Association of serum uric acid concentration with components of pediatric metabolic syndrome: A systematic review and meta-analysis

Parvin Goli, Roya Riahi, Seyede Shahrbanoo Daniali, Mohammadali Pourmirzaei, Roya Kelishadi
Child Growth and Development Research Center, Research Institute for Primordial Prevention of Non-Communicable Disease, Isfahan University of Medical Sciences, Isfahan, Iran

Background: Hyperuricemia is implicated in the pathogenesis of inflammatory diseases and metabolic disorders. Metabolic syndrome (MetS) in childhood is one of the most important causes of different noncommunicable diseases in adulthood. This study aimed to systematically review the association between serum uric acid (UA) concentration and components of pediatric MetS.

Materials and Methods: In this meta-analysis and systematic review, related articles were gathered by searching English databases including PubMed, Web of Science, Scopus, and Google Scholar. We used the following keywords: uric acid, metabolic syndrome, hypertension, fasting blood sugar (FBS), hyperglycemia; the search was limited to English language and included observational and cohort studies performed among children or adolescents. Pooled relative risks (odds ratio [OR]) and corresponding 95% confidence interval (95% CI) were extracted. A random-effect model was used.

Results: On the basis of 34 eligible studies, the pooled correlation between UA with metabolic components including FBS \((r = 0.24, 95\% \text{ CI} = 0.09–0.40)\), fasting insulin \((r = 0.26, 95\% \text{ CI} = 0.15–0.37)\), and hyperglycemia \((r \text{ for triglyceride and UA} = 0.23, 95\% \text{ CI} = 0.19–0.38; r \text{ for high-density lipoprotein and UA} = −0.28, 95\% \text{ CI} = −0.37 to −0.20)\) was statistically significant. The association of both diastolic blood pressure (DBP) and systolic blood pressure (SBP) was statistically significant with UA \((r \text{ for SBP and UA} = 0.34, 95\% \text{ CI} = 0.24–0.43; r \text{ for DBP and UA} = 0.18, 95\% \text{ CI} = 0.11–0.25)\). The OR between risk of abdominal obesity with UA was statistically significant \((OR = 2.62, 95\% \text{ CI} = 1.41–3.84)\).

Conclusion: Serum UA concentration is associated with major components of the pediatric MetS. Its measurement and control should be underscored in at-risk children and adolescents.

Key words: Abdominal obesity, dyslipidemia, hyperglycemia, hypertension, hyperuricemia, metabolic syndrome, uric acid

INTRODUCTION

Metabolic syndrome (MetS) is a group of adverse cardiometabolic risk factors.\(^1\)–\(^7\) It was first considered as a condition of adults and linked to their morbidity and mortality.\(^8\) More recently, children have been identified to have MetS.\(^9\) Data from the US National Health and Nutrition Examination Survey indicate that the prevalence of pediatric MetS increased from 4% to 9% from 1988 to 2006, with a prevalence of 30%–50% in obese children.\(^9\)–\(^12\) By rapid lifestyle change, pediatric MetS has also become a problem in developing countries.\(^10\)–\(^12\) Given the escalating trend of childhood obesity, pediatric MetS would become more prevalent in future years.\(^13\) The process of atherosclerosis origins from early life and is linked to the MetS components even from childhood.\(^14\) In addition to related health burden, it would also lead to a large economic burden in terms of hospital costs for chronic diseases.\(^15\)–\(^18\) Moreover, MetS would result in various disorders, including fibrinolysis, thrombosis,
inflammation, and endothelial dysfunction, as well as chronic noncommunicable diseases.\textsuperscript{1,9,17-20}

MetS is a cluster of factors that include general or central adiposity, elevated blood pressure (BP), dyslipidemia, low level of high-density lipoprotein (HDL), hyperglycemia, and hypertension. As obesity is the main factor of MetS, rapid increase in the prevalence of pediatric MetS and its long-term consequences in adulthood are anticipated.\textsuperscript{21,22}

Uric acid (UA) is produced by liver as the last item in the dietary and endogenous purine metabolism mechanisms; it is excreted by the kidneys.\textsuperscript{23} Although UA can be effective in the human body for its neuroprotective effects, it destroys free radicals and applies an antioxidant. Moreover, its role as the induction of platelet aggregation and chronic systemic inflammation has adverse health effects.\textsuperscript{24-26} Hyperuricemia is a pathologic description of increased serum UA levels (SUALs). There are several mechanisms considered for hyperuricemia; it may occur exogenously from purine-rich diet or endogenously from increased production, as in malignancies and inborn errors of metabolism, as well as in decreased renal clearance.\textsuperscript{27-34} Hyperuricemia increases the risk of comorbidities such as hypertension, renal diseases, and cardiovascular diseases.\textsuperscript{35}

Multiple mechanisms are involved in the relationship between UA and obesity.\textsuperscript{36} Obesity, especially its abdominal type, increases the activity of xanthine oxidase in the adipose tissues and would result in higher UA production and lower UA renal clearance.\textsuperscript{33,37-39}

Considering that gout is associated with elevated triglyceride (TG) and low-density lipoprotein (LDL) in the gout, it can be suggested that dyslipidemia, as a MetS component, might be related to UA.\textsuperscript{40-43} Furthermore, human hypertension may be developed by the key role of hyperuricemia; therefore, UA might increase the risk of MetS by rising another component of this inflammatory cluster.\textsuperscript{44,45} Based on epidemiological and observational studies, MetS is highly prevalent in adults.\textsuperscript{16,47} Carbone et al. have described the results from four longitudinal and 12 cross-sectional studies regarding the association between UA levels and MetS in adults.\textsuperscript{48} The meta-analysis of Yuan et al. included 11 studies on the relationship between UA levels and the MetS in adults. It showed that elevated UA level was an important factor for increasing the risk of MetS.\textsuperscript{49} MetS also commonly has been seen in children.\textsuperscript{1,14} Moreover, many cross-sectional and longitudinal investigations showed the relation between UA and MetS in both children and adults in different ethnic populations.\textsuperscript{2-14} Besides, the importance of the role of UA in MetS in the group of obese children was shown.\textsuperscript{5-13} Both of the review articles on relation between MetS and UA included studies on adults and did not investigate the components of MetS separately. The current study aims to systematically review the relationship between SUAL and components of MetS in the pediatric age group.

**MATERIALS AND METHODS**

This systematic review has been guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.\textsuperscript{50,51} The review focuses on the relation between SUAL and MetS in children and adolescents.

**Search strategy and data sources**

In July 2019, a systematic literature search was performed in the electronic databases of Web of Science, PubMed, Scopus, and Google Scholar; then, the search was updated in September 2019. The detailed search strategy for PubMed is presented in Supplementary Material 1. The following MeSH keywords were used: (“Uric acid” [Mesh]) OR “Uric acid” OR Hyperuricemia OR UA OR SUAL AND (“Metabolic Syndrome” [Mesh] OR “Metabolic Syndrome” OR “Metabolic Syndrome” OR “Metabolic Syndromes” OR “metabolic syndrome” OR “syndrome x” OR “insulin Resistance” OR “dysmetabolic Syndrome” OR “obesity” OR “diabetes mellitus” OR “Hypertriglyceridemia” OR “hyperlipidemia” OR “hypercholesterolemia” OR “hyponcholesterolemia” OR “dyslipidemia” OR “hyperinsulinism” OR “hyperglycemia” OR “hypertension”) AND (“Child AND adolescent” [Mesh]) OR “child AND adolescent” OR “children AND adolescent.”

**Study selection**

All identified articles were initially imported into Endnote X8 software (Clarivate Analytics (formerly Thomson Reuters), Philadelphia, PA, USA), and the duplicate records were removed. Two reviewers (PG and RR), a physician and a biostatistician, then independently screened each abstract and full-text article against the predefined inclusion/exclusion criteria. Only those records that were included by both reviewers were considered for the final review step. In the case of disagreement, a third researcher (ShD) specialist in Health Education and Health Promotion was consulted; the consensus was negotiated with a pediatrician, as the senior researcher of the study (RK). Discrepancies were resolved by discussion and consensus among the researchers. Reference lists of the eligible studies were also checked manually to ensure no potentially relevant article would be missed.

The inclusion criteria were as follows: (1) studies conducted in children and adolescents; (2) observational/cohort studies; (3) investigating the association of UA with MetS and its components including BP, hyperglycemia,
hyperlipidemia, and/or obesity; (4) available full-text article; (5) written in English; and (6) published before September 2019. If study populations overlapped between studies, only the most extensively described study was included. Interventional studies were excluded.

**Outcome variables**
The outcome variables consisted of pediatric MetS and its components (qualitative and quantitative variables) based on the WHO definition including abdominal obesity, hyper-TG, low HDL-cholesterol (HDL-C), elevated systolic or diastolic BP (SBP or DBP), and elevated fasting blood sugar (FBS).

**Data extraction**
The following study characteristics were collected in Excel: authors, year of publication, location, participants’ characteristics (gender, age, number of participants), study type, and covariate variables. Appropriate effect size (odds ratio [OR], regression coefficient, and correlation coefficient) or standard error were extracted from the different adjusted models of included studies in this meta-analysis. In the case which used regression coefficient, it was changed to correlation coefficient.

**Risk of bias and quality assessment**
Risk of bias and quality of studies in the eligible criteria was assessed using The Strengthening the Reporting of Observational studies in Epidemiology (STROBE) checklist[52] by two reviewers (PG and ShD) with regard to selection bias, detection bias, performance bias, and loss to follow-up. Three categories for quality assessment were established arbitrarily: (1) when the study fulfilled more than 80% criteria stated in STROBE; (2) when 50%–80% of STROBE criteria were fulfilled; and (3) if less than 50% criteria could be achieved.

**Statistical analysis**
The desired pooled effect size was considered as a correlation coefficient and OR with 95% confidence interval (CI). We used the forest plot to investigate the association between serum UA and MetS components in the pediatric age group. The fixed-effect model was used according to the nonexistence of significant heterogeneity. The Z-test was used to assess the significance of the pooled effect size; P < 0.05 was considered statistically significant. Heterogeneity between the included studies was assessed by Cochran’s Q statistic, which was quantified by calculating the inconsistency index (I^2). In cases with high heterogeneity among studies (substantial heterogeneity considered as I^2 > 50%), the random-effect model with DerSimonian and Laird method was used.[53] In addition, we used the meta-regression analysis (based on the age and body mass index [BMI]) to identify the source of heterogeneity. We assessed potential publication bias using funnel plots (not shown) and both Begg’s and Egger’s tests. The sensitivity analysis was conducted to assess the extent of the influence of omitting individual studies on the pooled OR. A P < 0.05 from both Begg’s and Egger’s tests and asymmetrical shape of the funnel plot showed statistically significant publication bias. The analysis was conducted by the Stata software, version 11.2 (STATA Corp, College Station, TX, USA).

**RESULTS**

**Description of the studies**
Of 1480 titles and abstracts screened, 370 studies were extracted for detailed evaluation, of which 34 adhered to our inclusion criteria [Figure 1]. They comprised seven prospective and 24 cross-sectional studies including 50,150 participants aged 2–18 years. The number of participants ranged from 128 to 6768. The WHO criteria were used in 33 studies, whereas the criteria of Adult Treatment Panel III modified for the pediatric age group were used in one study. The characteristics of all included studies are presented in Table 1.

**The association of uric acid with metabolic syndrome components**
The correlation between SUAL and some MetS components was equivocal.[54] Some studies did not show any significant correlation between UA and fasting blood glucose; for instance, Tang et al. investigated a group of 6–14-year-old children and adolescents, Hongo et al. assessed a group of Japanese juniors, Wang et al. studied a group of high-school students, and Civantos Modino et al. investigated on 10–16-year-old adolescents.[54‑58] On the other hand, some...
### Table 1: Characteristics of studies included in the review

| ID | First author name, publish year/location | Type of study | Sample size | Age group (years) | Gender | Outcome | Adjusted covariates | Finding |
|----|----------------------------------------|---------------|-------------|------------------|--------|---------|--------------------|---------|
| 1  | D Kızılay (2019), Turkey               | Cross‑sectional | 128         | 8‑18             | Girl/boy | WC, HC, insulin/FBS, HDL-LDL, TG, total cholesterol, BP, AST, ALT, UA | Age and sex | ↑SUAL was correlated with ↑TG, ↑WC, ↓HDL. Not related to BP |
| 2  | E Lurbe (2018), European origin        | Cross‑sectional | 333         | 5‑18             | Girl/boy | BP, HDL, TG, insulin, BMI, WC, UA, LDL | Age and pubertal stage | Participants with three or more metabolic risk factors showed ↑SUAL. ↑SUAL is related to ↑WC |
| 3  | E Patrícia (2018), Germany             | Cross‑sectional | 458         | 6‑18             | Girl/boy | BP, TG, HDL, BP, cysteine, C-peptide | Sex, age | ↑SUAL was associated with ↑SBP, ↓HDL |
| 4  | L Reis (2018), Brazil                  | Cross‑sectional | 2335        | 7‑17             | Girl/boy | BP, UA, BMI | Sex, age | ↑SUL was related to ↑SBP and ↑DBP |
| 5  | B Park (2017), South Korea             | Cohort         | 449         | *                | Girl/boy | UA, BMI, BP | Sex, current height, and body mass index | The group with ↑SUL had significantly increased SBP (96.4 mmHg [95% CI: 94.7-98.0] vs. 93.3 mm Hg [95% CI: 91.8-94.8]; P<0.01) and DBP (62.3 mm Hg [95% CI: 60.9-63.7] vs. 59.5 mm Hg [95% CI: 58.2-60.8]; P<0.01) at 3 years of age |
| 6  | E Perez (2017), Mexico                 | Cross‑sectional | 59          | 6‑9              | Girl/boy | BP, BMI, TG, HDL, LDL, UA, WC, tanner stage, total cholesterol | Gender-age-BMI | The results show that with one unit difference (1 unit=1 mg/dL) in UA, there were 3.9 times more likely to have a MetS diagnosis. ↑SUAL are associated with ↑SBP, ↑TG and ↓HDL |
| 7  | L Scheepers (2017), Germany            | Cross‑sectional | 246         | 6‑7              | Girl/boy | BP, BMI, UA, xanthine, hypoxanthine | Age, sex, and BMI | Multivariable analysis showed that a 1 SD (38 mmol/l) ↑SUAL was associated with ↑DBP, no association was found with SBP |
| 8  | B Jones (2017), Indiana                | Cross‑sectional | 57          | Preadolescents  | Girl/boy | Salivary UA, salivary C, peptide, BP | Age, gender, family income, and education level | These analyses did not yield any significant associated with HTN risk for children |
| 9  | N Li (2017), Tianjin                   | Cross‑sectional | 4073        | 3‑6              | Girl/boy | SUA, BP, TG | History of mother and father regarding gout, education of mother and father, family income, and health history of parents in addition to all variables listed in the model | The prevalence of hyperuricemia increased among children with overweight (9.9%) and obesity (18.9%) (P for trend <0.001). Children with ↑DBP or ↑TG (≥1.70 mmol/L) had higher prevalence of hyperuricemia |

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| ID  | First author name, publish year/location | Type of study | Sample size | Age group (years) | Gender | Outcome | Adjusted covariates | Finding |
|-----|----------------------------------------|--------------|-------------|------------------|--------|---------|---------------------|---------|
| 10  | R Luciano (2017), Italy                | Cross-sectional | 1364        | 4.1-17.9         | Girl/boy | SUA, BMI, WC, glucose, insulin, total cholesterol, HDL | Age, sex | There were statistically significant even weak correlations between SUA and WC ($\rho=0.467$). ↑SUA was also correlated with ↑TG ($\rho=0.165$), ↓HDL ($\rho=-0.149$), ↑FBS ($\rho=-0.107$, $P<0.001$) |
| 11  | S Safiri (2016), Iran                  | Cross-sectional | 367         | 10-18            | Girl/boy | BMI, WC, BP, HDL, LDL, SUA, TG, FBS | Age, living area, sex, PA, ST, and SES | The higher frequency of ↑BP associated with the ↑SUA tertiles. There were no significant differences in the number of metabolic syndrome components between tertiles of SUA, either. A↓HDL-C was associated with ↑SUA |
| 12  | V Hirschler (2016), Argentina          | Cross-sectional | 354         | 9.6±2.3          | Girl/boy | WC, serum magnesium, phosphorus | Age and gender | There was a significant association between WC and UA |
| 13  | H Sun (2015), Taiwan                   | Cohort       | 8005        | 10-15            | Girl/boy | WC, BMI, BP, FBS, TG, HDL, LDL, UA | * | ↑SUAL was either the second or third best predictor of HTN in both genders. HTN was the most important predictor for MetS in these adolescents, and ↑SUAL only predicted future MetS in males |
| 14  | F Viazzi (2015), Sangerado Hospital   | Cross-sectional cohort | 501 | 6-18 | Girl/boy | WC, pubertal stage, BP, glucose, insulin, total cholesterol, UA, HDL, BMI | Pubertal status, gender, BMI Z-score, and HOMA index | Children showed ↑SUAL along with ↑SBP (Z-score, $r=0.21$, $P=0.001$) and ↑DBP (Z-score, $r=0.11$, $P=0.02$), ↑TG ($r=0.23$, $P=0.001$), ↑LDL, ↑cholesterol ($r=-0.26$, $P=0.001$) |
| 15  | A Alper (2015), Bogalusa               | Cohort       | 577         | 5-17             | Girl/boy | UA, BP, BMI | age, sex, race, childhood body mass index, childhood UA levels, and change in levels of UA | ↑SUAL was associated with ↑SBP ($r=0.31$; $P=0.0001$) and ↑DBP ($r=0.20$; $P=0.0001$) |
| 16  | Z Wang (2015), China                   | Cross-sectional | 936         | 11-16            | Boy/girl | BP, WC, TG, HDL, LDL, FBS, HbA1c, insulin | * | BMI, WC, SBP, TG, were significantly higher in the highest SUA quartile (Q4) for both sexes. In all subjects, prevalence of MetS was higher in Q4 than Q1. No significant difference was observed between quartiles for SUA, FBS, or HbA1c in either gender. ↑SUAL was significantly associated with the ↑abdominal obesity, ↑dyslipidaemia and ↑HTN in Q4 in boys, and ↑abdominal obesity and ↑dyslipidaemia only in girls. The ORs (95% CI) of the highest quartile of SUA for MetS were |

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| ID | First author name, publish year/location | Type of study | Sample size | Age group (years) | Gender | Outcome | Adjusted covariates | Finding |
|----|-----------------------------------------|--------------|-------------|------------------|--------|---------|--------------------|---------|
| 17 | E Ford (2014), US                       | Cross-sectional | 1370        | 12-17            | Girl/boy | TG, HDL, WC, glucose, SUA | Age, sex, race or ethnicity, and concentrations of C-reactive protein | 7.67 (95% CI=2.58-22.78) for boys and 4.77 (95% CI=1.01-22.60) for girls |
|    |                                         |              |             |                  |         |         |                    | ↑SUAL was associated with ↑abdominal obesity, ↑hypertriglyceridemia, ↑hyperglycaemia. In addition, the association between high BP and concentrations of UA was of borderline significance. Concentrations of UA were significantly higher among teens with the metabolic syndrome (387.6 mol/L) than among those without the syndrome (319.7 mol/L) (P=0.001) |
| 18 | D Sun (2014), US                        | Cohort       | 2614        | 4-18             | Girl/boy | BMI, MAP, TG, Age HDL, insulin, UA | Age, sex, ethnicity, whereas UA was associated with other MetS components in selected subgroups. UA showed associations with MetS (OR=1.53-2.59, P=0.01) across race-gender groups. The risk of MetS associated with an increase of one unit (mg/dL) of UA was 1.74 times higher in children |
| 19 | S Pan (2014), China                     | Cross-sectional | 3778        | 10-15            | Girl/boy | BP, WC, total cholesterol, LDL, HDL, BUN, Cr | Age, sex, ethnicity, total cholesterol, HDL, LDL, TGs, GFR, fasting glucose, BMI |
| 20 | J Wang (2012), Taiwan                   | Cohort       | 613         | <18              | Girl/boy | UA, BMI, WC, BP, TG, HDL, LDL, FBS | Age, for each component of the MetS |
| 21 | S Civantos (2012), Madrid, Spain        | Cross-sectional | 148         | 5-19             | Girl/boy | BMI, WC, BP, glucose, HDL, TG, insulin, UA | The variables including WC, BMI, SBP, DBP, HDL, and log TG were significantly different among the UA quartiles Patients with hyperuricemia had more WC (101.4 vs. 91.1 cm, P<0.001) and higher BP both systolic (123.4 vs. 111.9 mm Hg, P<0.001) and diastolic (78.2 vs. 68.7 mmHg, P<0.001). HDL levels were significantly lower in patients with hyperuricemia (49.5 vs. 54.4 mg/dl P=0.02) and TG levels were higher (110.7 vs. 97.6 mg/dl, P=0.1). |

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| ID | First author name, publish year/location | Type of study | Sample size | Age group (years) | Gender | Outcome | Adjusted covariates | Finding |
|----|-----------------------------------------|--------------|-------------|------------------|--------|---------|---------------------|---------|
| 22 | A Kong (2012), Hong Kong                | Cross-sectional | 2067       | 6-20             | Girl/boy | BMI, LDL, HDL, BP, WC, glucose, LFT, TG, UA | Age, sex, and body mass index | There were no statistically significant differences in the levels of cholesterol or LDL. It was found that patients diagnosed with metabolic syndrome had higher levels of UA, (5.8 vs. 5.1 mg/dl, \(P=0.006\)). There were not statistically significant differences between hyperuricemia and waist size, TGs, fasting glucose |
| 23 | L Loeffler (2012), US                   | Cross-sectional | 6036       | 12-17            | Girl/boy | SUA, BMI, BP | Age, sex, race/ethnicity, and BMI percentile | High levels of UA (75\(^{th}\) percentile) were associated with cardiovascular risk factors including overweight/obesity and high BP. Participants with elevated BP had a mean UA of 5.6 mg/dL, compared to 5.0 mg/dL in the normal BP group (\(P=0.004\)). As UA quintile increased, participants were more likely to, have higher weight, height, BMI and systolic BP percentiles and have elevated BP |
| 24 | A Cardoso (2012), State of Paraiba, Brazil | Cross-sectional | 129        | 2 and 18         | Girl/boy | BMI, WC, BP, TG, HDL, insulin, UA | * | ↑SUAL were significantly associated with SBP, hypertriglyceridemia, and MetS. Also 4\(^{th}\) quartile (percentile >75\(^{th}\) for UA values) showed significantly higher values of BMI, WC, SBP, DBP, TG, and HOMA-IR, and lower mean of HDL-C |
| 25 | M Krzystek-Korpacka (2011), Poland     | -             | 184        | <17              | Girl/boy | WC, BP, puberty stage, C-peptide, glucose | Age, gender, BMI | Mean UA concentrations were significantly higher in patients who were overweight or obese, had MetS, ↑BP, hypertriglyceridemia, and low HDL-C |
| 26 | M DeBoer (2011), US                    | Cross-sectional | 3296      | 12-19            | Girl/boy | WC, BP, TG, HDL, glucose, SUA | Race, gender | Regarding MetS components commonly associated with elevated UA, HTN status, obesity status, and insulin status as each of these indices has been particularly tightly linked to UA elevations. ↑WC and ↑insulin had ↑SUAL |

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| ID | First author name, publish year/location | Type of study | Sample size | Age group (years) | Gender | Outcome | Adjusted covariates | Finding |
|----|-----------------------------------------|---------------|-------------|------------------|--------|---------|---------------------|---------|
| 27 | L Tang (2010), Amagasaki                 | Cross-sectional | 1027        | 6-14             | Girl/boy | BMI, WC, BP, TG, glucose, HDL, UA | Gender, age | Analysis revealed that hyperuricemia was independently associated with systolic BP, and HDL-C. On the other hand, no association was found between hyperuricemia and WC, DBP, TG, or fasting blood glucose |
| 28 | M Hongo (2010), Japan                    | Cross-sectional | 958         | 12.1-15.0        | Girl/boy | WC, BP, HDL, total cholesterol, TG, FBS, HbA1c, LDL, UA | Age, POW, and HbA1c | ↑SUAL was significantly associated with abdominal obesity, HTN, dyslipidemia and with HTN in the third quartile in boys, and it was associated with abdominal obesity in the highest quartile in girls. No significant association was found between quartiles of SUA and increased FBS in both genders. There were no correlations between percentage change in SUA and percentage changes in SBP, DBP, HDL-C, TG, or FBS |
| 29 | L Pacifico (2009), Italy                 | -             | 120         | 10-11.2          | Girl/boy | Total cholesterol, HDL, Cr, UA, BMI, BP, FBS, insulin | Age, sex | ↑SUAL was associated with SBP, TG, HDL-C. No correlation was found between UA and total cholesterol. When the association was restricted to the control group, UA levels were significantly correlated with BMI only. The mean concentrations of UA were significantly higher in the obese patients with MS compared with those without (0.32 [95% CI=0.30-0.34] vs. 0.27 [0.26-0.29]; P=0.0001) |
| 30 | M Gil-Campos (2009), Spain              | -             | 54          | 6-12             | Girl/boy | BMI, TS, SS, WC, BP, leptin, adiponectin, TNF, sex hormone (FSH, LH), glucose, C-peptide, insulin, UA | Sex, age | ↑SUAL was significantly higher in the obese children than in the normal weight controls. SUAL was correlated with↑SBP, DBP, ↑plasma insulin, ↑TG and↓HDL-C |
| 31 | P Muntner (2008), Bogalusa, Louisiana   | Cohort        | 517         | 5-17             | Girl/boy | BMI, BP, TG, HDL | Race and follow-up age, cigarette smoking, alcohol consumption, microalbuminuria | The mean SUAL was 6.56 mg/dL and 6.36 mg/dL for males with and without the metabolic syndrome, respectively, and 4.95 and 4.43 for females with and without |
Meta-analysis results

Correlation between metabolic syndrome components and uric acid

The forest plot with correlation coefficient (95% CI) for the associations between MetS components and serum UA in children and adolescents is shown in Figures 2 and 3.

The pooled correlation between fasting blood glucose and UA, according to random-effect model, was significant ($r = 0.24$, 95% CI = 0.09–0.40) with 94.2% heterogeneity...
The pooled correlation between SBP and DBP with UA (according to random-effect model) was statistically significant ($r$ for SBP and UA = 0.34, 95% CI = 0.24–0.43; $r$ for DBP and UA = 0.18, 95% CI = 0.11–0.25) with 96.2% ($F^2$ = 96.2%; $P < 0.001) and 92.5% heterogeneity ($F^2$ = 92.5%; $P < 0.001), respectively [Figure 4]. Based on the meta-regression analysis, the correlation between SBP, DBP, and UA was not significantly different according to age and BMI ($P > 0.05$).

**Association between uric acid and the risk of metabolic syndrome components**

Figure 5 shows that the pooled OR between risk of elevated FBS with high UA (according to fixed-effect model) was not significant (OR = 1.06, 95% CI = 0.60–1.52) without any significant heterogeneity ($I^2 = 25.4%$; $P = 0.24$).

As presented in Figure 6, the pooled OR between risk of abdominal obesity with UA (according to random-effect model) was statistically significant (OR = 2.62, 95% CI = 1.41–3.84) with 68.7% heterogeneity ($F^2$ = 25.4%; $P = 0.24$).

As depicted in Figure 7, the risk of hyper-TG (OR = 1.38, 95% CI = 0.90–1.86) and low HDL-C (OR = 1.63, 95% CI = 0.97–2.28) with UA (according to fixed-effect model) was not significant without significant heterogeneity ($P > 0.05$).

The risk of hypertension in individuals with elevated UA was 53% higher than others (according to fixed-effect model, OR = 1.38, 95% CI = 1.03–1.74) without significant heterogeneity ($F^2$ = 31.5%, $P = 0.177$) [Figure 8].

**Sensitivity analysis**

The sensitivity analysis showed that elimination of any individual studies did not result in significant change in the pooled effect size ($P = 0.26$).
Publication bias

Based on both Begg’s and Egger’s tests, there was no evidence of publication bias ($P > 0.05$). Results are shown in Supplementary Table 1.

DISCUSSION

In this systematic review and meta-analysis of the relationship between SUAL and MetS components, we found consistent evidence on significant association between elevated levels of UA and different components of pediatric MetS. Significant association was also documented between SUAL and elevated BP in children and adolescents.

UA has a role as an eminent biomarker of lifestyle-dependent diseases that would dispose individuals to MetS, hypertension, diabetes, cardiovascular diseases, and renal disorders. $^{[33,65,66]}$ These findings suggest that measuring serum UA in the pediatric age group and improving lifestyles, such as limiting purine-rich foods and high fructose diets, might reduce the risk of chronic diseases from childhood and mitigate the deleterious effect of noncommunicable diseases on adulthood.

Our findings showed that the association of SUAL with MetS could be explained by several potential underlying mechanisms. $^{[20,67]}$ The first mechanism is related to the effect of high UA on endothelial dysfunction by reducing nitric oxide level. The bioavailability of nitric oxide can be inhibited by UA. Nitric oxide acts as an antioxidant factor in the blood vessels, and it is necessary for glucose uptake, so increasing UA will increase blood glucose. $^{[3]}$ The second mechanism is related to the fact that UA might accelerate the adipogenesis process that would lead to oxidative and inflammatory alterations in the adipocytes, by expressing xanthine oxidoreductase, i.e., the enzyme that generates UA from xanthine. $^{[65,68]}$ Based on experimental studies, MetS in
The results of previous studies reported that the relationship between serum uric acid (UA) and risk of abdominal obesity among children was significant. Therefore, the relationship between UA and abdominal obesity is of great importance. Based on the fact that insulin increases renal tubular sodium and urate excretion, decreased renal excretion of UA is one of the potential pathophysiologic mechanisms linking hyperuricemia with insulin resistance in humans. It can justify the underlying process for our finding on the association between UA and fasting insulin.

We found that dyslipidemia, as a MetS component, was associated with hyperuricemia. Our results revealed strong association of elevated TG and LDL-cholesterol, as well as low HDL-C with high SUALs. Some previous studies showed that rise in the serum leptin levels was simultaneous with UA accumulation. Therefore, it can be suggested that renal reabsorption of UA was affected by leptin. Previous studies reported that the relationship between TGs and SUAL existed even in the normal population. Therefore, the relationship between UA and dyslipidemia might be determined by a variation in a few critical genes more than it would be expected by chance. A biological explanation of this event might be related to a high concentration of adenosine. Adenosine is produced in the situation of impaired oxidative phosphorylation, which occurs in the process of MetS. Therefore, adenosine could increase the renal reabsorption of sodium, urate, and water. Thus, over time, the increase in UA due to adenosine might increase the production of urate.

According to our results, interrelationships between SUAL and BP showed a strong positive association in children and adolescents. Both DBP and SBP were affected by a high level of UA. Our finding is in line with the previous assertion, which revealed that high UA has a key role in the pathogenesis of early life hypertension. The results of an experimental study also vindicated the probability of the relationship between BP and UA. There are possible biological mechanisms for this association; moreover, as high UA concentration reduces nitric oxide in the macula densa, UA directly activates the renin-angiotensin system; both of these mechanisms would cause hypertension by vasoconstriction. Previous studies among children supposed that UA can be considered as a useful and diagnostic factor for preventing hypertension in later life. These studies emphasized on the importance of early recognition of the MetS by measuring UA and assessment of hyperuricemia in children and adolescents. The early elevation of UA concentration could act as the main risk factor for MetS by developing hypertension.

A previous study also mentioned that there is a significant genetic correlation between serum level of UA and MetS components such as: abdominal obesity or hyperglycemia.
The limitation of the current study is the restriction of search to English-language publications, to the selected database sources. This study had some strength points: According to the STROBE checklist, all studies were classified as two categories of moderate (76.5%) and high (23.5%) quality. To the best of our knowledge, this is the first meta-analysis and systematic review to determine the relationship between MetS components and hyperuricemia in children and adolescents. The generalizability of the current review is strengthened by a large number of included studies, as well as by a very large and diverse baseline population with different ethnicities.

CONCLUSION

Considering all evidence, hyperuricemia has the ability for worsening MetS and it has a close relationship with its major components. SUAL increased the risk of abdominal obesity, hypertension, and FBS. Therefore, measurement and control of UA should be emphasized in at-risk children; it can be useful in the primary prevention of noncommunicable diseases.

Acknowledgments

We would like to thank the research team working on this review.

Financial support and sponsorship

The study was supported by Isfahan University of Medical Sciences.

Conflicts of interest

There are no conflicts of interest.

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### Supplementary Table 1: Results of publication studies according to Begg’s and Egger’s tests

| Studies for association between UA and the risk of MetS components ($P$) | Begg’s test | Egger’s test |
|---|---|---|
| High FBS | 0.999 | 0.655 |
| Abdominal obesity | 0.764 | 0.340 |
| HTN | 0.734 | 0.436 |
| Hyper-TG | 0.721 | 0.411 |
| Low HDL-C | 0.296 | 0.075 |
| FBS | 0.450 | 0.731 |
| Serum TG | 0.405 | 0.637 |
| Serum HDL-C | 0.308 | 0.301 |
| WC | 0.450 | 0.640 |
| Fasting insulin | 0.700 | 0.341 |
| SBP | 0.454 | 0.643 |
| DBP | 0.998 | 0.587 |

FBS=Fasting blood sugar; HDL-C=High-density lipoprotein-cholesterol; TG=Triglyceride; WC=Waist circumference; BP=Blood pressure; DBP=Diastolic BP; SBP=Systolic BP; MetS=Metabolic syndrome; HTN=Hypertension

### Supplementary Material 1: Data sheet I search strategy

| Data bases | Number of searched articles |
|---|---|
| Scopus | 143 |
| Web of Science | 1230 |
| PubMed | 407 |
| Google Scholar | 300 |
| Total | 2080 |