 29% in these females and 48% in males and was the highest among all phenotypes. Forty-one percent of hyperuricemic overweight/obese males presented this phenotype. In females not presenting elevated athero-genic index, glomerular filtration rate, BP, and HDL-C were subsequently used in decision-tree construction. In all node-pairs, phenotypes with higher cardiometabolic risk presented higher mean SUA levels. In males, the model subsequently selected BP, glycemia, and central obesity to predict SUA concentrations. Among normotensive males who did not present increased atherogenic index, normoglycemic sub-jects paradoxically displayed higher uricemia compared with their peers displaying elevated fasting glycemia.

Discussion

This study provides evidence that: (1) more than a half of adolescents with asymptomatic hyperuricemia are lean. (2) While normouricemic overweight/obese adolescents dis-play higher SUA levels compared with their lean counter-parts, hyperuricemic lean and overweight/obese subjects present similar SUA concentrations. (3) In lean adoles-cents, asymptomatic hyperuricemia is not associated with increased continuous cardiometabolic risk score. (4) Phenotypes associated with the highest SUA levels differ between lean and overweight/obese adolescents.

The prevalence of hyperuricemia in our study was similar to that reported for 18–25-year old healthy Slovaks (males: 12.7%, females: 4.0%).[24] Our data are also in line with other reports, indicating higher prevalence of hyperuricemia in overweight/obese adolescents (12%-38%) compared with the general population (7%-30%), and mostly higher in males (5%-27%) than in females (1%-19%).[25] To our knowledge, there are no data on the prevalence of hyperuricemia in lean adolescents. The Japanese study mentioned that a proportion of nonobese adolescent males was hyperuricemic but the authors did not comment on this finding.[1] We show that although the prevalence of hyperuricemia is higher in overweight/obese compared with lean subjects, more than a half of hyperuricemic adolescents are lean. In line with other studies,[26,27] overweight/obese adolescents presented higher SUA levels compared with their lean peers. However, overweight/obesity impacted SUA levels only in normouricemic subjects; hyperuricemic adolescents displayed similar SUA concentrations regardless of the presence or absence of overweight/obesity.

In the general population and in obese adolescents, rising SUA concentrations are associated with a worsening of different components of MetS.[2–4,10,26] Large studies on the general population of adolescents documented an increase in mean SUA levels across cardiovascular risk classes[4] and a worsening of continuous MetS z-score with rising SUA levels.[6] Our hyperuricemic overweight/obese adolescents also displayed higher continuous cardiometabolic scores compared with their normouricemic peers, suggesting that asymptomatic hyperuricemia is associated with worse cardiometabolic status only in overweight/obese adolescents. Even though, we neither revealed systematic worsening in variables characterizing cardiometabolic risk nor documented a significant deterioration in continuous cardiometabolic score in lean hyperuricemic vs normouricemic adolescents, these findings should be interpreted with caution.

Lean hyperuricemic adolescents displayed preserved insulin sensitivity. In overweight/obese subjects, hyperuricemia aggravated the already present overweight/obesity-associated insulin resistance.[25] Experimental studies document that uric acid increases hepatic fat accumulation and glucose production; induces proinflammatory endocrine imbalance in the adipose tissue, representing an underlying mechanism of the low-grade inflammation and insulin resistance; and inhibits insulin signalling in the muscle.[28,29] In young females, basal SUA levels or their change over three years did not track with changes in insulin sensitivity, beta-cell function or glycemia, even in those with recent gestational diabetes mellitus.[30]

A different study documented an increased risk for new-onset diabetes in healthy lean females presenting high normal SUA levels at baseline.[31] Whether these sex-specific results were affected by the transition of a proportion of females into postmenopausal state during the follow-up, remains unclear. Since hyperuricemia commonly precedes the development of hyperinsulinemia,[32] further studies are needed to clarify whether in lean adolescents elevation of SUA over prolonged periods is associated with increased risk of hyperinsulinemia, insulin resistance or diabetes.

We revealed a worse lipid profile only in hyperuricemic vs normouricemic overweight/obese males. This corresponds to the results from the Taiwanese military cohort, describing associations between atherogenic lipid profiles and hyperuricemia merely in males.[33] Whether the association between hyperuricemia and dyslipidemia is sex-specific remains unclear. In adults, hyperuricemia is a potential risk of later development of high LDL-C and hypertriacylglycerolemia.[34] In our multivariate analysis, the increased atherogenic index of plasma unequivocally predetermined high SUA levels in overweight/obese individuals of both sexes. Thus, in adolescents hyperuricemia accelerates manifestation of atherogenic dyslipidemia particularly in the presence of overweight/obesity, associated per se with this metabolic derangement.

Experimental and clinical studies (even in children and adolescents) suggest that SUA is a true modifying and possibly causal factor for essential hypertension, among others via reduction of nitric oxide levels in the endothelium, induction of oxidative stress, and activation of the renin–angiotensin system.[35,36] In our cohort, independent effects of hyperuricemia on SBP and DBP as well as odds to present BP ≥130/85 mmHg showed sex differences. Although overweight/obese hyperuricemic females displayed about 1.6-fold higher odds to present elevated BP compared with overweight/obese hyperuricemic males, overlapping confidence intervals suggest that this might be a tendency. In the Taiwanese military cohort, the association between hyperuricemia and raised blood pressure was greater in females than in males; while general as well as central obesity rose in parallel with an increase in SUA concentrations in both sexes.[33] In addition, other data from adults suggest a modifying effect of obesity on the association between hyperuricemia and hypertension.[37] However, a large Israeli study on healthy 40–70-year old subjects showed that high normal SUA levels (slightly above our reference range) at baseline predicted an

increased risk of developing hypertension during a 10-year follow-up, even in subjects nonobese at baseline.[38]

Pediatric patients with hyperuricemia had an increased risk of mortality, among others, due to kidney diseases.[39] Regardless of sex, our lean adolescents presented an inverse relationship between SUA levels and estimated glomerular filtration rate and the odds for glomerular filtration rate below the median was increased in hyperuricemic lean adolescents. Association between lower glomerular filtration rate and higher uric acid levels has formerly been documented in overweight/obese children and adolescents.[12,13] Similarly, apparently healthy hyperuricemic adolescents and adults presented lower glomerular filtration rate compared with their normouricemic peers.[31,38,40] In these studies, including ours, the decline in glomerular filtration rate was within the normal range values, reaching 7–10%. Such a mild decline cannot explain the observed rise in SUA levels: in adults, hypofiltration (estimated glomerular filtration rate less than age-/sex-specific fifth percentile) associated with about a 16% rise in uricemia.[41]

In adults, elevated CRP level is an independent predictor of all-cause, and cardiovascular mortality risk.[42] Moreover, baseline SUA level predicted probability of developing clinically relevant increased CRP during three years of follow-up.[43] In obese juveniles, associations between uricemia, markers of inflammation, and BMI have been described.[5] In our females, hyperuricemia was associated with higher CRP even in the absence of obesity. The linkage between hyperuricemia and low-grade inflammation might be sex-specific, similarly as the association between CRP and MetS, which is present in females but not in males.[44]

Observed discrete decline in glomerular filtration rate, and a mild rise of CRP levels in females, might be forerunners of overt manifestation of increased cardiometabolic risk in the future. The coexistence of elevated SUA with lower renal function over prolonged periods may eventually evoke elevation of BP. Hypertension frequently presents concurrently with other cardiovascular disease risk factors, such as insulin resistance, atherogenic dyslipidemia, and central obesity, constituting the MetS.[45–47] Compared with manifestation of isolated components, clustering of hyperuricemia with the components in MetS confers a higher probability of manifestation of cardiovascular and renal diseases, diabetes, and mortality.[45,47] As hyperuricemia is a marker of poor outcome,[39,48] a missing link between hyperuricemia and a continuous cardiometabolic score in our lean hyperuricemic adolescents might only be a temporary finding. Persistent elevation of SUA might, in the long-term, exert negative health effects even in lean subjects. In adults free from MetS at baseline, elevated baseline SUA levels increased the odds to manifest MetS seven years later, regardless of their BMI status at baseline.[49] Longitudinal studies are needed to elucidate whether cardiometabolic risk of lean hyperuricemic adolescents increases with aging, eventually with respect to body weight gain.

Decision-tree models confirmed the difference in determinants of uricemia in lean and overweight/obese adolescents. The model identified phenotypes displaying the highest mean SUA levels; but it did not meet our expectations in terms of prediction. Hyperuricemic subjects did not unequivocally cluster in certain phenotypes, their distribution among the end-nodes appeared to be rather random than reflecting preferential clustering. In the end-node pairs, phenotypes with higher cardiometabolic risk did not unambiguously present higher SUA levels. Nevertheless, these differences were not robust, suggesting rather a statistical than clinical significance. As the prevalence of MetS, its components, as well as that of other indicators of increased cardiometabolic risk increases by aging, the question arises whether decision-tree modelling might be a useful predictive tool for identification of hyperuricemia-associated phenotypes in older populations.

Metabolic derangements observed in lean hyperuricemic adolescents do not elucidate the background leading to rise in SUA levels to the range displayed by their overweight/obese peers. Since we neither have data on the consumption of purines-rich food, fructose-containing beverages, and alcohol, nor those on physical activity or genetics of our adolescents, we might only speculate on the role of lifestyle or genetic factors.

The strength of this study is a reasonably large sample of apparently healthy young adolescents that minimized confounding by comorbidities. Our study was probably the first to examine the associations between SUA levels and variables characterizing cardiometabolic risk separately in overweight/obese and in lean adolescents of both sexes. There is a limitation of generalizing our findings to populations with different epidemiological, anthropometric or clinical characteristics. Observed associations might be biased by voluntary participation and potential participation of close relatives. Although we were able to examine the relationship between SUA levels and other variables, cross-sectional design did not allow for examination of causality.

Conclusions

About seven out of 100 apparently healthy adolescent males and about three out of 100 females present

hyperuricemic lean phenotypes. These individuals remain largely undiagnosed, unless there is a reasonable indication to analyze SUA concentration. Different associations of hyperuricemia with variables characterizing cardiovascular risk in lean and overweight/obese subjects remains undiscovered unless these groups are analyzed separately. Further studies are needed to elucidate which mechanisms lead to hyperuricemia in lean adolescents, and whether hyperuricemia in lean adolescents might have clinical consequences in later life. Knowledge on prognosis of these individuals is essential to identify potential proper follow-up strategies.

Data Sharing Statement

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

Acknowledgments

Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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