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Uric acid relationships with lipid profile and adiposity indices: Impact of different hyperuricemic thresholds

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Abstract

Previous studies focused on the relationships between Serum Uric Acid (SUA) and lipids have found an association mainly with triglycerides. Furthermore, previous studies on adiposity indices have been focused on the evaluation of the Visceral Adiposity Index (VAI). The present study was aimed at providing within the same population a systematic evaluation of lipids and adiposity indices with SUA, employing both the classic cutoff for hyperuricemia and the newly one identified by the Uric Acid Right for Heart Health (URRAH) study. We analyzed data collected in 1892 subjects of the Pressioni Arteriose Monitorate E loro Associazioni (PAMELA) study with available SUA, lipid profile and variables necessary to calculate VAI, Cardio-Metabolic Index (CMI) and Lipid Accumulation Product (LAP). At linear regression model (corrected for confounders) SUA correlated with all the lipids values (with the strongest β for triglycerides) and adiposity indices. When the two different cutoffs were compared, the URRAH one was significantly related to atherogenic lipids profile (OR 1.207 for LDL and 1.33 for non-HDL, $P < 0.001$) while this was not the case for the classic one. Regarding adiposity indices the classic cutoff displays highest OR as compared to the URRAH one. In conclusions, newly reported URRAH cutoff for hyperuricemia better relate to atherogenic lipoprotein (LDL and non-HDL) when compared to the classic one. The opposite has been found for adiposity indexes where the classic cut-off seems to present highest performance. Among adiposity indexes, LAP present the highest OR for the relationship with hyperuricemia.

KEYWORDS
adiposity indices, cardiometabolic index, lipid accumulation product, lipids, uric acid, visceral adiposity index

1 | INTRODUCTION

Previous studies have shown that serum uric acid (SUA) exerts an independent pathophysiological role in the development and progression of high blood pressure and hypertension-related fatal and non-fatal cardiovascular events,[1] such as acute coronary syndrome,[2] heart failure,[3] stroke[2] and atrial fibrillation.[4] This has led the most recent european guidelines on hypertension to include SUA among the factors that may affect cardiovascular risk in the hypertensive population.[5]

The mechanisms responsible for the close association between SUA and cardiovascular are complex and multifactorial, including among others, the participation of metabolic factors. Indeed, hyperuricemia has been strongly associated with the metabolic syndrome[6,7] and with some of its components such as dyslipidaemia[8,9] and adiposity.[10–11] Regarding lipids, the closest association found was between SUA and tryglicerides[12] while, for adiposity indices the most common one has been the visceral adiposity index (VAI),[12] the cardiometabolic index (CMI) and lipid accululation product (LAP) being less frequently used[13] in this regard. These anthropometric and biochemical indices are of major clinical relevance because they allow to better define the visceral adipose tissue accumulation that is variable more closely related to cardiovascular risk.[13]

A number of limitations, however, weaken the strength of the above mentioned findings. First, the SUA threshold values used for defining SUA normality and predicting total and cardiovascular mortality were in the reported studies greater than the ones recently described in one of the largest study published so far on this topic, the Uric Acid Right for Heart Health (URRAH), involving more than 22000 subjects representative of the general population.[1] An additional limitation is represented by the fact that the information provided by the studies mentioned above were collected in clinical phenotypes selectively characterized either by lipid alterations or adipose tissue abnormalities, and thus scarcely representative of the association between lipid alterations and body fat accumulation commonly detected in current clinical practice. To overcome these limitations, the present study was designed at providing information on the associations between SUA, lipid profile and adiposity indices following two specific criteria. First, both classic and the new SUA thresholds for cardiovascular and total mortality were taken into account, allowing us to determine which method is more adequate for such evaluation. Second, we assessed extensively and concomitantly in a large general population sample, the one examined in the Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) study,[14] the association between SUA, lipid profile and adipose tissue abnormalities, thus allowing us to obtain information closely related to daily life.

2 | METHODS

2.1 | Study population

The details of the study population have been previously reported.[14] Briefly, the PAMELA study was performed in 3200 subjects of the population of Monza (a town near Milan, Italy) stratified according to gender, age (decades), and other characteristics from 25 to 74 years old. At the initial evaluation, carried out between 1990 and 1993, participation rate was 64% and data were thus available in 2051 individuals. The demographic and clinical characteristics of participants and nonparticipants, as assessed by phone interviews, were similar. Participants were evaluated at the S. Gerardo Hospital (Monza, Italy) outpatient clinic in the morning of a working day (Monday to Friday), following an overnight fast and abstinence from alcohol and smoking since the previous day.

2.2 | Measured variables

Data collection included medical history, office blood pressure (BP) and 24-hour Ambulatory BP Monitoring. Office BP was measured three times with the subject in the sitting position, using a mercury sphygmomanometer and taking the first and fifth Korotkoff sounds to identify systolic and diastolic values, respectively (first and second survey). 24-h Ambulatory BP (Spacelabs 90207, Issaquah, WA, USA) was set to obtain automated oscillometric BP and heart rate readings every 20 min over the 24 h. Subjects were asked to pursue their normal activities during the monitoring period, holding the arm still at time of the BP readings, going to bed not later than 11.00 PM and waking up not before 7.00 AM. Height and weight were obtained to calculate body mass index (BMI) and waist circumference (WC) was assessed halfway between the lower ribs and the iliac crest. Laboratory analyses included SUA, glucose, total cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides and creatinine. Glomerular filtration rate was estimated (eGFR) by the Chronic Kidney Disease EPIdemiology (CKD-EPI) equation. low density lipoprotein (LDL) cholesterol was estimated according to the Friedewald equation.

In the cross-sectional analysis of the present study only patients with available lipids and data necessary to calculate VAI, CMI and LAP were included (total n = 1892). Hyperuricemia was diagnosed both with the classic cut-off of 6.0 mg/dl for females and 7.0 mg/dl for males, but also with the newly identified one in the URRAH study that is 5.1 mg/dl for females and 5.6 mg/dl for males.[1] The study protocol complied with the Declaration of Helsinki and it was approved by the Ethics Committee of the Institution involved. All participants provided written consent after being informed of the study nature and purpose. No data were available regarding the use of allopurinol in the PAMELA population.

2.3 | Adiposity indices

The following formulas were used for adiposity indices calculation as reported in literature.[10,11] VAI and LAP present different formulas for males and females:

VAI (males) = [WC (cm)/39.68 + (1.88*BMI)] * [triglycerides (mg/dl)/1.03] * [1.31/HDL-Cholesterol (mg/dl)];

VAI (females) = [WC (cm)/36.58 + (1.89*BMI)] * [triglycerides (mg/dl)/0.81] * [1.52/HDL-Cholesterol (mg/dl)];

CMI = triglycerides/HDL-Cholesterol * [WC/height (cm)];

LAP (males) = triglycerides (mg/dl) * [WC (cm) − 65].

LAP (females) = triglycerides (mg/dl) * [WC (cm) − 58];

2.4 | Data analysis

Data related to subjects characteristics were analysed by descriptive statistics. Normality of continuous variables was tested by qq-plot and Kolmogorov-Smirnov test. Variables with normal distribution were reported as mean ± standard deviation, non-normal as median (interquartile range). For discrete variables numbers and percentages in each category were reported. Groups were compared using t-test or nonparametric Mann Whitney test. Chi-square test was used for categorical variables. Relationship between SUA and lipids and adiposity indices was analyzed using SUA both as a continuous and a categorical binary variable (hyperuricemia). Non-normal variables were log transformed. Because of LAP index assume also zero and negative values, before log transformation, it was scaled by adding minimum variable value. Linear regression models were used for analysing relationship between continuous SUA and independent variables. Logistic regression models were used to evaluate association between hyperuricemia, lipids and adiposity indices. Independent variables were also standardized so βetas of linear model and odds ratios (ORs) of logistic model refer to association between 1 standard deviation incremental and SUA or hyperuricemia. Models were unadjusted and adjusted for age, gender, office systolic BP, body mass index, eGFR, angiotensin converting enzyme inhibitors, diuretics, statins and diabetes mellitus. We assessed the prognostic accuracy of lipids and adiposity indices using the receiver operating characteristic (ROC) to calculate the area under the curve (AUC).

All analyses were conducted using SAS 9.4 software (SAS Institute, Cary, NC, USA), and a P value < 0.05 was considered statistically significant.

3 | RESULTS

3.1 | Population characteristics

Table 1 shows baseline data of the whole population analyzed. Mean age was 50.5 ± 13.6 years and males prevalence amounted to 50.2%. Diabetes mellitus was detected in 3.4%, while hypertension in 18.9%, with 5.8% of the total population treated with angiotensin converting enzyme inhibitors, 9.7% with diuretics and 0.9% with statins. Mean systolic and diastolic clinic BP amounted to 132.5 ± 21.5 and 83.7 ± 10.7 mmHg, respectively, while the corresponding 24-h Ambulatory BP values amounted to 120.1 ± 11.8 and 74.3 ± 7.5 mmHg, respectively. Biochemical analysis included serum glucose, eGFR and SUA, all within the normal range. Lipid profile included total cholesterol, HDL cholesterol and tryglicerides. Derivate parameters were LDL cholesterol, total/HDC cholesterol ratio and non-HDL cholesterol. As far as metabolic anthropometric indices mean body mass index amounted to 25.5 ± 4.4 kg/m2 and WC to 85.6 ± 12.4 cm. For adiposity indices the mean values were 1.18, 0.40 and 25.01 for VAI, CMI and LAP, respectively.

3.2 | Normouricemic vs hyperuricemic subjects

Table 2 shows data collected in the study population, when classified according to the presence/absence of hyperuricemia. Employing the classic cutoff values (6.0 and 7.0 mg/dl for females and males respectively) the prevalence of the SUA abnormality amounted to 9.7%, while it significantly increased to 32.5% when the newly described cardiovascular cutoff values were employed (5.1 and 5.6 mg/dl for females and males, respectively). With the classic SUA cutoff values hyperuricemic patients showed statistically significant differences in all the evaluated variables, except for statin use. They were older, more frequently males, with higher BP values, more frequently treated with angiotensin converting enzyme inhibitors and diuretics and displayed higher glucose and lower eGFR values. Regarding lipids, LDL cholesterol was significantly higher in hyperuricemia patients when compared to normouricemic as well as non-HDL cholesterol. Finally, regarding adiposity indices all of them were significantly higher in hyperuricemic subjects. Almost superimposable data were found for lipid profile and adoposity indices when the data were analyzed emplying the most recent SUA cutoff values (Table 2).

3.3 | Linear and logistic regression analysis

Figure 1 shows unadjusted and adjusted linear analyses between SUA (dependent variable) and lipids and adiposity indices. SUA was significantly associated with all the examined variables and the association remained significant at the multivariate model including age, gender, office SBP, BMI, eGFR, drugs (angiotensin converting enzyme inhibitors, diuretics and statins) and diabetes mellitus.

When logistic models were applied (Figure 2) SUA was significantly associated with lipids and adiposity indices with both cutoff at unadjusted analysis. However, at adjusted analysis (with same covariates of the previous linear model) HDL cholesterol lost its significance with the 5.1 and 5.6 mg/dl SUA cutoff values. With the classic hyperuricemia cutoff total cholesterol, LDL and non-HDL cholesterol became non significant at the multivariate model. Finally, higher ORs were found at multivariate analysis for the association between SUA and lipids (total, LDL and non-HDL cholesterol) for the 5.1 and 5.6 mg/dl cutoff values. As far as the three adiposity indices are concerned, the higher ORs were found for 6.0 and 7.0 mg/dl cutoff values.

The ROC curves of all the evaluated lipids and adiposity parameter are presented in Supplementary figure S1. Triglycerides, VAI and LAP (the three parameters with the more significant association with UA) ROC curves and relative AUC are reported in Figure 3. LAP AUC is

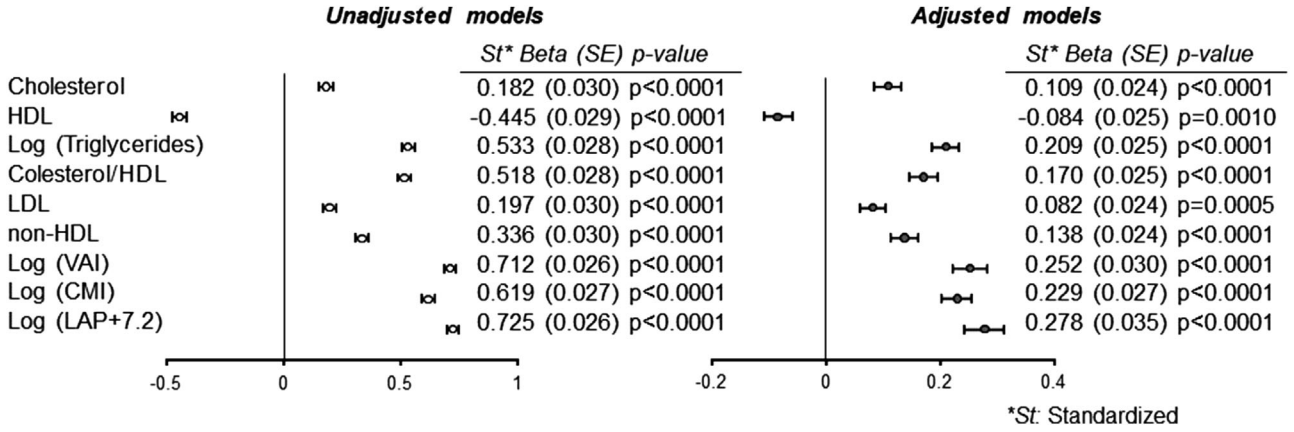

FIGURE 1 Unadjusted and adjusted linear models for uric acid (dependent variable). Non-normal variables were log transformed. Because of LAP index assumes also zero and negative values, before log transformation, it was scaled by adding minimum variable value. Independent variables were also standardized so betas of linear model and odds ratios (ORs) of logistic model refer to association between 1 standard deviation incremental and UA or hyperuricemia. BMI = Body Mass Index; SBP = Systolic Blood Pressure; ACE-I = Angiotensin Converting Enzyme Inhibitors; DM = Diabetes Mellitus; eGFR = estimated Glomeraul Filtration Rate; HDL = High Density Lipoprotein; LDL = Low Density Lipoprotein; VAI = Visceral Adiposity Index; CMI = Cardio Metabolic Index; LAP = Lipid Accumulation Product

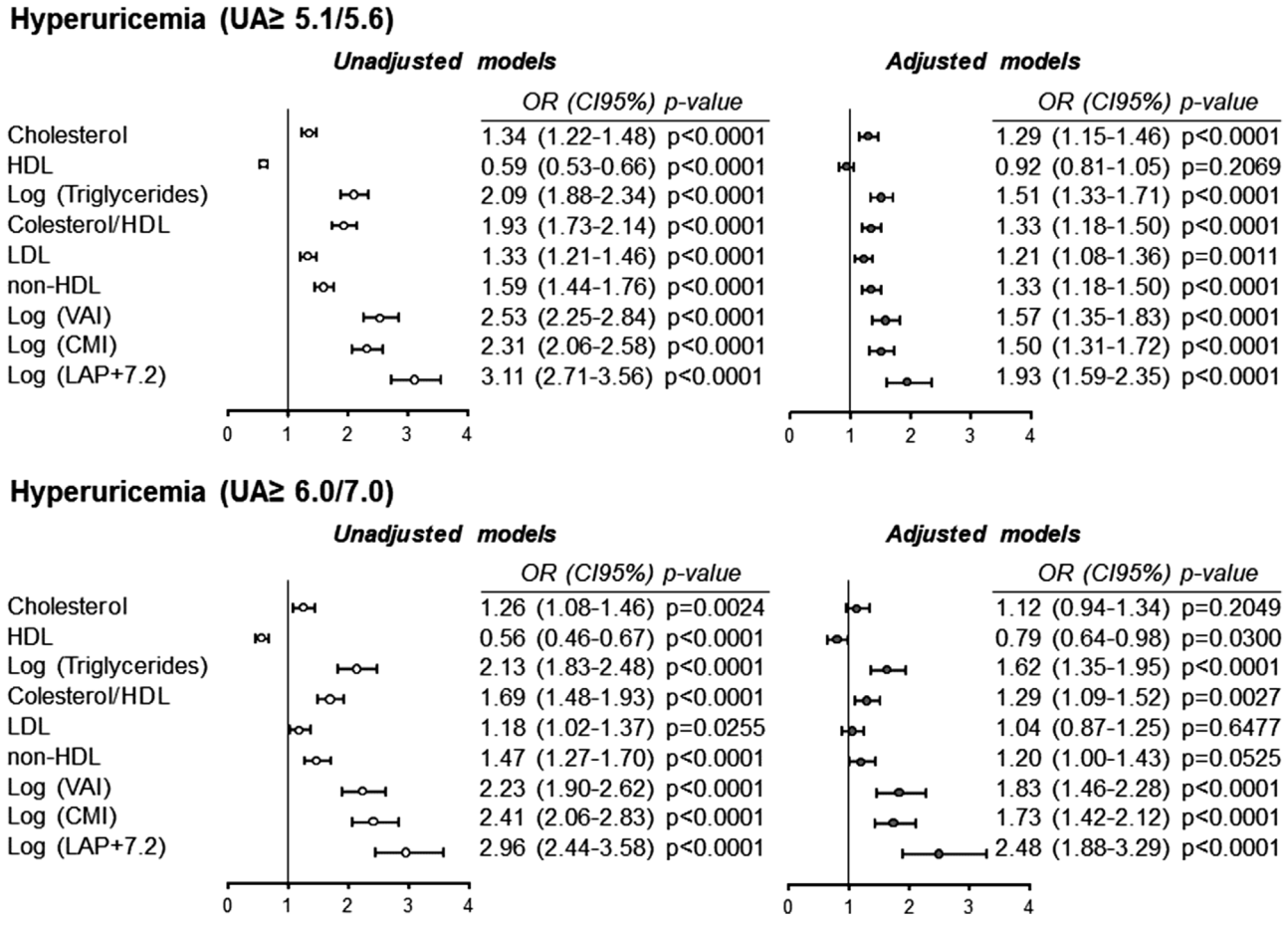

FIGURE 2 Unadjusted and adjusted logistic model for uric acid (dependent variable) with both cut-offs used. Non-normal variables were log transformed. Because of LAP index assumes also zero and negative values, before log transformation, it was scaled by adding minimum variable value. Independent variables were also standardized so betas of linear model and odds ratios (ORs) of logistic model refer to association between 1 standard deviation incremental and UA or hyperuricemia. BMI = Body Mass Index; SBP = Systolic Blood Pressure; ACE-I = Angiotensin Converting Enzyme Inhibitors; DM = Diabetes Mellitus; eGFR = estimated Glomeraul Filtration Rate; HDL = High Density Lipoprotein; LDL = Low Density Lipoprotein; VAI = Visceral Adiposity Index; CMI = Cardio Metabolic Index; LAP = Lipid Accumulation Product

TABLE 1 Demographic, anamnestic, blood pressure, drug, biochemical and adiposity indices of the whole population

Number	1892
Demographic and anamnestic	
Age, years	50.5 ± 13.6
Male, n(%)	950 (50.2%)
DM, n(%)	64 (3.4%)
Arterial Hypertension	359 (18.9%)
Blood Pressure	
Office SBP, mmHg	132.5 ± 21.5
Office DBP, mmHg	83.7 ± 10.7
24 h SBP, mmHg	120.1 ± 11.8
24 h DBP, mmHg	74.3 ± 7.5
Pharmacological Treatment	
ACE-I, n(%)	111 (5.8%)
Diuretics, n(%)	185 (9.7%)
Statins, n(%)	17 (0.9%)
Biochemical	
Serum Glucose, mg/dl	87 (81-95)
eGFR, mL/min	90.0 ± 16.7
Uric Acid, mg/dl	4.9 ± 1.3
Lipids	
Total cholesterol, mg/dl	224.0 ± 42.9
HDL cholesterol, mg/dl	55.6 ± 15.6
Triglycerides, mg/dl	96 (69-137)
T-chol/HDL-C ratio	4.3 ± 1.4
LDL cholesterol, mg/dl	145.3 ± 39.3
non-HDL cholesterol	168.4 ± 43.9
Metabolic and adiposity indices	
BMI, Kg/m^2	25.5 ± 4.4
Waist circumference, cm	85.6 ± 12.4
VAI	1.18 (0.68-2.20)
CMI	0.40 (0.24-0.71)
LAP	25.01 (10.83-48.51)

Data are shown as absolute numbers, percent values (%) or mean ± standard deviation or median (Interquartile range). BMI = Body Mass Index; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; ACE-I = Angiotensin Converting Enzyme Inhibitors; DM = Diabetes Mellitus; eGFR = estimated Glomerular Filtration Rate; HDL = High Density Lipoprotein; LDL = Low Density Lipoprotein; VAI = Visceral Adiposity Index; CMI = Cardio Metabolic Index; LAP = Lipid Accumulation Product.

higher than triglycerides and VAI AUC for discriminate hyperuricemic subjects with both cut-offs ($P < 0.001$).

4 | DISCUSSION

The results of the present study confirm in a large general population sample the close relationships between SUA, lipid profile and adiposity indices (VAI, CMI and LAP) reported in previous studies.[10–12,15–17] They add to this information two novel sets of data. First, our study provides new data on the above mentioned SUA association in a clinical phenotype of common detection characterized by the concomitant presence of both lipids profile and adiposity indices alterations. Second, the newly proposed threshold SUA values, lower than the previous ones, make the SUA association with lipid and adiposity alterations (1) of more frequent detection in daily clinical practice and (2) highly significant for the association with lipid profile, even when multivariate analysis adjusted for confounders were taken into account, thereby strengthening the clinical relevance of the relationships.

The association between SUA and lipids could be explained by a variety of mechanisms.[18] The most significant one is probably the oxidative stress determined by the two final biochemical reactions of SUA production. In fact, during the conversion of hypoxanthine to xanthine (and hence to SUA) determined by the xanthine oxidase enzyme, superoxide

TABLE 2 Demographic, anamnestic, blood pressure, drug, biochemical and adiposity indices characteristics of the population classified accordingly to the presence/absence of hyperuricemia both with the classic cutoff and with the newly described URRAH ones

	Uric Acid			Uric Acid		
Cutoff Males	**<5.6**	**≥5.6**		**<7**	**≥7**	
Females	**<5.1**	**≥5.1**	*P* value	**<6**	**≥6**	P-value
N	1277	615		1707	185	
Demographic and anamnestic						
Age, years	48.9 ± 13.3	53.8 ± 13.6	<.0001	49.6 ± 13.5	58.8 ± 11.9	<.0001
Male, n(%)	500 (39.1%)	450 (73.2%)	<.0001	832 (48.7%)	118 (63.8%)	0.0001
DM, n(%)	38 (2.9%)	26 (4.2%)	0.1583	50 (2.9%)	14 (7.6%)	0.0009
Arterial Hypertension, n(%)	167 (13.1%)	192 (31.2%)	<.0001	257 (15.1%)	102 (55.1%)	<.0001
Blood Pressure						
Office SBP, mmHg	129.4 ± 20.7	138.9 ± 21.7	<.0001	131.2 ± 21.1	144.8 ± 21.2	<.0001
Office DBP, mmHg	82.1 ± 10.4	87.1 ± 10.7	<.0001	83.2 ± 10.6	89.1 ± 10.1	<.0001
24 h SBP, mmHg	118.7 ± 11.6	122.9 ± 11.9	<.0001	119.6 ± 11.6	124.4 ± 12.9	<.0001
24 h DBP, mmHg	73.5 ± 7.3	76.1 ± 7.6	<.0001	74.1 ± 7.4	76.3 ± 8.0	0.0002
Pharmacological Treatment						
ACE, n(%)	49 (3.8%)	62 (10.1%)	<.0001	75 (4.4%)	36 (19.5%)	<.0001
Diuretics, n(%)	75 (5.9%)	110 (17.9%)	<.0001	115 (6.7%)	70 (37.8%)	<.0001
Statins, n(%)	8 (0.6%)	9 (1.4%)	0.1146	14 (0.8%)	3 (1.6%)	0.2274
Biochemical						
Serum Glucose, mg/dl	85 (80-92)	91 (84-99)	<.0001	86 (81-94)	94 (87-104)	<.0001
eGFR, mL/min	93.1 ± 15.1	83.5 ± 18.0	<.0001	91.7 ± 15.7	74.5 ± 18.1	<.0001
Lipids						
Total cholesterol, mg/dl	219.9 ± 42.5	232.5 ± 42.8	<.0001	223.0 ± 42.8	233.2 ± 43.2	0.0024
HDL cholesterol, mg/dl	57.9 ± 15.3	50.7 ± 14.9	<.0001	56.3 ± 15.4	48.8 ± 15.3	<.0001
Triglycerides, mg/dl	85 (63-119)	124 (90-179)	<.0001	92 (66-131)	138 (102-203)	<.0001
T-chol/HDL-C ratio	4.0 ± 1.3	4.9 ± 1.6	<.0001	4.2 ± 1.4	5.1 ± 1.6	<.0001
LDL cholesterol, mg/dl	141.7 ± 38.0	152.8 ± 40.9	<.0001	144.7 ± 39.2	151.5 ± 39.9	0.0254
non-HDL cholesterol	161.9 ± 42.3	181.9 ± 44.2	<.0001	166.7 ± 43.7	184.4 ± 43.3	<.0001
Metabolic and adiposity indices						
BMI, Kg/m^2	24.7 ± 4.1	27.2 ± 4.5	<.0001	25.2 ± 4.4	28.4 ± 3.8	<.0001
Waist circumference, cm	82.6 ± 11.9	91.9 ± 10.9	<.0001	84.6 ± 12.3	94.6 ± 9.9	<.0001
VAI	0.90 (0.55-1.72)	1.96 (1.16-3.42)	<.0001	1.09 (0.63-2.03)	2.28 (1.38-3.73)	<.0001
CMI	0.33 (0.21-0.55)	0.60 (0.38-1.05)	<.0001	0.38 (0.23-0.64)	0.83 (0.51-1.22)	<.0001
LAP	18.22 (7.12-35.54)	44.07 (27.05-71.46)	<.0001	22.78 (9.83-43.98)	53.02 (32.95-86.78)	<.0001

Data are shown as absolute numbers and percent values (%) or media ± standard deviation or median (interquartile range). T-test o mann whitney u test (Gli trig VAI CMI e LAP) per var continue or fisher exact test for % values. BMI = Body Mass Index; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; ACE-I = Angiotensin Converting Enzyme Inhibitors; DM = Diabetes Mellitus; eGFR = estimated Glomerular Filtration Rate; HDL = High Density Lipoprotein; LDL = Low Density Lipoprotein; VAI = Visceral Adiposity Index; CMI = Cardio Metabolic Index; LAP = Lipid Accumulation Product.

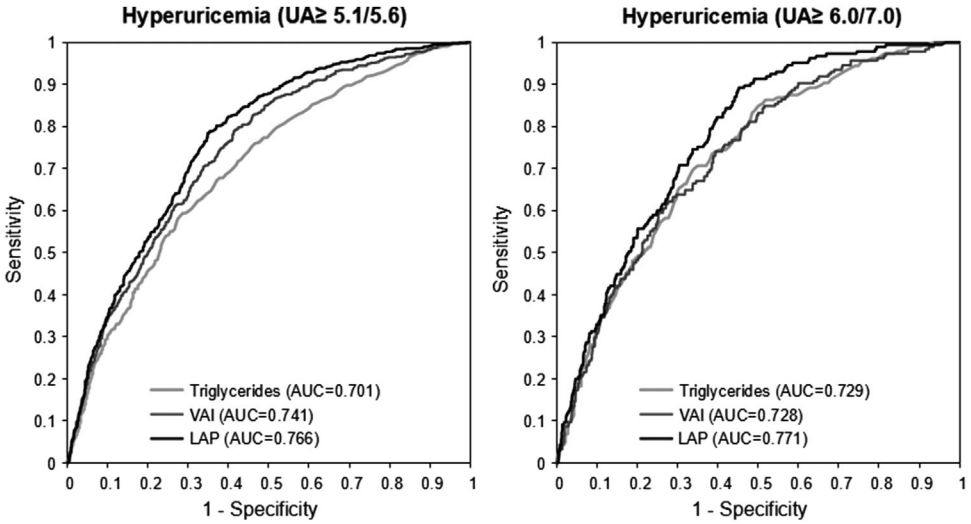

FIGURE 3 ROC curves and relative AUC for the three parameter that are more strongly associated with hyperuricemia (triglycerides, VAI and LAP). ROC = Receiver Operating Characteristic; AUC = Area Under the Curve; VAI = Visceral Adiposity Index; LAP = Lipid Accumulation Product

anions generated increase in oxidative stress.[19–20] This process may favour mitochondrial dysfunction and citrate release to the cytosol increeasing the *de-novo* lipogenesis and triglycerides synthesis.[21–22] A second potential mechanism relates to the role of SUA in inhibiting lipoprotein lipase activity in endothelial cells that triggers an increase in circulating LDL levels.[23] Indeed, higher SUA levels are able to predict the development of high LDL and triglycerides levels during a 5-year follow-up.[24]

The relationship between SUA and adiposity indices appears to be more complex and also bidirectional. Adiposity-related insulin resistance is able to determine hyperuricemia through an increased reabsorption of SUA from renal tubules.[25] However, hyperuricemia is also able to worsen insulin resistance due to the oxidative stress leading to a vicious cycle.[25] Furthermore, in obesity adipose tissue expression and activity of xanthine oxidase is increased and SUA is actively secreted into the blood stream.[26] Finally, high fructose diet is a cause of both obesity and hyperuricemia.[27]

The most relevant element of novelty of our study is represented by the evaluation of the relationships between SUA, lipid profile and adiposity indices not only as continuous variables but also as a dichotomous ones (i.e. hyperuricemia). To do this, we made use two different cutoffs, i.e. the classic treshold and the lower and most recent one identified in the URRAH study to be closely related to cardiovascular mortality.[1] The classic cutoff is determined by the precipitation threshold of SUA that is related to crystal formation, and thus to articular and kidney gout more than to cardiovascular events. Recent evidence suggests that SUA could exert adverse cardiovascular effects even at lower circulating blood levels throughout mechanisms more complex than crystals precipitation and involving the previously mentioned oxidative stress and xanthine oxidase hyperactivity.[19–20]

No definitive hyperuricemia cardiovascular cutoff has been internationally accepted and several have been proposed. The data recently collecteded in the frame of the URRAH project[1,3,28] lead to different cutoffs for different cardiovascular conditions, being the ones for cardiovascular mortality 5.1 mg/dl for females and 5.6 mg/dl for males. We found that these lower cutoff values were more strongly related to total cholesterol, LDL cholesterol and non-HDL cholesterol when compared to the classic ones. Indeed by applying the classic SUA cutoff values the relationships of these parameters with SUA are no longer correlated at multivariate analysis. On the other hand, the classic cutoff values are characterized by higher OR for the association with adiposity indices (in particular LAP that present the highest OR) when compared with the URRAH one. Based on these findings one can speculate that lower levels of SUA are needed in order to determine and/or worsen dyslipidaemia while, in presence of higher SUA levels also the mechanisms of metabolic derangements and adiposity could be activated. In other words we can hypothesize that hyperuricemia can determine cardiovascular events at lower cutoffs mainly through proatherogenic lipoprotein alterations while, when SUA further increases, also adiposity and general metabolic abnormalities may participate.

The ROC curves analysis showed that the best parameter able to discriminate for the presence of hyperuricemia is the LAP adiposity index. This should be considered in the choice of indices to be evaluated in future studies regarding SUA and adiposity/lipid profile.

Although interesting this remains a hypothesis that should be proposed taking into acoount the limitations of our study. The first limitation is represented by the cross-sectional design of our study that prevented us to collect longitudinal information on the behaviour of the relationships between SUA, lipid profile and adiposity indices. The second limitation is the impossibility to distinguish the different conditions of reduced excretion and overproduction of SUA (due to the lack of data on urinary uric acid) and thus selectively discriminate the different impact of these two causes of hyperuricemia. Furthermore, despite the fact that population sample of our study was large, some subgroups display a low number of subjects (i.e. hyperuricemic subjects with the classic cutoff). In this instance the limited subgroups sample size can reduce the power to detect important associations or findings. A further limitation is that no information was available regarding the use of allopurinol in the PAMELA study leading to a possible underestimation

of our results (i.e. some subjects could have lower SUA levels due to hypouricemic therapies). However, depending on the median patients age at enrollment and to their median SUA levels, probably only few patients were taking allopurinol. Finally, although used in only 9.7% of the subjects, diuretics are a well-known cause of hyperuricemia. However, their use has been included into the multivariate models.

In conclusions, the newly reported URRAH cutoff values for hyperuricemia better relate to atherogenic lipoprotein (LDL and non-HDL) when compared to the classic one. The opposite has been found for adiposity indices where the classic cutoff seems to present highest performance.

ACKNOWLEDGEMENTS

None.

CONFLICT OF INTEREST

Nothing to disclose.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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