



RESEARCH ARTICLE

Uric acid versus metabolic syndrome as markers of fatty liver disease in young people with overweight/obesity

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Abstract

Aims: To compare the association of high serum uric acid (HUA) or metabolic syndrome (MetS) with fatty liver disease (FLD) in youths with overweight/obesity (OW/OB).

Materials and Methods: Cross-sectional study of anthropometrics, biochemical variables, and liver ultrasound of 3104 individuals with OW/OB (age 5–17 years). Metabolic syndrome was defined by ≥ 3 criteria among (1) high waist circumference; (2) high triglycerides; (3) low high-density lipoproteins; (4) fasting glucose ≥ 100 mg/dl; (5) blood pressure $\geq 95^{\text{th}}$ percentile in children, and $\geq 130/80$ mmHg in adolescents. High serum uric acid was defined as serum UA value $\geq 75^{\text{th}}$ percentile adjusted for sex. Fatty liver disease was determined by echography.

Results: The sample was stratified in four categories: (1) no HUA, no MetS (reference category); (2) MetS; (3) HUA; (4) HUA and MetS (HUA + MetS). The prevalence of FLD increased across the four categories from 29.9%, 44.0%, 52.2%, to 67.1%, respectively

Abbreviations: ADA, American Diabetes Association; ATP III, Adult Treatment Panel III; BMI, Body mass index; BP, Blood pressure; CI, Confidence interval; cMetS, Continuous MetS score; CVD, Cardiovascular disease; FG, Fasting glucose; FLD, Fatty liver disease; HDL, High density lipoproteins; HOMA-IR, Homoeostasis Model Assessment for Insulin Resistance; HUA, High serum uric acid; MetS, Metabolic syndrome; NASH, Non-alcoholic steatohepatitis; OW/OB, Overweight/obesity; SDS, Standard deviation score; SIEDP, Società Italiana di Endocrinologia e Diabetologia Pediatrica; TG, Triglycerides; WC, Waist circumference.

Procolo Di Bonito and Giuliana Valerio both authors contributed equally.

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($p < 0.0001$). The ORs for the categorical variables were 1.33 (1.06–1.68) for MetS ($p = 0.02$), 3.19 (2.51–4.05) for HUA ($p < 0.0001$) and 3.72 (2.65–5.21) for HUA + MetS ($p < 0.0001$), versus the reference category regardless of the body mass index.

Conclusions: HUA represents a useful marker of FLD in youths with OW/OB, given its greater ability to identify those at increased risk of the disease compared to MetS. The ability of both to predict incident FLD must be investigated in longitudinal study.

KEYWORDS

children, fructose, metabolic syndrome score, non-alcoholic fatty liver disease, obesity, uric acid

1 | INTRODUCTION

Considering childhood obesity (OB) epidemic, non-alcoholic fatty liver disease (FLD) has become the leading cause of chronic hepatic disease in youths.¹ Although FLD has long been considered as a mere hepatic manifestation of the metabolic syndrome (MetS), its mutual relationship with the MetS has been recognized as a prevailing driver of hepatic inflammation and progressively fibrosing liver disease.^{1,2} Recognition of metabolic traits among young obese subjects has the potential to increase awareness of high-risk populations for FLD and its related complications.^{1,3} On the other hand, particularly in the paediatric age, FLD may occur independently of the co-existence of metabolic abnormalities¹ and referring to metabolic abnormalities as means of risk estimation may cause a missed diagnosis of FLD in subjects with no cardiometabolic factors but severe steatosis.^{4,5} Emphasis on metabolic dysfunction as a criterion to identify subjects with FLD might cause the underestimation of the prognostic value of hepatic steatosis itself. Therefore, there is need of a marker of fatty liver that is independent of the metabolic components and relates somehow to the process of fat accumulation within the liver.

High levels of uric acid (UA) are a common hallmark of FLD in adult and young^{6–9} people with OB. In the latter ones, high serum uric acid (HUA) has been associated with increased risk of FLD,^{7,8} reduced glomerular filtration,⁷ prediabetes,⁹ and subclinical atherosclerosis.¹⁰

Taking into account the ability of both HUA⁷ and/or MetS¹¹ to predict FLD, and, at the same time, the well-known pitfalls in the definition of MetS in young people,^{12–14} the questions arise whether HUA performs better than MetS in identifying young people with FLD, and, at the same time, representing a simpler and more practical estimate of disease risk in the outpatient's clinic.

Aim of the present study was to compare the strength of the cross-sectional associations of HUA with FLD as compared to that of MetS with FLD in a large sample of children and adolescents with excess body weight.

2 | SUBJECTS AND METHODS

2.1 | Study design

The CARdiometabolic risk factors in Overweight (OW) and obese children in ITALY (CARITALY Study) is a cross-sectional study

endorsed by the Childhood OB Group of the Italian Society for Paediatric Endocrinology and Diabetology (SIEDP, Società Italiana di Endocrinologia e Diabetologia Pediatrica). Its aim is to investigate Cardiovascular disease risk factors in young individuals with overweight/obesity (OW/OB) (aged 5–17 years) referred between 2003 and 2016 from general practitioners to secondary or tertiary centres belonging to SIEDP network of collaborating centres for the diagnosis and care of paediatric OB.¹⁵ Exclusion criteria were a recent history of acute infectious or non-infectious inflammatory disorder; secondary OB; known type 2 diabetes; known hypertension; low-density lipoprotein-cholesterol ≥ 190 mg/dl. In the enrolled participants, liver diseases (i.e. viral liver disease, autoimmune hepatitis, Wilson's disease, α -1-antitrypsin deficiency, endocrine, genetic and metabolic diseases, coeliac disease, alcohol consumption, and use of drugs known to induce hepatic steatosis) were excluded according to a standardized protocol.²

For the purpose of the present study, we analysed the records of 3104 anonymised participants who had a complete dataset of anthropometrics, biochemical variables including levels of UA and liver enzymes, Blood pressure (BP) data, and ultrasound liver evaluation.

The CARITALY study was approved by the Ethics Committee of the University of Campania "Luigi Vanvitelli" (reference number 834/2016) and conformed to guidelines of the European Convention of Human Rights and Biomedicine for Research in Children. At the time of outpatients' visit and blood testing, parents provided informed consent to use and share child anonymised data.

2.2 | Anthropometrics, clinical, and biochemical data

Anthropometric measurements were obtained with standard methods.¹⁵ Body mass index (BMI) was calculated as weight (kg)/height (m)² and transformed into standard deviation score (SDS) using the Italian BMI normative curves.¹⁶ Waist circumference (WC) was measured by using flexible measuring tape to the nearest 0.1 cm with the child standing, and at the end of normal expiration at a point midway between the inferior margin of the lowest rib and the iliac crest. Blood pressure was measured with standard procedure.¹⁵

Biochemistry was assessed in the laboratory of each clinic centre participating in the study.¹⁵ All the centres belong to the Italian National Health System and are certified according to International

Standards ISO 9000 (www.iso9000.it/), undergoing semi-annual quality controls and inter-lab comparisons.

2.3 | Case definitions and calculations

Prepubertal stage was defined by the Tanner Stage I (no breast development in girls and testicular volume below 4 ml in boys).¹⁷ High BP was defined using the 95th percentiles for height, age, and sex for children (age <13 years), and BP \geq 130/80 in adolescents (age \geq 13 years).¹⁸ Impaired fasting glucose (FG) was defined by a value of FG \geq 100 mg/dl. Metabolic syndrome was defined using the modified criteria suggested by the Adult Treatment Panel (ATP) III¹⁹ as previously described since they allow definition also in children below 10 years of age.²⁰ In brief, MetS diagnosis was based on the presence of at least 3 risk factors: high WC, impaired FG, high Triglycerides (TG) and low high density lipoprotein cholesterol (HDL-C) [defined using the gender-specific cut-offs intercepting at 18 years the ATP III cut-points^{19,20}], and high BP [according to the most recent Clinical Practice Guidelines¹⁸]. High serum uric acid was defined using the 75th percentile for gender, that is, UA \geq 6.1 mg/dl in boys and UA \geq 5.8 mg/dl in girls.⁷

The Homoeostasis Model Assessment for Insulin Resistance (HOMA-IR) was calculated according to the formula [fasting plasma glucose (mg/dl) x fasting plasma insulin (μ U/ml)/405].

2.4 | Ultrasound diagnosis of fatty liver disease

Hepatic ultrasound was performed in each centre by a single expert sonographer.⁷ Diagnosis of fatty liver was based upon liver echogenicity exceeding that of the renal cortex and spleen, attenuation of ultrasound wave, loss of definition of the diaphragm, and poor delineation of the intrahepatic architecture.⁷

2.5 | Statistical analysis

Continuous data were expressed as mean \pm standard deviation (SD), proportions as percentage (%), and 95% confidence interval (CI). Variables with skewed distribution (i.e. HOMA-IR, TG) were log transformed for the analysis and expressed as median and inter-quartile range. Mean values were compared using Student's *t* test or Analysis of Variance. Distribution of categories by χ^2 and, when needed, exact tests were performed using the Monte Carlo method. The *P* value is relative to the overall difference between groups. A continuous MetS (cMetS) score was calculated by using the Z-score approach as described in Eisenmann et al.²¹ We used a linear regression analysis standardized for age and gender separately for each of the following variables: WC, FG, TG, SBP, and HDL-C (the latter was multiplied by (-1)). The standardized residuals were summed to obtain a cMetS score. The performance of cMetS score was tested by the receiving operator characteristic (ROC) analysis using

cMetS score as variable of interest and the categorical definition of MetS as state variable.

Logistic regression analyses were performed to assess the relationship between MetS or HUA and FLD. People without MetS and HUA represented the reference category. Performances of the high UA or the MetS to identify subjects with FLD were estimated as compared to the reference category. Sensitivity, specificity, positive and negative predictive value, and positive and negative likelihood ratio were assessed by 2 \times 2 tables.

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 20.0.

3 | RESULTS

Anthropometric and metabolic features of participants according to the presence of FLD are summarised in Table 1. Children with FLD were older, more likely to be males, and had greater BMI, BMI-SDS, WC, as well as higher HOMA-IR, TG, BP, UA, cMetS, and lower levels of HDL-C as compared to those without FLD. They also showed higher prevalence of MetS (31.9%) and HUA (35.9%) than those without liver involvement. The whole sample was stratified into four categories: (1) no HUA and no MetS (reference category); (2) MetS; (3) HUA; (4) HUA and MetS (HUA + MetS) (Table 2). The prevalence of FLD increased across the four categories from 29.9%, 44.0%, 52.2%, to 67.1%, respectively, as shown in Figure 1. Using the independent variables as categorical, the OR for FLD was 1.33 (1.06–1.68) for MetS, 3.19 (2.51–4.05) for HUA and 3.72 (2.65–5.21) for HUA + MetS, versus the reference category, independently by centres, age, sex, prepubertal stage, and BMI-SDS (Table 3). Supplementary Table 1 shows diagnostic accuracy of categories of MetS, HUA, and HUA plus MetS to identify patients with FLD, as compared to the reference category. Both MetS and high UA performed poorly, albeit high UA presented with slightly higher sensitivity and positive predictive values than MetS. The combination of MetS and high UA offered the highest specificity and positive predictive values.

Results were not affected by including HOMA-IR and ALT levels into the model; by performing the analysis exclusively in people with OB or in those with OW (Table 3) and after having excluded subjects with UA below 3 mg/dl and above 8 mg/dl (Table 4).

The ROC analysis for the accuracy of the cMetS score provided an area under the curve of 0.892 (95%CI 0.878–0.906, *p* < 0.0001), demonstrating the high performance in predicting the dichotomous classification of the syndrome. Using the independent variables as a continuum, the odds ratio (95% CI) for FLD was 1.13 (1.09–1.18) for 1-unit SDS increase of cMetS score and 1.78 (1.63–2.00) for 1-unit SDS increase of UA. The OR of single components of MetS, expressed as Z-score, were lower than the OR of UA-Z-score, in relation to FLD (Supplementary Table 2).

Data on estimated glomerular filtration rate (eGFR) were available in a reduced sample of 2474 subjects. Adjustment for eGFR did not affect OR of FLD in the reduced sample (Supplementary Table 3).

	No FLD	FLD	P value
<i>n</i> = 3104	1902	1202	
Age (years)	10.5 ± 2.5	10.8 ± 2.5	<0.0001
Male gender, <i>n</i> (%)	960 (50.5)	715 (59.5)	<0.0001
Prepubertal stage, <i>n</i> (%)	505 (26.6)	246 (20.4)	<0.0001
BMI, kg/m ²	27.7 ± 4.4	30.7 ± 5.6	<0.0001
BMI-SDS	2.0 ± 0.5	2.3 ± 0.6	<0.0001
OW/OB/MOD, <i>n</i>	467/1361/74	121/958/123	<0.0001
WC (cm)	85.6 ± 11.6	95.2 ± 13.2	<0.0001
WC Z-score	-0.29 ± 0.9	0.46 ± 1.0	<0.0001
FG (mg/dl)	84.4 ± 9.5	84.8 ± 10.7	0.252
HOMA-IR	2.7 (1.7–3.9)	3.3 (2.2–4.9)	<0.0001
Cholesterol (mg/dl)	156.8 ± 29.4	156.6 ± 33.4	0.874
HDL-C (mg/dl)	48.6 ± 11.8	46.5 ± 10.9	<0.0001
Triglycerides (mg/dl)	70.0 (52.0–98.0)	86.0 (61.0–118.0)	<0.0001
Systolic BP (mmHg)	107.8 ± 12.5	111.2 ± 14.1	<0.0001
Diastolic BP (mmHg)	69.4 ± 10.2	67.4 ± 9.8	<0.0001
Uric acid (mg/dl)	4.9 ± 1.1	5.6 ± 1.3	<0.0001
MetS, % (95%CI)	366 (19.2)	383 (31.9)	<0.0001
cMetS Z-score (SDS)	-0.6 ± 2.5	0.9 ± 2.8	<0.0001
High UA, % (95%CI)	330 (17.4)	431 (35.9)	<0.0001

Note: Mean ± SD, *n* (%), median (IQR range).

Abbreviations: BMI, body mass index; cMetS Z-score, continuous metabolic syndrome Z-score; FG, fasting glucose; HOMA-IR, homeostasis model assessment; MetS, metabolic syndrome; MOD, morbidly obese; OB, obese; OW, overweight; UA, uric acid; WC, waist circumference.

TABLE 1 Characteristics of the sample study by fatty liver disease (FLD)

4 | DISCUSSION

The present study provides evidence that UA is more strongly associated with FLD than MetS, when using either a categorical or a continuous approach (supplemental material). High uric acid and MetS categorisation identified different phenotypes of OB with a relatively small percentage of individuals with high uric acid and MetS overlap. The combination of HUA and MetS did not improve the strength of the association of the single variables with FLD. Therefore, UA turns out as a more practical and cost-effective diagnostic tool than MetS for identifying patients with OB at increased risk for FLD.

We found a significant, but weak, association between MetS and FLD, without substantial differences using either dichotomous or continuous approach. Of note, the WC Z-score performed better than the cMetS score as well as the other individual components of MetS, with a near two-fold increased risk of FLD (OR 1.73) compared to the OR 1.13 for cMetS, 1.22 for TG Z-score, and 1.24 for HDL z-score (supplementary material). Certainly, this finding supports the importance of visceral adiposity in the pathogenesis of FLD,²² confirming previous evidence in obese youths with metabolically

unhealthy and healthy phenotype, with or without the features of the syndrome.^{23,24}

First Gerald Reaven,²⁵ the father of MetS, and then other eminent scientists,^{26,27} all remarked the limited practical utility of the syndrome as diagnostic and management tool, emphasising its drawbacks. The World Health Organization expert committee,²⁶ the American Diabetes Association, and the European Association for the Study of Diabetes²⁷ suggested the use of a continuous score for defining the MetS (rather than the dichotomous classification with its inherent limitations), in order to enhance its diagnostic sensitivity. In the paediatric setting, the use of the dichotomous definition is even more questionable given the heterogeneous definition and the unstable pattern of MetS.^{28,29} On the contrary, a score that adopts z-score standardized values for all different parameters might be introduced in order to consider covariates that may influence the risk, that is, pubertal status and ethnicity,²⁹ and, more importantly, to overcome the inconsistency of the cutoffs used to define MetS components across the various definitions.^{21,25–29}

Our findings demonstrate that both approaches used to define the syndrome, categorical or continuous as z-score, perform poorly to predict FLD.

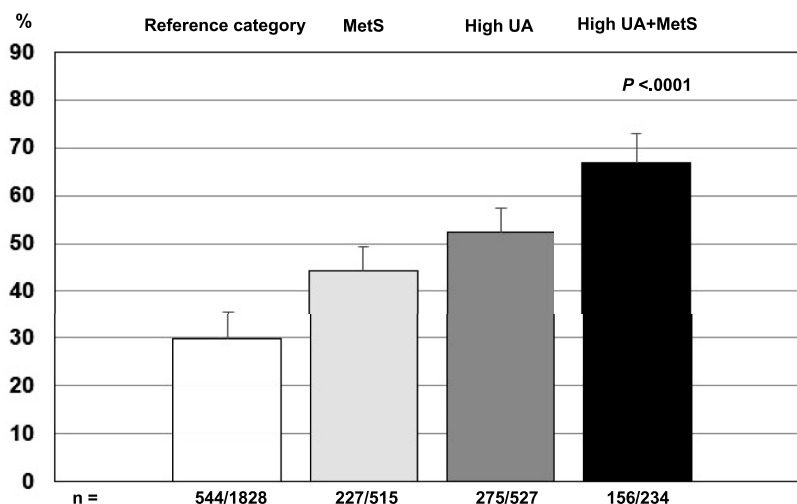
TABLE 2 Characteristics of the sample study by sex-specific quartiles of uric acid in young people with Overweight (OW)/obesity (OB)

	Reference category	MetS	High UA	High UA + MetS	P value
<i>n</i> = 3104	1828	515	527	234	
Age, years	10.4 ± 2.5	10.1 ± 2.5	10.6 ± 2.6	11.4 ± 2.5	<0.0001
Male gender, <i>n</i> (%)	1000 (54.7)	267 (51.8)	292 (55.4)	116 (49.6)	0.309
Prepubertal stage, <i>n</i> (%)	477 (26.1)	160 (31.3)	80 (15.2)	32 (13.7)	<0.0001
BMI, kg/m ²	27.7 ± 4.3	30.1 ± 5.5	30.0 ± 5.1	32.6 ± 6.1	<0.0001
BMI-SDS	2.0 ± 0.6	2.3 ± 0.5	2.2 ± 0.6	2.5 ± 0.6	<0.0001
WC (cm)	86.0 ± 11.7	92.5 ± 13.4	93.1 ± 13.0	99.7 ± 13.7	<0.0001
WC Z-score	-0.24 ± 0.9	0.40 ± 1.0	0.12 ± 1.0	0.74 ± 1.0	<0.0001
FG (mg/dl)	84.0 ± 8.8	86.1 ± 10.5	83.8 ± 8.8	87.7 ± 16.5	<0.0001
HOMA-IR	2.6 (1.7–3.8)	3.5 (2.4–5.0)	3.1 (1.9–4.4)	4.0 (2.9–6.6)	<0.0001
Cholesterol (mg/dl)	155.9 ± 29.4	158.8 ± 33.0	156.3 ± 33.1	159.1 ± 33.5	0.154
HDL-C (mg/dl)	50.9 ± 11.5	40.2 ± 7.7	48.3 ± 10.9	39.4 ± 7.9	<0.0001
Triglycerides (mg/dl)	68.0 (52.0–90.0)	117.0 (76.0–155.0)	74.0 (54.0–100.0)	118.5 (74.2–163.6)	<0.0001
Systolic BP (mmHg)	106.6 ± 12.2	115.1 ± 13.0	107.6 ± 12.8	119.1 ± 13.8	<0.0001
Diastolic BP (mmHg)	67.5 ± 9.6	71.4 ± 11.0	67.7 ± 9.9	73.2 ± 10.1	<0.0001
UA (mg/dl)	4.6 ± 0.8	4.7 ± 0.8	6.8 ± 0.8	6.8 ± 0.8	<0.0001
cMetS Z-score (SDS)	-1.0 ± 2.0	2.6 ± 2.1	-0.5 ± 2.2	3.3 ± 2.9	<0.0001

Note: Mean ± SD, *n* (%), median (IQ range).

Abbreviations: BMI, body mass index; cMetS Z-score, continuous metabolic syndrome Z-score; FG, fasting glucose; HOMA-IR, homoeostasis model assessment; MetS, metabolic syndrome; MOD, morbidly obese; OB, obese; OW, overweight; UA, uric acid; WC, waist circumference.

FIGURE 1 Proportion (95%CI) of individuals with fatty liver disease (FLD) among reference category (white bar), metabolic syndrome (MetS) (grey bar), high UA (dark grey), high UA and MetS (black bar)



5 | URIC ACID AND FATTY LIVER DISEASE

After a long period of forgetfulness, UA has regained researchers' and clinicians' interest, since a strong link was established between this metabolite and the increased fructose consumption from corn syrup and sugar-sweetened beverages.^{30,31} Fructose-induced overproduction of urate enhances de novo lipogenesis.³¹ Growing evidence suggests that UA is not just a marker of FLD but it plays a role in the onset and progression of the disease. To this regard,

hypothesised mechanisms include increased reactive oxygen species production and oxidative stress; induced lipogenesis by endoplasmic reticulum generation and activation of fatty acid synthase and acetyl-CoA carboxylase; deterioration of the endothelial function and nitric oxide bioavailability causing insulin resistance.³²

Large meta-analyses on adult Chinese people^{33–35} found a linear relationship between increasing levels of uric acid and risk of NAFLD. Specifically, these studies found individuals in the highest category of UA having a significantly increased risk of FLD.

TABLE 3 Odds Ratio (95% confidence interval (CI))^a of fatty liver disease (FLD) by high UA and/or metabolic syndrome (MetS) in the overall sample, in non-obese and obese youths

	Reference category	MetS	High UA	High UA + MetS
All subjects (n)	1828	515	527	234
Model A ^a	1.00	1.29 (1.01–1.65) ^d	2.96 (2.29–3.83) ^e	3.46 (2.38–5.04) ^e
Model B ^b	1.00	1.23 (0.96–1.58)	2.98 (2.30–3.86) ^e	3.28 (2.25–4.78) ^e
Model C ^c	1.00	1.19 (0.91–1.55)	2.80 (2.13–3.67) ^e	2.74 (1.82–4.12) ^e
Overweight (n)	457	49	76	6
Model A ^a	1.00	2.16 (0.97–4.84)	5.54 (2.86–10.72) ^e	20.64 (2.81–151.48) ^e
Model B ^b	1.00	2.23 (0.99–5.03)	5.78 (2.96–11.28) ^e	21.87 (2.91–164.15) ^e
Model C ^c	1.00	1.52 (0.58–3.97)	4.23 (2.03–8.85) ^e	7.56 (0.79–72.21) ^e
Obese (n)	1371	466	451	228
Model A ^a	1.00	1.26 (0.99–1.61)	2.94 (2.27–3.80) ^e	3.44 (2.45–4.85) ^e
Model B ^b	1.00	1.20 (0.94–1.53)	2.91 (2.25–3.77) ^e	3.25 (2.30–4.57) ^e
Model C ^c	1.00	1.15 (0.89–1.49)	2.78 (2.12–3.66) ^e	2.59 (1.79–3.74) ^e

^aAdjusted for centres, age, prepubertal stage and BMI-SDS.

^bAdjusted for centres, age, prepubertal stage and BMI-SDS and HOMA-IR.

^cAdjusted for centres, age, prepubertal stage and BMI-SDS, HOMA-IR and ALT.

^dP value < 0.05 versus reference category.

^eP value < 0.025 versus reference category.

	Reference category	MetS	High UA	High UA + MetS
Model A ^a	1.00	1.32 (1.03–1.68) ^d	3.30 (2.57–4.24) ^e	3.63 (2.53–5.22) ^e
Model B ^b	1.00	1.26 (0.98–1.61)	3.32 (2.58–4.27) ^e	3.41 (2.37–4.91) ^e
Model C ^c	1.00	1.20 (0.93–1.56)	3.08 (2.36–4.01) ^e	2.76 (1.86–4.11) ^e

^aAdjusted for centres, age, prepubertal stage and BMI-SDS.

^bAdjusted for centres, age, prepubertal stage and BMI-SDS and HOMA-IR.

^cAdjusted for centres, age, prepubertal stage and BMI-SDS, HOMA-IR and ALT.

^dP value < 0.05 versus reference category.

^eP value < 0.025 versus reference category.

In the present series of children, we found a near two-fold increased risk of FLD for each 1 SDS unit increase of UA z-score as compared to 1.13 for 1-unit SDS increase of MetS score. Since many subjects in our study presented with both HUA and MetS, we disentangled the independent association of MetS and/or HUA with FLD. The combination of MetS with HUA shows a better specificity, positive predictive value, and positive likelihood ratio in FLD prediction (Table 3).

Interestingly, exclusion of people with UA at the extreme of the population distribution (lower than 3 mg/dl and higher than 8 mg/dl) as well as of people with morbid OB (i.e. Body mass index z-score higher than 3SD) did not affect findings of the study, demonstrating that use of UA as marker of FLD risk is also suitable in these individuals. Both UA and ALT levels as continuous variables were associated with significantly increased risk of FLD but the performance of the former was higher than that of the latter, while it was not different when categories of high UA and high ALT levels were applied (Supplementary Tables 2 and 3). The strength of the association of

TABLE 4 Odds Ratio (95% confidence interval (CI))^a of fatty liver disease (FLD) by high UA and/or metabolic syndrome (MetS) as categorical variables after exclusion of youths with UA <3>8 mg/dl and youths with morbidly obesity (OB) (n = 2907)

FLD was greater with high uric acid than with MetS, while the performances of both were not brilliant in terms of diagnostic accuracy (Supplementary Table 1). Given the limited utility in the everyday practice of estimating the occurrence of the MetS as discussed above, point-of-care testing of uric acid, nevertheless, can be more practical in the outpatients' clinic than estimating the former one.

The strengths of our study include a very large sample size of the study population, and the adoption of two different approaches, either categorical or continuous, when comparing the association of UA and MetS with FLD. To the best of our knowledge, the present study provides the first assessment of the strength of the independent association of MetS and UA with FLD. On the other hand, we also acknowledge major study limitations that include cross-sectional design, lack of normal-weight individuals, use of population specific z-scores for metabolic variables³⁶ that are not generalizable and need replication in different populations, and investigation of fatty liver by ultrasounds without grading the severity of fatty liver infiltration or the parenchyma derangement.

Therefore, we could not explore the association between levels of uric acid and grade of steatosis and, more importantly, any relationship to non-alcoholic steatohepatitis. Furthermore, we could not adjust our analyses for dietary intake, that is, of fructose and simple sugars, and physical activity levels.

Testing of high uric acid might be useful to identify normal-weight individuals and those who are obese at risk of FLD despite normal levels of liver enzymes. The accuracy of uric acid as a marker of FLD in comparison to the MetS must be replicated in general population as well as in people with OB but more severe metabolic impairment (i.e. type 2 diabetes and/or severe dyslipidemia). Owing to the design of the study, we could also not answer the question whether high uric acid predicts incident FLD in youths as it does in adults.³⁷ Large cohort study would be useful to rule out definitively the diagnostic accuracy of uric acid as a marker of FLD in the clinical practice.

6 | CONCLUSIONS

We demonstrate that HUA is a more useful and effective marker of fatty liver risk as compared to MetS (defined as either continuous or categorical variable). The present study extends our previous findings showing the suitability of UA to identify at-risk people with OB.⁷

In view of the epidemic of OB in childhood, testing serum UA levels, and using appropriate sex and age-derived cutoffs, appears to be a valuable and advantageous method for screening for FLD. Indeed, UA is a very simple and easy laboratory measure, and much more practical and cost effective than the use of multiple MetS criteria. Therefore, measurement of UA might be recommended in the routine assessment in at-risk young individuals with OB.

AUTHOR CONTRIBUTION

Conceptualisation Procolo Di Bonito, Giuliana Valerio, Melania Manco; Data curation Procolo Di Bonito, Giuliana Valerio; Formal analysis Giuliana Valerio, Procolo Di Bonito; Investigation Mariarosaria Licenziati, Anna Di Sessa, Emanuele Miraglia del Giudice, Anita Morandi, Claudio Maffei, Claudio Chiesa, Lucia Pacifico, Melania Manco; Methodology Procolo Di Bonito, Giuliana Valerio, Melania Manco; Project administration Procolo Di Bonito, Giuliana Valerio; Supervision Procolo Di Bonito, Giuliana Valerio; Writing - original draft Procolo Di Bonito, Melania Manco; Writing - review & editing all the authors.

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CONFLICTS OF INTEREST

The authors disclose there are no conflicts of interest, real and perceived, and funding sources related to the submitted study.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

The study was approved by the Ethics Committee of the Azienda Ospedaliera di Rilievo Nazionale Santobono-Pausilipon (reference number 22877/2020) and conformed to the guidelines of the European Convention of Human Rights and Biomedicine for Research in Children. The study was also in agreement with the 1975 Declaration of Helsinki, revised in 1983, and informed consent was obtained from the parents or tutors of all participants.

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PEER REVIEW

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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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