Increased childhood BMI is associated with young adult serum uric acid levels: a linkage study from Japan

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BACKGROUND: Growth pattern in early life is one of the most important factors affecting the pathogenesis of metabolic-associated diseases. The associations between serum uric acid (SUA) and hypertension, kidney disease, and coronary heart disease have been recognized. We investigated the association between increased BMI during childhood and adult SUA levels in Japan.

METHODS: We included 298 children with health examination data between 1981 and 2002 who had also undergone physical examinations after reaching early adulthood (approximately 27 y old). Subjects were divided into sex-specific tertiles based on the difference in their BMI (DBMI) over a 6-y period (6–12 y of age). The association between the three DBMI groups and SUA in adults was analyzed.

RESULTS: The predicted average SUA level in adults from the high DBMI group was 5.32 mg/dl after adjustment for related factors in a combined sex analysis. This was significantly higher than among the low DBMI group.

CONCLUSION: Excessive BMI increases during childhood led to young adult SUA elevation even after adjusting for several factors. Lifestyle in early life may be a strong predictor of future uric acid metabolism and the resulting disease risk.

It has been well recognized that uric acid causes gout and is one of the markers for several lifestyle-related diseases. Since the 1950s, the associations between serum uric acid (SUA) and hypertension (1), kidney diseases (2), and coronary heart disease (3) have been recognized. Increased SUA level may be an independent risk factor for chronic kidney disease (4,5), stroke (6), coronary heart disease (7), and cardiovascular diseases (8). Moreover, some studies have shown that SUA is a risk factor for metabolic syndrome among children and adolescents (9,10). These findings suggest that prevention of SUA level elevation in early life has a potential protective effect.

The association between SUA and obesity is also well known. Overweight and obesity among children have been globally recognized as a public health concern. Recently, growth pattern during early life, not merely a single assessment of childhood body weight or BMI, is considered to be one of the most important risk factors for the pathogenesis of metabolic-associated diseases (11–17). However, to the best of our knowledge, no study has evaluated the association between early-life growth patterns and SUA levels later in life. Therefore, we investigated the association between increased BMI during childhood and subsequent SUA level during early adulthood in Japan.

METHODS

Study Population and Design

The Japanese law mandates annual physical examinations for students in all schools in Japan. We obtained anonymous secondary data from these examinations from towns A and B in Nagano Prefecture, with populations of approximately 11,000 and 5,000, respectively, in 2015. Previously, we performed a similar linkage study in town A to investigate the association between an increase in BMI during 6 y of primary school and blood pressure in adolescents (18). Data collection was started in 1981 in town A and 1996 in town B. Town A has one and town B has two primary schools, which were attended by almost all children living in this area. The eligible study population comprised 1,711 children (850 boys and 861 girls) who entered primary school (aged 6 y) by 2002. Of these, 1,621 (809 boys and 812 girls) graduated from the same school when they were 12 y old. After the age of 18 y, 298 (18.4%; 144 boys and 154 girls) remained in the same town or a neighboring area and received a health examination, including blood tests at the local hospital (Saku Central Hospital) at least once.

Physical Examinations and Laboratory Measurements

Regular mandatory school physical examinations included a medical interview, height, and weight each school year. Height and weight were measured by a school nurse and rounded to the nearest integer. BMI was calculated as weight in kilograms divided by the square of height in meters. To confirm the representativeness of the sample, we converted BMI to BMI SD scores (BMI-SDSs) according to the LMS method (19,20). The mean ± SD of BMI-SDSs for all first-grade students (aged 6 or 7 y) were −0.10 ± 0.87. (boys, −0.12 ± 0.91; girls, −0.08 ± 0.83). The BMI-SDS for sixth-grade students (aged 11 or 12 y) were −0.06 ± 1.03 (boys, −0.01 ± 1.03; girls, −0.11 ± 1.04). The BMI-SDS analysis verified that the subjects were representative of Japanese school children in terms of BMI.

DBMI was calculated for each subject and divided into sex-specific tertiles (low, moderate, and high for the first, second, and third tertiles, respectively). These tertiles were used as an indicator of physical change. Japanese primary schools include first through sixth grades;

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thus, the use of DBMI during this period is convenient for continuous health assessment. Guardians of children who were overweight or believed to be unhealthy in any way after the examination were advised to seek medical advice. However, no systematic interventions relating to obesity in children were implemented during the observation period.

The mandated regular physical examination for adults included blood tests, blood pressure, and a chest X-ray in addition to the aforementioned items on the school health examination. SUA and Cre were measured using the uricase–peroxidase method and creatinase–sarcosine oxidase–peroxidase method, respectively (Hitachi 736-50E and Hitachi 7600-300, respectively; Hitachi High-Technologies Corporation, Tokyo, Japan). Blood pressure was measured by nurses using an automated oscillometric sphygmomanometer (ES-H51T3 or ES-H55; Terumo Corporation, Tokyo, Japan).

Statistical Analysis

For comparing the tertiles of DBMI, ANOVA and post hoc tests with Bonferroni correction were used for continuous variables, and Pearson's chi-square tests were used for categorical variables. Next, we conducted a linear regression analysis to examine the association between DBMI and SUA among young adults after adjusting for other covariates. Model 1 was used for the crude analysis of the association between DBMI and SUA. Model 2 included BMI, year of entrance, and area of residence during the first grade as covariates. Sex was also adjusted for in analyses that included boys and girls. Model 3 included BMI, Cre, systolic blood pressure (SBP), and age at the adult follow up, in addition to the variables in Model 2. SUA and all covariates except for sex and area of residence were treated as continuous variables. Using these regression equations, predicted SUA levels were calculated by simply substituting a value (0, 1, or 2) for the explanatory variable (low, moderate, or high DBMI, respectively) and substituting average values for the other independent variables (with the margins command in STATA).

We conducted three additional analyses. First, we only included subjects who had information on alcohol consumption at the adult examination (n = 236) and repeated the analysis with adjustment for alcohol consumption and the variables included in Model 3. Second, the representativeness of the sample was assessed by a comparison of baseline characteristics between the group with childhood data alone and this study population using Student's t-test. Third, SUA levels were classified as <7 mg/dl and ≥7 mg/dl, using the cutoff level for hyperuricemia that was recommended by the Japanese Society of Gout and Nucleic Acid Metabolism (21,22), and a logistic regression analysis was conducted using the same covariates as Models. Thirty-three of the 34 subjects with a high SUA level were males; therefore, this logistic regression analysis was only conducted for males.

All analyses were performed with STATA, version 12.0 (STATA, College Station, TX). All CIs were estimated at the 95% level, and P values of <0.05 were considered statistically significant.

Ethical Considerations

All data provided by Saku Central Hospital were anonymized and rendered unlinkable after they were given an identification number for research. Thus, the researchers could not access personal information for any of the subjects. Therefore, the requirement for informed consent was waived according to the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan. This study was approved by Saku Central Hospital's Ethics Committee (approval number: 31) and the Ethics Committee of Toho University, Faculty of Medicine (approval number: 25011).

RESULTS

Table 1 shows subjects' baseline characteristics by tertile of difference in BMI (DBMI). The mean ± SD of DBMI between the first and sixth grades was 2.9 ± 2.4 in boys and 2.7 ± 1.9 in girls (P = 0.82, Mann–Whitney U-test). Most baseline variables, except for area of residence during the first grade overall and for boys, differed among tertiles of DBMI.

Figure 1 shows the distribution of SUA after reaching adulthood. The peak totals reached 6.0–6.49 mg/dl for boys and 4.0–4.49 mg/dl for girls. **Table 2** shows the characteristics at the last health examination after 18 y of age (mean age: 26.7 y) by tertile of DBMI. There was a significant difference in young adult SUA between the tertiles of DBMI. Among both boys and girls, SUA differed by approximately 0.4 mg/dl between the low and high DBMI groups. BMI and weight maintained similar tendencies as that of SUA between the three groups for both sexes.

Table 3 shows the predicted SUA levels from the result of the sex-combined and sex-stratified univariate (unadjusted) regression analysis. There was no statistical interaction between sex and DBMI for SUA (P = 0.45). The high DBMI group had a higher adult SUA level than the low DBMI group for the combined sex analysis (Model 1, P = 0.009). These associations persisted after adjusting for childhood BMI, year of entrance to the primary school, and area of residence (Model 2, P = 0.001). When we further adjusted for adult BMI, serum creatinine (Cre), SBP, and age (Model 3), the positive association between DBMI and SUA was attenuated but remained statistically significant (P = 0.014). Further adjustment by alcohol consumption did not change the results substantially. The adjusted difference for the high DBMI group in the combined sex analysis was 0.39 (95% confidence interval (CI): 0.04–0.73).

The childhood baseline of each group with and without the adult data was compared (**Supplementary Table S1** online). Majority of the data were similar between the two groups. However, year of entrance and area of residence were different (P < 0.001 and P = 0.001, respectively) and the DBMI was marginal (P = 0.052). The results of the univariate and multivariate logistic regression analysis, in which the SUA cutoff level was 7 mg/dl using the same models described above, were not statistically significant (**Supplementary Table S2** online).

DISCUSSION

The present study demonstrated that higher DBMI among primary school students is associated with increased SUA level in young adults compared with lower DBMI. The association between DBMI groups and young adult SUA levels was

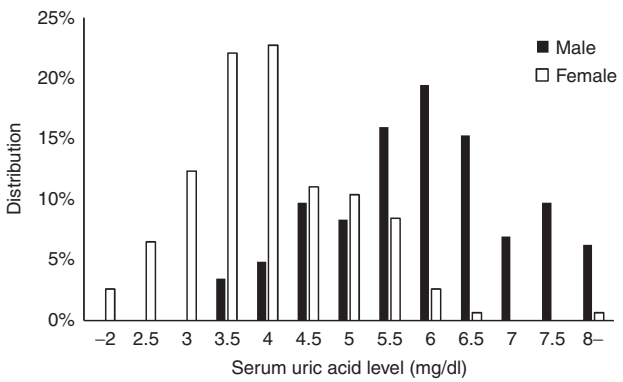

Figure 1. The distribution of SUA after reaching early adulthood (n = 298). Boys: black bar; Girls: white bar.

Table 1. Comparison of physical growth and the associated factors during childhood in all subjects and for three groups of study participants with different degrees of BMI change between first and sixth grade and boys and girls as independent groups

			All	Difference of BMI group[a]			
		Grade	Mean ± SD or *n* (%)	Mean ± SD or *n* (%)	Mean ± SD or *n* (%)	Mean ± SD or *n* (%)	*P*[†]
All			*n* = 298	Low (*n* = 99)	Moderate (*n* = 99)	High (*n* = 100)	
	DBMI (kg/m^2)	1st-6th	2.8 ± 2.1	0.9 ± 0.5	2.3* ± 0.5	5.3* ± 1.8	<0.001
	BMI (kg/m^2)	1st	15.6 ± 1.6	15.2 ± 1.3	15.4 ± 1.4	16.2* ± 1.9	<0.001
		6th	18.4 ± 3.1	16.1 ± 1.4	17.6* ± 1.4	21.4* ± 3.0	<0.001
	Height (cm)	1st	115.1 ± 4.8	113.6 ± 5.4	115.7* ± 3.9	116.1* ± 4.6	<0.001
		6th	144.3 ± 6.8	141.1 ± 7.7	145.3* ± 5.4	146.5* ± 6.1	<0.001
	Weight (kg)	1st	20.7 ± 3.1	19.7 ± 2.9	20.6 ± 2.5	21.9* ± 3.6	<0.001
		6th	38.6 ± 8.6	32.2 ± 5.3	37.3* ± 4.6	46.2* ± 8.6	<0.001
	Year of entrance						
	1981–1990		176 (59.1%)	64 (64.6%)	63 (63.6%)	49 (49.5%)	0.042
	1991–2002		122 (40.9%)	35 (35.4%)	36 (36.4%)	51 (50.5%)	
	Living area at 1st grade						
	A[b]		248 (83.2%)	81 (81.8%)	87 (87.9%)	80 (80.0%)	0.298
	B		50 (16.8%)	18 (18.2%)	12 (12.1%)	20 (20.0%)	
Boys			*n* = 144	Low (*n* = 48)	Moderate (*n* = 48)	High (*n* = 48)	
	DBMI (kg/m^2)	1st-6th	2.9 ± 2.4	0.9 ± 0.6	2.2* ± 0.4	5.7* ± 2.0	<0.001
	BMI (kg/m^2)	1st	15.6 ± 1.5	15.3 ± 1.5	15.3 ± 1.4	16.1* ± 1.6	0.01
		6th	18.5 ± 3.1	16.2 ± 1.5	17.5 ± 1.4	21.8 ± 2.9	<0.001
	Height (cm)	1st	115.4 ± 5.0	113.9 ± 5.8	115.8 ± 3.9	116.5* ± 4.9	0.03
		6th	143.2 ± 7.0	140.9 ± 8.2	143.3 ± 4.9	145.5* ± 6.9	0.005
	Weight (kg)	1st	20.8 ± 3.2	19.9 ± 3.3	20.6 ± 2.4	22.0* ± 3.6	0.005
		6th	38.3 ± 9.0	32.4 ± 6.0	36.0* ± 4.0	46.5* ± 9.2	<0.001
	Year of entrance						
	1981–1990		87 (60.4%)	36 (75.0%)	27 (56.3%)	24 (50.0%)	0.033
	1991–2002		57 (39.6%)	12 (25.0%)	21 (43.7%)	24 (50.0%)	
	Living area at 1st grade						
	A[b]		123 (85.4%)	45 (93.8%)	40 (83.3%)	38 (79.2%)	0.106
	B		21 (14.6%)	3 (6.2%)	8 (16.7%)	10 (20.8%)	
Girls			*n* = 154	Low (*n* = 51)	Moderate (*n* = 51)	High (*n* = 52)	
	DBMI (kg/m^2)	1st-6th	2.7 ± 1.9	0.8 ± 0.5	2.4* ± 0.5	4.9* ± 1.4	<0.001
	BMI (kg/m^2)	1st	15.6 ± 1.7	15.2 ± 1.2	15.4 ± 1.4	16.2* ± 2.1	0.004
		6th	18.3 ± 3.0	16.0 ± 1.3	17.8* ± 1.5	21.1* ± 3.2	<0.001
	Height (cm)	1st	114.9 ± 4.5	113.3 ± 5.1	115.6* ± 3.8	115.8* ± 4.2	0.007
		6th	145.3 ± 6.5	141.3 ± 7.2	147.2* ± 5.2	147.3* ± 5.1	<0.001
	Weight (kg)	1st	20.6 ± 3.1	19.5 ± 2.5	20.6 ± 2.6	21.8* ± 3.6	<0.001
		6th	38.9 ± 8.3	32.0 ± 4.6	38.6* ± 4.8	45.9* ± 8.1	<0.001
	Year of entrance						
	1981–1990		89 (57.8%)	28 (54.9%)	36 (70.6%)	25 (48.1%)	0.061
	1991–2002		65 (42.2%)	23 (45.1%)	15 (29.4%)	27 (51.9%)	
	Living area at 1st grade						
	A[b]		125 (81.2%)	36 (70.6%)	47 (92.2%)	42 (80.8%)	0.017
	B		29 (18.8%)	15 (29.4%)	4 (7.8%)	10 (19.2%)	

[a]ANOVA and *post hoc* tests with Bonferroni correction were used to compare the differences among the three DBMI groups. [b]The present study has started since 1996 at area B.
*$P < 0.05$ for post-hoc tests with Bonferroni correction using the low group as a reference. [†]*P* values for ANOVA, Pearson's chi-square test or Fisher's exact test.

Table 2. Comparison of physical condition, serum uric acid levels, and associated factors after reaching physical maturity in all study participants and for three groups with different degrees of BMI change between first and sixth grade for boys and girls as independent groups

		All	Difference of BMI group[a]			
		Mean ± SD or *n* (%)	Mean ± SD or *n* (%)	Mean ± SD or *n* (%)	Mean ± SD or *n* (%)	*P*[†]
All		*n* = 298	Low (*n* = 99)	Moderate (*n* = 99)	High (*n* = 100)	
	Age (year)	26.7 ± 5.6	26.9 ± 5.9	26.9 ± 5.7	26.2 ± 5.3	0.58
	BMI (kg/m^2)	22.3 ± 3.9	21.1 ± 3.2	21.3 ± 2.6	24.4* ± 4.7	<0.001
	Height (cm)	164.4 ± 8.7	164.1 ± 8.6	165.5 ± 8.2	163.8 ± 9.3	0.33
	Weight (kg)	60.6 ± 13.7	57.3 ± 12.6	58.4 ± 9.8	66.0* ± 16.2	<0.001
	Cre[b] (mg/dl)	0.7 ± 0.2	0.7 ± 0.2	0.8 ± 0.2	0.7 ± 0.2	0.57
	SBP (mmHg)	111.3 ± 12.9	110.3 ± 13.1	110.4 ± 12.0	113.2 ± 13.3	0.19
	Alcohol consumption[c]					
	Never	142 (60.2%)	38 (52.1%)	47 (61.0%)	57 (66.3%)	0.25
	Sometimes	79 (33.5%)	27 (37.0%)	27 (35.1%)	25 (29.1%)	
	Almost everyday	15 (6.3%)	8 (10.9%)	3 (3.9%)	4 (4.6%)	
	UA(mg/dl)	5.1 ± 1.5	4.9 ± 1.6	5.1 ± 1.4	5.4* ± 1.5	0.03
	–6.9	264 (88.6%)	89 (89.9%)	91 (91.9%)	84 (84.0%)	0.19
	–7.0	34 (11.4%)	10 (10.1%)	8 (8.1%)	16 (16.0%)	
Boys		*n* = 144	Low (*n* = 48)	Moderate (*n* = 48)	High (*n* = 48)	
	Age (year)	27.3 ± 5.6	28.9 ± 5.9	26.5 ± 5.3	26.5 ± 5.5	0.056
	BMI (kg/m^2)	23.4 ± 4.0	22.5 ± 3.5	22.0 ± 2.3	25.6* ± 4.8	<0.001
	Height (cm)	171.2 ± 5.8	170.6 ± 5.8	171.9 ± 5.6	171.1 ± 6.1	0.54
	Weight (kg)	68.6 ± 13.1	65.6 ± 12.2	65.1 ± 8.1	75.1* ± 15.5	<0.001
	Cre[b] (mg/dl)	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.86
	SBP (mmHg)	117.9 ± 11.2	116.4 ± 11.6	116.8 ± 10.0	120.6 ± 11.7	0.13
	Alcohol consumption[c]					
	Never	56 (47.9%)	13 (36.1%)	20 (52.6%)	23 (53.5%)	0.25
	Sometimes	49 (41.9%)	16 (44.4%)	16 (42.1%)	17 (39.5%)	
	Almost everyday	12 (10.2%)	7 (19.4%)	2 (5.3%)	3 (7.0%)	
	UA(mg/dl)	6.2 ± 1.2	6.0 ± 1.2	6.0 ± 1.2	6.5* ± 1.0	0.02
	–6.9	111 (77.1%)	38 (79.2%)	40 (83.3%)	33 (68.8%)	0.25
	–7.0	33 (22.9%)	10 (20.8%)	8 (16.7%)	15 (33.2%)	
Girls		*n* = 154	Low (*n* = 51)	Moderate (*n* = 51)	High (*n* = 52)	
	Age (year)	26.1 ± 5.6	25.0 ± 5.2	27.4 ± 6.1	25.9 ± 5.3	0.09
	BMI (kg/m^2)	21.3 ± 3.6	19.8 ± 2.4	20.5 ± 2.6	23.4* ± 4.3	<0.001
	Height (cm)	158.1 ± 5.7	157.9 ± 5.8	159.4 ± 4.9	157.0 ± 6.1	0.09
	Weight (kg)	53.1 ± 9.3	49.5 ± 6.6	52.2 ± 6.5	57.7* ± 11.7	<0.001
	Cre (mg/dl)	0.6 ± 0.1	0.6 ± 0.1	0.6 ± 0.1	0.6 ± 0.1	0.23
	SBP (mmHg)	105.1 ± 11.1	104.6 ± 11.9	104.3 ± 10.5	106.4 ± 10.9	0.59
	Alcohol consumption[c]					
	Never	86 (72.3%)	25 (67.6%)	27 (69.2%)	34 (79.1%)	0.81
	Sometimes	30 (25.2%)	11 (29.7%)	11 (28.2%)	8 (18.6%)	
	Almost everyday	3 (2.5%)	1 (2.7%)	1 (2.6%)	1 (2.3%)	
	UA(mg/dl)	4.2 ± 1.0	3.8 ± 1.1	4.3 ± 0.9	4.4* ± 1.0	0.02
	–6.9	153 (99.4%)	51 (100%)	51 (100%)	51 (98.1%)	1.000
	–7.0	1 (0.6%)	0 (0%)	0 (0%)	1 (1.9%)	

[a]ANOVA and post-hoc tests with Bonferroni correction were used to compare the differences between the three DBMI groups. [b]Creatinine data was missing from one boy in the high BMI change group. [c]Data were available for 117 boys and 119 girls.
SBP, systolic blood pressure.
*$P < 0.05$ for post-hoc tests with Bonferroni correction using the low group as a reference. [†]*P* values for ANOVA, Pearson's chi-square test or Fisher's exact test.

Table 3. Regression analysis results of associations in differences in BMI between first and sixth grade with serum uric acid after reaching physical maturity

					Model2		Model3	
		Adjusted Factors	None (crude analysis)		Sex[b], BMI, year and living area at 1st grade		model 2 + BMI, age, SBP and Cre at last follow-up	
			Predicted SUA level	(95% CI)	Predicted SUA level	(95% CI)	predicted SUA level	(95% CI)
All	DBMI group	Low	4.86	(4.57, 5.15)	4.87	(4.65, 5.09)	4.91	(4.71, 5.12)
		Moderate	5.10	(4.81, 5.39)	5.11	(4.89, 5.33)	5.14	(4.93, 5.34)
		High	5.42*	(5.13, 5.71)	5.40*	(5.18, 5.63)	5.32*	(5.11, 5.54)
Boys	DBMI group	Low	5.95	(5.62, 6.28)	5.99	(5.65, 6.34)	6.05	(5.72, 6.37)
		Moderate	5.96	(5.63, 6.29)	5.96	(5.62, 6.30)	6.01	(5.69, 6.33)
		High	6.54*	(6.21, 6.87)	6.50*	(6.15, 6.84)	6.40	(6.06, 6.74)
Girls	DBMI group	Low	3.83	(3.56, 4.11)	3.85	(3.57, 4.14	3.95	(3.68, 4.21)
		Moderate	4.29*	(4.02, 4.57)	4.29	(4.01, 4.57)	4.28	(4.02, 4.54)
		High	4.38*	(4.11, 4.66)	4.37*	(4.09, 4.65)	4.29	(4.01, 4.56)

[a]No creatinine data was available for one boy; therefore, data from 297 participants were analyzed in Model 3. [b]Sex was adjusted for only sex-combined analysis.
*$P < 0.05$ for univariate or multivariate regression analysis compared to the low group as a reference.

significant even after adjusting for baseline and adult BMIs. This association suggests that increases in BMI during childhood have an effect on SUA elevation, irrespective of the specific value of BMI.

The results of the sex-combined and sex-stratified analyses were similar, with a few exceptions. We did not observe a statistical interaction between sex and DBMI, and there was no difference in coefficients in the multivariate regression analysis between men and women. Small sample size may be one reason that some results of the sex-stratified adjusted multivariate regression analysis were not statistically significant.

It is possible that the study results are affected by residual confounders. SUA level is affected by alcohol consumption (23). Our results did not change after we adjusted for alcohol consumption but the number of subjects with data available for this analysis was relatively small. In addition, some medications affect SUA levels. Antihypertensive medications, such as calcium antagonists (24), angiotensin-converting enzyme inhibitors (25), and angiotensin II receptor blockers (26), decrease SUA level. Diuretics (25), β-blockers (27), and cyclosporine increase SUA level (28). However, since the subjects in our study were young, there may be few patients with serious diseases. There were only two hypertension patients and two diabetes patients receiving medication in our sample. When we conducted a multivariate regression analysis excluding the subjects who took medication for hypertension or diabetes, the results were not different (data not shown).

We found that SUA levels were associated with a BMI increase in childhood even after adjusting for BMI in adulthood. This suggests an SUA elevation pathway that is independent of adult obesity. One possibility is that dietary habits that result in excessive increases in BMI in childhood continue into adulthood, with a consequent increase in purine consumption.

The results of the multivariate logistic regression analysis did not show a statistically significant association between DBMI tertile in childhood and hyperuricemia (SUA ≥ 7 mg/dl) in adults. Perhaps a larger sample size would reveal a significant association. The mean SUA level among the male high DBMI group was 6.5 ± 1.0 mg/dl in our study. A previous study demonstrated that even lower SUA levels were linearly associated with chronic kidney disease (29) and metabolic syndrome prevalence (30). Moreover, a cohort study concluded that higher SUA levels were an independent predictor of cardiovascular disease mortality, even for SUA >6.27 mg/dl (373 μmol/l/l) among males (31). Therefore, the SUA levels in our sample, particularly in the highest DBMI group for boys, could be a risk factor for cardiovascular disease in the future.

Strengths and Limitations

An important strength of this study is that it is one of the few investigations of childhood BMI and young adult SUA that use a longitudinal dataset. It is important to focus on childhood because early lifestyle trends often result in the development of a behavior that has a significant influence later in life. As the measurement protocol had been well standardized during the long study period, the dataset was reliable.

The study also has some limitations. First, the study sample may not be a representative of the entire Japan because the study areas included only a part of the Nagano Prefecture. Second, we did not have information regarding factors related to SUA, such as current diet and exercise patterns. Instead, we adjusted for adult BMI, Cre, and SBP to partly reflect the subjects' daily lives. Third, it is not evident whether DBMI between the first and sixth grades was representative of the change in BMI during childhood. Further studies are needed to determine the representative DBMI during childhood. Fourth, we could not determine the mechanism of SUA elevation among people who showed increased BMI during childhood in the present study. The elucidation of the mechanism for this association should be a topic for future research.

We found that a large BMI increase in childhood was associated with elevated young adult SUA level after adjusting for BMI at baseline and in early adulthood. Additional researches on increases in BMI are required to clarify the mechanisms that may lead to later metabolic-related diseases.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/pr

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AUTHOR CONTRIBUTIONS

Study concept and design: E.K., Y.M., T.O., Y.N.; collection and assembly of data: H.K., A.N., F.M., H.U., Y.N.; statistical analysis: E.K., Y.M., Y.N.; manuscript write-up: E.K., Y.M., T.O., Y.N.; manuscript review and revision: E.K., Y.M., T.O., Y.N., A.N., H.U., Y.N., H.K., F.M.; final approval of the article: E.K., Y.M., T.O., Y.N., A.N., H.U., Y.N., H.K., F.M.

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