Uric Acid in Children at Cardiovascular Risk

Increased Serum Uric Acid Levels Blunt the Antihypertensive Efficacy of Lifestyle Modifications in Children at Cardiovascular Risk

Francesca Viazzi, Paola Rebora, Marco Giussani, Antonina Orlando, Andrea Stella, Laura Antolini, Maria Grazia Valsecchi, Roberto Pontremoli, Simonetta Genovesi

See Editorial Commentary, pp 845-847

Abstract—Primary hypertension is a growing concern in children because of the obesity epidemic largely attributable to western lifestyles. Serum uric acid is known to be influenced by dietary habits, correlates with obesity, and could represent a risk factor for hypertension. Preliminary studies in children highlighted uric acid as a potentially modifiable risk factor for the prevention and treatment of hypertension. The effect of lifestyle changes (increase of physical activity and dietary modifications) on blood pressure values, weight status, and serum uric acid levels in a cohort of 248 children referred for cardiovascular risk assessment were evaluated over a mean 1.5-year follow-up. At baseline, 48% of children were obese and 50% showed blood pressure values >90th percentile. At follow-up, a significant improvement in weight class (24% obese; P<0.0001) and blood pressure category (22% >90th percentile; P<0.0001) was found. Systolic blood pressure z-score (P<0.0001), uric acid value (P=0.0056), and puberty at baseline (P=0.0048) were independently associated with higher systolic blood pressure z-score at follow-up, whereas a negative association was observed with body mass index z-score decrease during follow-up (P=0.0033). The risk of hypertension at follow-up was associated with body mass index (P=0.0025) and systolic blood pressure (P<0.0001) z-score at baseline and inversely related to delta body mass index (P=0.0002), whereas the risk of showing hypertension ≥99th percentile was more than doubled for each baseline 1 mg/dL increase of serum uric acid (P=0.0130). Uric acid is a powerful determinant of blood pressure over time, independent of lifestyle modifications. (Hypertension. 2016;67:934-940. DOI: 10.1161/HYPERTENSIONAHA.115.06852.) • Online Data Supplement

Key Words: blood pressure ▪ body weight ▪ children ▪ hypertension ▪ lifestyle ▪ obesity ▪ uric acid

Primary hypertension is a growing concern in children and adolescents in western countries largely because of its association with the ongoing obesity epidemic. Elevated serum uric acid (SUA) levels are frequently found in children with hypertension and obesity.1 Although primary hypertension in children was initially thought to reflect the underlying presence of subtle renal damage and insulin resistance, recent epidemiological and experimental data support the hypothesis that SUA may play an independent pathogenetic role in the early stages of vascular damage and the subsequent development of hypertension.2 Moreover, hyperuricemia has been associated with increased risk of hypertension development in adults in a large number of studies published to date.3-5 Among participants in the Bogalusa Heart Study, SUA levels measured during childhood and greater changes in SUA from youth to adulthood were significant predictors of adult blood pressure (BP) values.6 Accordingly, recent meta-analyses indicate that high SUA levels entail an increased risk of hypertension incidence7 with a consistent dose–response relationship, which supports causal disease-exposure association.8

Western lifestyles, namely purine- and fructose-rich diet,9 have consistently been demonstrated to induce significant increases in SUA levels. In this context, SUA is emerging as a potentially modifiable risk factor for the prevention and treatment of hypertension. In fact, a reduction in SUA levels has been shown to prevent the development of hypertension in animal models10,11 and preliminary clinical trials indicate a BP-lowering effect of SUA reduction by either xanthine

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oxidase inhibitors or uricosuric agents in adolescents. Appropriate lifestyle changes should therefore be a cornerstone for prevention and treatment of hypertension. Because the contribution of specific pathogenetic mechanisms to the onset of hypertension may be more easily identified in the early course of life, we investigated the role of implementing healthy lifestyle changes on BP values, weight status, and SUA levels in a large cohort of children at increased cardiovascular risk.

Methods

Subjects
We studied a cohort of children consecutively referred by their primary care pediatricians to our Unit for Cardiovascular Risk Assessment in Children because of evidence of elevated BP values and excess of weight or dyslipidemia or a positive family history of cardiovascular disease. The latter was defined as the presence in one or both of the parents of at least one among hypertension, type 2 diabetes mellitus, dyslipidaemia, early ischemic heart disease, and cerebrovascular disease.

We considered an initial cohort of 486 subjects between January 2005 and January 2014, which at the first assessment showed at least one among these conditions: (1) elevated BP values, (2) excess of weight, (3) dyslipidemia, and (4) positive family history of cardiovascular disease. None of these children were affected by impaired glucose tolerance, diabetes mellitus, chronic kidney disease, or other forms of secondary hypertension.

After the first visit, children and their parents were offered to be included in a study involving a baseline assessment (see Expanded Methods in the online-only Data Supplement), lifestyle changes recommendations, including nutrition and physical activity (see Expanded Methods in the online-only Data Supplement), and a follow-up revaluation after 1.5 years (follow-up assessment). Between the baseline and the follow-up assessment, periodic visits were performed every 3 months, during which the children’s anthropometric parameters were recorded, information regarding treatment adherence was obtained by a nonstructured interview of the parent, and any necessary changes in the dietary regime were introduced.

A total of 278 families agreed to participate in the study and performed the complete protocol. Thirty subjects were excluded because of incomplete carrying out of the requested examinations, ending up with a final cohort of 248 subjects (mean follow-up = 1.5 years, SD=0.66 years).

Informed consent was obtained from the children’s parents, and the Local Ethical Committee approved the study protocol.

Anthropometric Parameters and BP
Height, weight, and waist circumference were measured in children according to standard procedure. Body mass index (BMI) z-scores were calculated using the Centres for Disease and Control prevention charts available at http://www.cdc.gov/nchs/. Weight class was defined according to the tables of the International Obesity Task Force distinguishing among normal weight, overweight, and obese classes. Systolic BP (SBP) and diastolic BP (DBP) percentiles and z-scores were calculated according to the recommended nomograms, and children were classified according to the percentile of the mean of the 3 measurements as follows: normotensive if both SBP and DBP percentiles were <90th; prehypertensive if the SBP and DBP percentile was ≥90th, but both ≤95th; hypertensive if the SBP and DBP percentile ≥95th, but both were <99th; hypertensive ≥99th percentile if the SBP and DBP percentile was ≥99th.

Biochemical Parameters
At baseline, anthropometric parameters, BP, and haematochemical variables were evaluated for all children enrolled in this study (see Expanded Methods in the online-only Data Supplement).

Recommended Lifestyle Modifications
Changes in lifestyle were proposed involving the caregivers of the child and taking into consideration the actual difficulties and resources of the family. Physical activity and eating habits were accurately assessed by means of an interview with one of the parents administered by a single expert nutritionist, and changes were prescribed as appropriate on the basis of recommendations of Italian Society of Pediatrics (see Expanded Methods in the online-only Data Supplement).

Statistical Methods
The cohort was categorized into groups according to hypertension category at baseline. The continuous variables were described by median and quartiles and compared by the analysis of variance. The categorical variables were described by percentages and compared by the Chi-square test. Box plots and bar plots were used to describe the distribution of SBP z-score, BMI z-score, SUA, BP category, and weight class at baseline and follow-up. SBP z-score, BMI z-score, and SUA modifications after the follow-up were evaluated by paired t test, while BP category and weight class by the ordinal logistic model, as extension of the McNemar test for categorical data with >2 levels. The factors associated with SUA increase (defined as presence of a positive difference between follow-up and baseline measurements) during follow-up were evaluated by a logistic model, including age, puberty, sex, BMI and SBP z-scores, and SUA level at baseline as covariates. Multiple linear models were used to assess the influence of age, puberty, sex, BMI z-score (or waist to height ratio), SBP z-score, SUA, and homeostatic model assessment index values at baseline on SBP z-score at follow-up. The logistic model was used to assess the influence of age, puberty, sex, BMI and SBP z-score, SUA, and homeostatic model assessment index values at baseline on BP category at follow-up; in particular, hypertension and hypertension ≥99th percentile have been compared with normotensive category in 2 separate models.

Results
Table 1 shows anthropometric and clinical characteristics of the cohort at recruitment according to BP category. Half the population was composed of subjects with high BP (16% prehypertensive, 24% hypertension, and 10% hypertension ≥99th percentile), whereas the other half was normotensive. Among BP categories, there were no significant differences for any of the parameters considered, except, as expected, for absolute values and z-scores of SBP and DBP. Excess weight was present in 82% of children (34% were overweight and 48% were obese) and dyslipidemia in 20% (n=51). At the end of follow-up, there was a significant improvement in BP category (P<0.0001) and weight class (P<0.0001; Figure A and B). In addition, the average values of SBP z-score (0.68 versus 1.22; P<0.0001) and BMI z-score (1.22 versus 1.55; P<0.0001) were significantly lower compared with baseline (Figure C and D).

SUA slightly, but statistically significantly, increased during follow-up (mean SUA values from 4.36 to 4.52 mg/dL [259–269 μmol/L], difference between follow-up and baseline 0.16 [95% confidence interval 0.06; 0.26] mg/dL and 9.5 [95% confidence interval 3.56–15.46] μmol/L, P=0.002; Figure S1 in the online-only Data Supplement). In Table S1, it is shown that the risk of an increment in SUA from baseline to follow-up was inversely related to SUA values at baseline (P<0.0001), whereas it was directly associated to male sex (P=0.0042), age at baseline (P=0.0072), the switch to puberty during follow-up (P=0.0141), and BMI z-score basal value (P=0.003). For each decrease of 1 BMI z-score, the risk of having an SUA increment at follow-up was reduced by 70% (P=0.0062).
In the multivariable analysis showed in Table 2, factors independently associated with higher SBP z-score at the end of follow-up were the presence of puberty at recruitment ($P=0.0048$), basal SBP z-score ($P<0.0001$), and basal SUA values ($P=0.0056$). Age at recruitment ($P=0.0005$) was inversely associated to BP values at follow-up. BMI reduction was related to changes in SBP z-score: the greater the decrease of BMI z-score, the lower was the SBP z-score ($P=0.0033$) at follow-up. The only predictive variable of DBP z-scores at follow-up was DBP z-score at baseline ($P<0.0001$, data not shown). When BMI z-score was replaced with waist to height ratio value in the statistical model, results were superimposable, and baseline SUA remained significantly associated with higher SBP z-score at follow-up ($P=0.0028$, data not shown).

The values of SBP z-score predicted by the model described in Table 2 are shown in Table 3. For instance, an overweight (BMI z-score=1) or obese (BMI z-score =2) girl, with a reduction in BMI z-score equal to the average obtained in the follow-up (delta BMI z-score =0.26) and a baseline SUA value of 6 mg/dL (357 μmol/L), is expected to have an SBP z-score at the end of follow-up (1.08) higher than the expected SBP z-score (0.47) of a girl with the same BMI and SBP z-score at baseline, but with a value of basal SUA of 2 mg/dL (119 μmol/L).

Logistic regression analysis (Table S2) showed that using the normotensive as comparison, the risk of being hypertensive at follow-up, after adjustment for age, sex, pubertal status, homeostatic model assessment index, and BMI z-score...

### Table 1. Anthropometric and Clinical Characteristics of Study Subjects According to Blood Pressure Category at Baseline (248 Children)

<table>
<thead>
<tr>
<th>Variable</th>
<th>NT, n=124, 50%</th>
<th>PH, n=41, 16%</th>
<th>HYP, n=59, 24%</th>
<th>HYP ≥99th, n=24, 10%</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>10.2 [8.6–11.9]</td>
<td>10.8 [9–12.1]</td>
<td>11.0 [8.8–12.6]</td>
<td>11.6 [8.8–13.2]</td>
<td>0.1582</td>
</tr>
<tr>
<td>Sex, n of boys (%)</td>
<td>66 (53.2)</td>
<td>25 (61)</td>
<td>30 (50.8)</td>
<td>16 (66.7)</td>
<td>0.4795</td>
</tr>
<tr>
<td>Puberty, yes (%)</td>
<td>46 (37.1)</td>
<td>17 (41.5)</td>
<td>31 (52.5)</td>
<td>12 (50.0)</td>
<td>0.2146</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.4 [1.4–1.5]</td>
<td>1.5 [1.4–1.5]</td>
<td>1.5 [1.3–1.6]</td>
<td>1.6 [1.3–1.6]</td>
<td>0.3113</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>46.5 [37.5–59.4]</td>
<td>54.0 [41.3–65.5]</td>
<td>51.5 [38.8–67.5]</td>
<td>59.0 [37.5–75.8]</td>
<td>0.0815</td>
</tr>
<tr>
<td>Weight class</td>
<td>0.7638</td>
<td>0.53 [0.49–0.56]</td>
<td>0.55 [0.5–0.59]</td>
<td>0.51 [0.47–0.59]</td>
<td>0.3690</td>
</tr>
<tr>
<td>NW, n (%)</td>
<td>22 (17.7)</td>
<td>5 (12.2)</td>
<td>12 (20.3)</td>
<td>6 (25.0)</td>
<td>0.1582</td>
</tr>
<tr>
<td>OW, n (%)</td>
<td>44 (35.5)</td>
<td>12 (29.3)</td>
<td>21 (35.6)</td>
<td>7 (29.2)</td>
<td>0.1582</td>
</tr>
<tr>
<td>OB, n (%)</td>
<td>58 (46.8)</td>
<td>24 (58.5)</td>
<td>26 (44.1)</td>
<td>11 (45.8)</td>
<td>0.1582</td>
</tr>
<tr>
<td>Waist, cm</td>
<td>77.0 [69.3–82.3]</td>
<td>79.0 [73.5–88]</td>
<td>73.5 [68.5–83]</td>
<td>77.0 [66–91.5]</td>
<td>0.2084</td>
</tr>
<tr>
<td>WtHr</td>
<td>0.53 [0.49–0.56]</td>
<td>0.55 [0.5–0.59]</td>
<td>0.51 [0.47–0.59]</td>
<td>0.52 [0.47–0.58]</td>
<td>0.3690</td>
</tr>
<tr>
<td>SBP, z-score</td>
<td>0.56 [0.1–0.97]</td>
<td>1.41 [1.31–1.48]</td>
<td>1.90 [1.72–2.08]</td>
<td>2.82 [2.49–3.55]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>66 [61–70]</td>
<td>70 [68–76]</td>
<td>72 [65–74]</td>
<td>79 [72–85]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DBP, z-score</td>
<td>0.42 [0–0.81]</td>
<td>0.76 [0.33–1.33]</td>
<td>0.78 [0.19–1.25]</td>
<td>1.52 [0.87–1.91]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>4.5 [4.4–4.8]</td>
<td>4.6 [4.3–4.9]</td>
<td>4.7 [4.3–5.0]</td>
<td>4.7 [4.5–4.9]</td>
<td>0.7435</td>
</tr>
<tr>
<td>Insulin, pmol/L</td>
<td>60 [41–89]</td>
<td>79 [55–110]</td>
<td>70 [43–100]</td>
<td>83 [34–111]</td>
<td>0.1423</td>
</tr>
<tr>
<td>HOMA Index</td>
<td>2.05 [1.34–3.08]</td>
<td>2.71 [1.92–3.87]</td>
<td>2.47 [1.42–3.4]</td>
<td>2.84 [1.21–3.69]</td>
<td>0.1943</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.2 [3.7–4.7]</td>
<td>4.4 [4.2–4.7]</td>
<td>4.2 [3.9–4.6]</td>
<td>4.0 [3.6–4.6]</td>
<td>0.3683</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.4 [1.2–1.5]</td>
<td>1.3 [1.2–1.6]</td>
<td>1.4 [1.2–1.6]</td>
<td>1.5 [1.3–1.6]</td>
<td>0.7211</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>0.67 [0.50–0.91]</td>
<td>0.84 [0.63–1.08]</td>
<td>0.68 [0.51–0.99]</td>
<td>0.68 [0.48–0.97]</td>
<td>0.0899</td>
</tr>
</tbody>
</table>

Median [interquartiles range]. BMI indicates body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HOMA, homeostatic model assessment; HYP, hypertensive; HYP ≥99th, hypertensive ≥99th percentile; NT, normotensive; NW, normal weight; OB, obese; OW, overweight; PH, prehypertensive; SBP, systolic blood pressure; and WtHr, waist to height ratio.
Viazzi et al  Hypertension, Uric Acid, and Lifestyle in Children 937

(both at baseline and variations at follow-up) was directly associated with BMI z-score at baseline \((P=0.0025)\) and SBP z-score at baseline \((P<0.0001)\) and inversely related to size of BMI z-score reduction \((P=0.0002)\). The risk of being hypertensive \(\geq 99\text{th}\) percentile at follow-up was almost 3× greater for each increase of 1 SBP z-score \((P=0.0019)\) and for an increase of 1 mg/dL \((59.48 \mu\text{mol/L})\) of SUA at baseline \((P=0.0130)\).

**Discussion**

Baseline SUA levels are strongly related to changes in BP values after long-term implementation of healthy lifestyle modifications in a cohort of children at cardiovascular risk. Moreover, the presence of even moderately increased SUA levels at baseline significantly blunted the decrease in BP values observed in association to weight loss during the study period.

Although a relationship between SUA and future BP levels has already been described both in adults \(^7\) and young populations,\(^6\) the use of BP z-scores, an appropriate and powerful way to investigate these variables in a growing population, rather than raw BP values makes our findings more accurate and reliable as compared with previous studies.\(^6\) Furthermore, by gathering data on SUA and insulin sensitivity, we were able to investigate the independent role of these 2 traditionally entangled factors on the rise in BP in children at risk. Our results indicate that future arterial pressure is mainly predicted by SUA levels even independently of insulin homeostasis and weight variations, suggesting that previous cross-sectional studies reporting an association between adiposity, hyperinsulinemia/metabolic syndrome, and hypertension in adolescents\(^17\)\(^\text{–}\)\(^19\) were showing only part of the complex pathogenetic mechanisms of BP modulation in children.

We cannot rule out the possibility that in our study patients, higher baseline BP values may well have tracked into follow-up. However, even when baseline BP is taken as a covariate,
SUA remains a significant, independent predictor of subsequent BP (Table 2).

Epidemiological reports describe an increase in children BP levels and a rise in prevalence of hypertension, which is largely driven by escalation in childhood obesity with concurrent changes in diet habits, including salt and possibly fructose exposure.20,21

Although a Dietary Approaches to Stop Hypertension (DASH)–type diet, weight loss, and increases in physical activity are being advocated by leading health experts to treat high BP in childhood and adolescence,15,21 the efficacy of the diet and intervention strategies that maximize such efficacy in real-life settings among youth is yet to be ascertained.20 Few studies demonstrated the effect of body weight changes on BP values,20 and only one randomized study showed the effectiveness of physical exercise in lowering elevated BP in obese hypertensive children.24 Therefore, our findings of an effective reduction in body weight and BP values after implementation of long-term lifestyle modifications in our large cohort of high cardiovascular risk children corroborate the role of nonpharmacological intervention for prevention and treatment of hypertension in this age group. Although preliminary clinical trials reported remarkable BP benefits by pharmacological lowering of SUA,12,17 the opportunity of embracing this therapeutic strategy to prevent hypertension development in children must await further evidence, and for the time being, nonpharmacological approaches should be preferred.

We found that the risk of experiencing an increase of SUA at follow-up was higher in males with higher BMI z-score and in those who reached puberty during the study period or had an increase in weight at follow-up. The analysis of the relationship between SUA and BP changes in time is complicated in youth. In fact, although estrogen is known to increase urinary uric acid excretion during pubertal status in girls,25 SUA is expected to increase with the age and the physiological BMI increment.26 All these factors could have contributed to attenuate/mask the effect of lifestyle modification on SUA in our study sample. As a matter of fact, for each decrease of 1 BMI z-score, the risk of having an SUA increment at follow-up was reduced by 70% in our study children.

Several studies demonstrated a significant relationship between BMI and its changes overtime with BP levels in childhood.27 Thus, BMI should be taken as a potential confounder in the relationship between SUA and BP. The reduction of SUA we observed in our patients in association to weight loss was somewhat predictable given the type of intervention used in the present study. However, we did not find a significant relationship between changes in SUA and BP levels at follow-up. In our study, BMI z-score reduction seems to be an important determinant for both SUA and SBP decrease. Thus, one may speculate that the observed impact of BMI z-score reduction on BP levels may have masked any additional effect linked to a concomitant decrease in SUA. Alternatively, it is possible that relatively high SUA levels at baseline may have already created a situation of sustained BP elevation that is no longer susceptible to change with SUA reduction. It has been proposed that the pathogenetic mechanisms linking SUA to the development of hypertension may follow a step-wise path, with an initial functional phase mainly mediated by vasoconstriction because of angiotensin II increase and nitric oxide reduction and a subsequent, not reversible one wherein structural changes, such as proliferation and hypertrophy of vascular smooth muscle cells, have developed at the tissue level.9 A similar hypothesis would account for the observed smaller BP benefits we observed after intervention in those patients presenting with higher baseline SUA values. In particular, our statistical model indicates that SBP z-score reduction because of nonpharmacological intervention is much smaller in a subject with 6 mg/dL (357 μmol/L) baseline SUA as compared with a child peer in sex, BMI, and SBP z-score with, for instance, 2 mg/dL (119 μmol/L) of SUA at baseline.

Our study has both strengths and weaknesses that deserve to be commented on. Among the former is the fact that the definition of elevated BP and the allocation of children into different BP categories was not based on a single physical examination. BP was measured in at least 2 different occasions, and in

<table>
<thead>
<tr>
<th>Sex</th>
<th>Baseline SBP Z-Score</th>
<th>Baseline Uric Acid mg/dL (μmol/L)</th>
<th>Predicted SBP Z-Score at Follow-Up (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Baseline BMI Z-Score 1* Baseline BMI Z-Score 2†</td>
</tr>
<tr>
<td>F</td>
<td>2</td>
<td>2 (119)</td>
<td>0.47 (0.14; 0.80) 0.52 (0.16; 0.88)</td>
</tr>
<tr>
<td>F</td>
<td>2</td>
<td>6 (357)</td>
<td>1.08 (0.73; 1.43) 1.12 (0.79; 1.45)</td>
</tr>
<tr>
<td>F</td>
<td>1</td>
<td>2 (119)</td>
<td>−0.07 (−0.38; 0.24) −0.03 (−0.37; 0.31)</td>
</tr>
<tr>
<td>F</td>
<td>1</td>
<td>6 (357)</td>
<td>0.53 (0.19; 0.87) 0.58 (0.26; 0.89)</td>
</tr>
<tr>
<td>M</td>
<td>2</td>
<td>2 (119)</td>
<td>0.58 (0.27; 0.90) 0.63 (0.27; 0.98)</td>
</tr>
<tr>
<td>M</td>
<td>2</td>
<td>6 (357)</td>
<td>1.19 (0.9; 1.48) 1.23 (0.96; 1.5)</td>
</tr>
<tr>
<td>M</td>
<td>1</td>
<td>2 (119)</td>
<td>0.04 (−0.27; 0.34) 0.08 (−0.26; 0.42)</td>
</tr>
<tr>
<td>M</td>
<td>1</td>
<td>6 (357)</td>
<td>0.64 (0.36; 0.92) 0.69 (0.43; 0.94)</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; CI, confidence interval; F, female; HOMA, homeostatic model assessment; M, male; and SBP: systolic blood pressure. Predicted values have been derived for a prepuberty children of 10 years of age at baseline, with HOMA index of 2.3 at baseline (median value) that reduced the BMI z-score of 0.26 during follow-up (median reduction). *Z-score value of 1 corresponds to 84th percentile. †Z-score value of 2 corresponds to 98th percentile.
both cases, the mean of 3 measurements was used for analysis. Moreover, to fully account for the fact that children grow and body weight, waist circumference, and BP values increase in a physiological manner, we used BMI and BP z-score rather than raw values (nomograms of National High Blood Pressure Education Program Fourth Report). This rigorous methodological approach makes our observations more reliable as compared with those of a variety of previous reports. Moreover, our study represents one of the few evidences reported in the literature of the effectiveness of an educational program of lifestyle changes in a large cohort of children in a real life context.

Finally, there are some limitations to our study. First, the clinical cohort in this study is not representative of the population of children in general, but is characteristic of children at relative high cardiovascular risk and, therefore, is not generalizable. Moreover, the lack of data about level of adherence to prescribed lifestyle changes and on consumption of sugar-sweetened beverages may limit our inductive reasoning on the pathophysiological mechanisms underlying the recorded variations in BP profile.

Conclusions
SUA shows to be a reliable predictor of coming BP values even independently of anthropometric parameters of body composition and their variations in children and adolescents. These data are mainly interesting from a pathophysiological point of view, suggesting an active role for SUA as a determinant of BP values and their variations throughout life and also as a bystander of high risk conditions, such as hypertension, obesity, and metabolic syndrome.

Perspectives
Our study adds to the growing body of evidence on the association between SUA and BP in adolescents and indicates that increased SUA levels retain an unfavorable predicting power in the long term even after implementation of appropriate lifestyle changes. Thus, our data support the view that maintaining relatively low uric acid values over time could be more effective at preventing the onset of hypertension than lowering uric acid to reduce BP levels once hypertension is established.

Understanding the early stages of the relationship between SUA and BP values will help in the early identification and prevention of hypertension; in fact, once a vascular lesion is established, SUA and BP values will help in the early identification and prevention of hypertension; in fact, once a vascular lesion is established.

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Conclusions
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References

**Novelty and Significance**

**What Is New?**
- Our findings of an effective reduction in body weight and blood pressure values after implementation of long-term lifestyle modifications represent one of the few evidences of the effectiveness of an educational program based on lifestyle changes in a large cohort of children in a real life context.
- Moreover, we found that the presence of even moderately increased serum uric acid levels at baseline significantly blunted the decrease in blood pressure values associated with weight loss.

**What Is Relevant?**
- Our data corroborate the role of nonpharmacological intervention for prevention and treatment of hypertension in children and strongly suggest that relatively high serum uric acid levels at baseline may contribute to create a situation of sustained blood pressure increase that is no longer likely to improve with serum uric acid reduction.

**Summary**

Serum uric acid shows to be a reliable predictor of future blood pressure values even independently of anthropometric parameters of body composition and their variations in children and adolescents. Our data support the view that maintaining relatively low uric acid levels over time could be more effective in preventing the onset of hypertension than lowering uric acid to reduce blood pressure levels once hypertension is established.
Increased Serum Uric Acid Levels Blunt the Antihypertensive Efficacy of Lifestyle Modifications in Children at Cardiovascular Risk
Francesca Viazzi, Paola Rebora, Marco Giussani, Antonina Orlando, Andrea Stella, Laura Antolini, Maria Grazia Valsecchi, Roberto Pontremoli and Simonetta Genovesi

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Increased serum uric acid levels blunt the antihypertensive efficacy of lifestyle modifications in children at cardiovascular risk

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Short title: Hypertension, uric acid and lifestyle modifications in children
Expanded materials and methods

Subjects
We studied a cohort of children, consecutively referred by their primary care paediatricians to our Unit for Cardiovascular Risk Assessment in Children, because of evidence of elevated BP values and/or excess of weight and/or dyslipidemia and/or a positive family history of CV disease. The latter was defined as the presence in one or both of the parents of at least one among: hypertension, type 2 diabetes, dyslipidaemia, early ischaemic heart disease, and cerebrovascular disease.

We considered an initial cohort of 486 subjects between January 2005 and January 2014 which at the first assessment showed at least one among these conditions: 1) elevated BP values, 2) excess of weight, 3) dyslipidaemia 4) positive family history of CV disease. None of these children were affected by impaired glucose tolerance, diabetes, chronic kidney disease or other forms of secondary hypertension.

After the first visit, children and their parents was offered to be included in a study involving a baseline assessment, (see Anthropometric parameters and blood pressure and Biochemical parameters paragraphs) lifestyle changes recommendations, including nutrition and physical activity (see Recommended lifestyle modifications paragraph) and a follow-up revaluation after about 1.5 years (follow-up assessment). Between the baseline and the follow-up assessment, periodic visits were performed every three months, during which the children’s anthropometric parameters were recorded, information regarding treatment adherence was obtained by a non-structured interview of the parent, and any necessary changes in the dietary regime were introduced. A total of 278 families agreed to participate in the study and performed the complete protocol. Thirty subjects were excluded because of incomplete carrying out of the requested examinations, ending up with a final cohort of 248 subjects (mean follow-up=1.5 years, SD=0.66 years). Informed consent was obtained from the children’s parents, and the Local Ethical Committee approved the study protocol.

Anthropometric parameters and blood pressure
Height, weight and waist circumference (WC) were measured in children according to standard procedure. Weight was approximated to the nearest 100 gram, while height precision was approximated to the nearest 0.5 cm. BMI was calculated as weight (kg)/height (m)^2. BMI z-scores were calculated using the Centres for Disease and Control prevention charts available at http://www.cdc.gov/nchs/. Weight class was defined according to the tables of the International Obesity Task Force (1) distinguishing among: normal weight (NW), overweight (OW) and obese (OB) classes. Waist circumference was measured to the nearest 0.5 cm by a non-elastic flexible tape in standing position. The tape was applied horizontally midway between the lowest rib margin and the iliac crest. Waist-to-height- ratio (WtHr) was calculated dividing WC by height. Blood pressure was measured using an aneroid sphygmomanometer with the appropriate cuff for the children's upper arm size. This sphygmomanometer was calibrated at baseline and twice a month with a mercury sphygmomanometer. Measurements were performed after at least 5 min of rest. Systolic BP (SBP) was defined by the first Korotkoff sound (appearance of sounds) and diastolic BP (DBP) by the fifth Korotkoff sound (disappearance of sounds). Blood pressure values were approximated to the nearest 2 mmHg. Blood pressure measures were taken three times (at 3-5 min intervals) and SBP and DBP percentiles and z-scores were calculated according to the nomograms recommended by the National High Blood Pressure Education Program (NHBPEP) Working Group on High Blood Pressure in Children and Adolescents (2). The children were classified according to the percentile of the mean of the three measurements as follows. Normotensive (NT) if both SBP and DBP percentiles were less than the 90th; pre-hypertensive (PH) if the SBP and/or DBP percentile was greater than or equal to the 90th, but both were less than the 95th; hypertensive (HYP) if the SBP and/or DBP percentile was greater than or equal to the 95th, but both were less than the 99th; HYP ≥ 99th if the SBP and/or DBP percentile was greater than or equal to the 99th.
Children were defined with dyslipidemia showed total Cholesterol > 5.17 mmol/l or LDL-cholesterol > 0.38 mmol/l or triglycerides > 1.48 mmol/l or HDL-cholesterol < 0.91 mg% \(^3\).

**Biochemical parameters**

At baseline, anthropometric parameters, BP and hematochemical variables were evaluated for all children enrolled in this study. Blood samples were taken from all subjects after a 12-hour fasting period in order to measure plasma glucose and insulin, and SUA, total cholesterol, triglycerides, and high density lipoprotein (HDL) cholesterol concentrations. Plasma glucose was measured by a glucose oxidase method and insulin was evaluated by chemiluminescent immunometric assay. HOMA index was calculated by dividing the product of plasma insulin (µU/ml) and plasma glucose (mmol/L) by 22.5 \(^4\).

Glomerular filtration rate was estimated (eGFR) by means of the updated Schwartz formula using serum creatinine and height measurements and a k constant of 0.413 \(^5\). Serum creatinine level was measured using the Jaffe method referable to the standardized reference measurement procedure (Isotope dilution mass spectrometry-IDMS), as recommended.

**Recommended lifestyle modifications**

Changes in lifestyle were proposed involving the caregivers of the child and taking into consideration the actual difficulties and resources of the family. Physical activity and eating habits were accurately assessed, by means of an interview with one of the parents administered by a single expert nutritionist.

With regard to physical activity, all children were advised to perform at least two hours per week of structured physical activity \(^6\). Furthermore, they were advised to increase the time dedicated to movement-play and to reduce the time spent in sedentary activities, particularly those involving videogames or TV-watching, to no more than one hour daily, following the recommendations of the Società Italiana di Pediatria (Italian Society of Pediatrics) (http://sip.it/pianeta-sip/stati-generali-della-pediatria/cambiare-gli-stili-di-vita-ecco-come-la-sip-presenta-la-piramide-dellattivita-motoria).

Concerning dietary treatment, a nutritional analysis was performed in order to prepare a personal dietary scheme for each child, developed by dedicated software (DIETOSYSTEM, DS MEDICA MILANO). In the dietary recommendations the following clinical conditions were considered (separately or in association with one another):

- **Overweight.** OW or OB subjects were supplied with a weekly dietary scheme, whose caloric content had been calculated according to the basal metabolic rate, obtained by the Schofield equation \(^7\) and on the basis of functional metabolism \(^8\). In younger children a balanced dietary model was proposed, equal to the calculated energy expenditure (normocaloric regime), whereas in adolescents with severe overweight a mildly hypocaloric regime (-10%) was suggested.

- **High blood pressure.** In hypertensive or pre-hypertensive subjects a diet with reduction of salt intake was proposed (salt intake less than 5 grams a day, i.e., 2 grams of sodium, as advised by the World Health Organization (Prevention of cardiovascular disease: guidelines for assessment and management of cardiovascular risk, Geneva, World Health Organization, 2007 http://whqlibdoc.who.int/publications/2007/9789241547178_eng.pdf).

- **Dyslipidemia.** To subjects with dyslipidemia, in addition to a decrease in excess weight if present, a diet with limitation of cholesterol and saturated fatty acids was given. The objective was to provide an amount of cholesterol not exceeding 100 mg per 1000 kcal of energy. Saturated fatty acids did not exceed one third of the 30% of the calories provided by lipids. The intake of mono- and polyunsaturated fatty acids by consuming olive oil and fish was encouraged \(^9\).

In general it was advised to all mothers to increase the consumption of fruit, vegetables, milk and dairy products, and to reduce the intake of simple sugars and eliminate soft drinks.
**Statistical Methods**

The cohort was categorized into groups according to hypertension category at baseline. The continuous variables were described by median and quartiles and compared by the analysis of variance. The categorical variables were described by percentages and compared by the Chi-square test. Box-plots and bar-plots were used to describe the distribution of SBP z-score, BMI z-score, SUA, BP category and weight class at baseline and follow-up. SBP z-score, BMI z-score and SUA modifications after the follow-up were evaluated by paired t-test, while BP category and weight class by the ordinal logistic model, as extension of the McNemar test for categorical data with more than two levels (10).

The factors associated with SUA increase (defined as presence of a positive difference between follow-up and baseline) during follow-up were evaluated by a logistic model, including age, puberty, gender, BMI and SBP z-score and SUA level at baseline as covariates. Multiple linear models were used to assess the influence of age, puberty, gender, BMI z-score (or Waist to Height ratio), SBP z-score, SUA and HOMA index values at baseline on SBP z-score at follow-up. The logistic model was used to assess the influence of age, puberty, gender, BMI and SBP z-score, SUA and HOMA index values on BP category at follow-up; in particular HYP and HYP \( \geq 99^{th} \) percentile have been compared with NT category in two separate models.
Supplemental References


S1. Supplemental Figure 1. Serum uric acid behavior after lifestyle modifications

A) Distribution of uric acid at baseline and follow-up by box-plot, B) Distribution of the difference between the uric acid at follow-up and baseline by histogram.

In box-plots the inner line indicates the median and the cross indicates the mean value; the whiskers are located at the maximum and minimum observation (outside observations indicated with dots are those out of the 1.5 × interquartile range). Serum uric acid in mg/dL, to convert mg/dL in µmol/L multiply by 59.48.
**S2. Supplemental Table 1.**

Factors associated with serum uric acid variations after lifestyle modifications

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uric Acid mg/dl (59.48 µmol/L), Baseline</td>
<td>0.42(0.30-0.59)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age y, Baseline*</td>
<td>1.29(1.07-1.56)</td>
<td>0.0072</td>
</tr>
<tr>
<td>Puberty, Baseline</td>
<td>1.32(0.50-3.48)</td>
<td>0.5713</td>
</tr>
<tr>
<td>Switch to Puberty at Follow-Up</td>
<td>2.87(1.24-6.65)</td>
<td>0.0141</td>
</tr>
<tr>
<td>Gender, girls</td>
<td>0.41(0.22-0.75)</td>
<td>0.0042</td>
</tr>
<tr>
<td>BMI z-score, Baseline</td>
<td>1.79(1.22-2.63)</td>
<td>0.003</td>
</tr>
<tr>
<td>Delta BMI z-score, Baseline- Follow-Up</td>
<td>0.30(0.13-0.71)</td>
<td>0.0062</td>
</tr>
<tr>
<td>SBP z-score, Baseline</td>
<td>1.02(0.76-1.37)</td>
<td>0.8906</td>
</tr>
</tbody>
</table>

*Values centered at the median values (10 years)

CI: confidence interval, BMI: body mass index, SBP: systolic blood pressure
S3. Supplemental Table 2. Predictors of blood pressure category after lifestyle modifications

<table>
<thead>
<tr>
<th>Variable</th>
<th>HYP (n=28) vs NT (n=178)</th>
<th>≥ 99\textsuperscript{th} (n=13) vs NT (n=178)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Age, y, Baseline*</td>
<td>0.96(0.67;1.38)</td>
<td>0.8393</td>
</tr>
<tr>
<td>Puberty, Baseline</td>
<td>2.93(0.52;16.57)</td>
<td>0.2219</td>
</tr>
<tr>
<td>Switch to Puberty at Follow-Up</td>
<td>3.80(0.88;16.46)</td>
<td>0.0736</td>
</tr>
<tr>
<td>Gender, girls</td>
<td>1.28(0.40;4.11)</td>
<td>0.6717</td>
</tr>
<tr>
<td>BMI z-score, Baseline</td>
<td>5.91(1.87;18.67)</td>
<td>0.0025</td>
</tr>
<tr>
<td>Delta BMI z-score, Baseline-Follow-Up</td>
<td>0.02(0.01;0.15)</td>
<td>0.0002</td>
</tr>
<tr>
<td>SBP z-score, Baseline</td>
<td>3.84(2.08;7.08)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Uric Acid mg/dl (59.48 µmol/L), Baseline</td>
<td>1.26(0.74;2.17)</td>
<td>0.3942</td>
</tr>
<tr>
<td>Delta Uric Acid mg/dl (59.48 µmol/L), Baseline-Follow-Up</td>
<td>1.62(0.70;3.78)</td>
<td>0.2615</td>
</tr>
<tr>
<td>HOMA index, Baseline*</td>
<td>0.78(0.48;1.25)</td>
<td>0.2955</td>
</tr>
</tbody>
</table>

*values centered at the median values (10 years for age and 2.3 for HOMA index)

NT: normotensive, PH: pre-hypertensive, HYP: hypertensive, ≥ 99\textsuperscript{th}: hypertensive ≥ 99\textsuperscript{th} percentile, BMI: body mass index, SBP: systolic blood pressure, CI: confidence interval