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Relationships of adult body height and BMI status to hyperuricemia in general Japanese male population: The Nagasaki Islands Study

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Several studies have reported that adult height is positively associated with risk of cancer on the hypothesis that height is a marker of childhood physical condition, and others that the risk of cancer was higher for participants with higher serum uric acid levels. We conducted a cross sectional study of 1,350 men aged 30-89 years undergoing general health check-ups. Since body mass index (BMI) is regarded as a surrogate marker of current physical condition for hyperuricemia risk, we performed a stratified analysis of this risk based on BMI. Of the total study population, 368 men were diagnosed with hyperuricemia (serum uric acid>7.0mg/dl), and a positive association between height and prevalence of hyperuricemia was detected, which was independent of classical cardiovascular risk factors. The adjusted odds ratio (OR) and 95% confidence interval (CI) for hyperuricemia of an increment of 1 SD for height (6.7cm) was 1.17 (CI: 1.01-1.35). Analysis of this association according to BMI status (non-overweight or overweight) disclosed a positive association only for non-overweight men. The adjusted ORs and CIs for hyperuricemia of an increment of 1 SD for height were 1.26 (1.05-1.52) for non-overweight and 1.01 (0.79-1.29) for overweight subjects. Height was found to be positively associated with the risk of hyperuricemia for Japanese men, especially non-overweight men (BMI<25kg/^{2}) which suggests that childhood social and physical conditions may contribute to the development of hyoeruricemia in adulthood.

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1. Introduction

Height is an easily measured variable, and is thought to be determined during childhood and adolescence by genetic predisposition, nutrition, physical and social environments, as well as other factors.[1,2] Recent studies have confirmed that taller people are at greater risk of death from several organ specific malignancies such as melanoma and cancer of the pancreas, breast, ovary, prostate and colorectum.[3-7]

Another study reported that the prevalence of malignant neoplasms was higher for participants with gout than those without gout.[8]

However, no published study thus far has examined the possible association between height and hyperuricemia in a general population, although the prevalence of hyperuricemia was reportedly higher among obese than non-obese indi-

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viduals.[9,10] For an investigation of the association between height and elevated serum uric acid, BMI status should thus be taken into account.

We hypothesized that height is positively associated with risk of hyperuricemia (serum uric acid>7.0mg/dl) especially for non-overweight (BMI<25kg/m^2) because status of overweight (BMI≥25kg/m^2) might reduce the effects of childhood social and physical conditions on hyperuricemia.

To examine this hypothesis, we conducted a cross-sectional study of a general population of Japanese men who received general health check-ups between 2005 and 2012.

2. Material and Methods

2.1 Participants

The survey population included 1,538 men aged 30 to 89 years, all residents of the western rural community of the Goto Islands, who participated in this study between 2005 and 2012. A total of 32 individuals with missing data and 156 individuals with a history of cardiovascular disease were excluded, leaving 1,350 men for enrolment in this study. The mean age of the study population was 64.8 years (±10.7 SD; range 30-89). Written consent forms were available in Japanese to ensure comprehensive understanding of the study objectives, and informed consent was signed by the participants. This study was approved by the Ethics Committee for Use of Humans of Nagasaki University (project registration number 0501120073).

2.2 Data collections and laboratory measurements

Body weight and height were measured with an automatic body composition analyzer (BF-220; Tanita, Tokyo, Japan) when blood was drawn.

Fasting blood samples were obtained and the serum was separated and centrifuged after blood coagulation. Serum samples were also obtained in individual siliconized tubes.

Serum triglycerides, HDL cholesterol, aspartate aminotransferase (AST), γ-glutamyltraspeptidase (γ-GTP), HbA_{1c}, serum uric acid, and serum creatinine were measured with standard laboratory procedures. Since the method recently proposed by a working group of the Japanese Chronic Kidney Disease Initiative (JCKDI)[11] does not take the influence of height and weight into account, whereas Horio's method[12] does, we estimated the glomerular filtration rate (GFR) by using both methods. The first method was established with three variations, resulting in: GFR (JCKD) (ml/min/1.73m^2) = 194×(serum creatinine (enzyme method))$^{-1.094}$×(age)$^{-0.287}$. The other method was the one reported by Horio as the following equation: GFR(Horio) (ml/min)= (33-0.065×age –0.493×BMI) ×weight / serum creatinine (enzyme method)× 14.4 for men.

Trained interviewers obtained information on smoking status, drinking status, medical history, and use of antihypertensive agents, medication for diabetes mellitus, and medication for dyslipidemia. HbA_{1c}, as defined by the National Glycohemoglobin Standardization Program (NGSP) was calculated with the following equation, which was recently proposed by a working group of the Japanese Diabetes Society (JDS): HbA_{1c} (NGSP) = HbA_{1c} (JDS) + 0.4%.[13] Presence of diabetes was defined as HbA_{1c} (NGSP) ≥ 6.5%, and/or initiation of glucose-lowering medication or insulin therapy.[14] Hyperuricemia was defined as a serum uric acid level >7mg/dl.[15]

2.3 Statistical analysis

Differences in age-adjusted mean values or prevalence of potential confounding factors by quartile of height were calculated by using covariance or general linear models, while logistic regression models were used for calculating odds ratios (OR) and 95% confidence intervals (CI) for the association of hyperuricemia with body height. In addition, subjects were stratified by BMI status because higher BMI was reported to be associated with hyperuricemia. [9,10]

Three different approaches were used for making adjustments for confounding factors. For Model 1, the data were adjusted only for age. For Model 2, we included other possible confounding factors, namely smoking status (never smoker, former smoker, current smoker), alcohol consumption [non-drinker, current light to moderate drinker (1-6 times/week), current heavy drinker (every day)], body mass index (kg/m^2), diabetes mellitus (no, yes), systolic blood pressure (mmHg), antihypertensive medication use (no, yes), antihyperlipidemic agent use (no, yes), serum triglycerides (mg/dl), serum HDL cholesterol (mg/dl), serum AST (IU/L), and serum γ-GTP serum (IU/L). For Model 3, serum creatinine (mg/dl) was included.

All statistical analyses were performed with the SAS system for Windows (version 9.3; SAS Inc., Cary, NC). All p-values for statistical tests were two-tailed, and values of <0.05 were regarded as statistically significant.

3. Results

Of the 1,350 men taking part in the general health check-up program, 368 were diagnosed with hyperuricemia (serum uric acid>7.0mg/dl). Table 1 shows age-adjusted characteristics for this study population in relation to body height. Current drinker status, serum uric acid, serum creatinine, and estimated glomerular filtration rate (Horio; ml/min) were significantly positively associated, and estimated glomerular filtration rate (JCKD)(ml/min/1.73m^2) inversely associated with body height.

To assess the ability of serum creatinine to modify renal function, we performed an additional analysis of the association between hyperuricemia and chronic kidney disease (CKD) using two different criteria: CKD (JCKD)<60mL/min/1.73m^2, and CKD (Horio)<60mL/min. We found that serum creatinine was a significant determinant of CKD as a risk factor for hyperuricemia in terms of either JCKD or Horio. The age-adjusted ORs (Model 1) were 2.76 (2.09-3.64), P<0.001 for CKD (JCKD) and 3.97 (2.61-6.06), P<0.001 for CKD (Horio). Those associations remained valid even after adjustment for other classical cardiovascular risk factors except for serum creatinine (Model 2). The resultant adjusted ORs were 2.52 (1.89-3.36), P<0.001 for CKD (JCKD) and 3.95 (2.54-6.14), P<0.001 for CKD (Horio). When we made further adjustment for serum creatinine (Model 3), those associations disappeared. The adjusted ORs after this final adjustment were 0.90 (0.58-1.39), P=0.636 for CKD(JCKD) and 1.00 (0.55-1.83), P=0.995 for CKD(Horio).

As shown in Table 2, height was positively associated with risk of hyperuricemia. The age-adjusted OR and CI for hyperuricemia of an increment of 1 SD for height (6.7cm) was 1.26 (1.11-1.44). Even after adjustment for serum creatinine, which resulted in a slight reduction in the OR, the association remained significant. The adjusted OR after further adjustment for other CVD risk factors except serum cratinine (Model 2) and including serum creatinine (Model 3) were 1.24 (1.08-1.43) and 1.17 (1.01-1.35), respectively.

The risk of hyperuricemia for being overweight was subjected to further analysis, which showed that the age-adjusted OR was significant: 1.91(1.49-2.45), (P<0.001).

Table 3 shows the associations between height and risk of hyperuricemia stratified by BMI status (non-overweight or overweight), indicating that height was positively associated with risk of hyperuricemia for non-overweight but not for overweight men. The fully-adjusted ORs were 1.26 (1.05-1.52) for non-overweight and 1.01 (0.79-1.29) for overweight.

Table 1. Age-adjusted mean numerical and percentage values according to body height

	Height quartiles				p
	Q1 (low)	Q2	Q3	Q4 (high)	
Median value of height, cm	155.8	161.0	165.0	170.1	
No. at risk	339	344	328	339	
Age, years	69.7±9.4	67.2±9.0	63.2±10.5	59.0 ± 10.5	
Systolic blood pressure, mmHg	142.5	143.0	141.2	142.9	0.622
Antihypertensive medication use, %	28	27	26	27	0.926
Antihyperlipidemic agent use, %	6	4	5	6	0.503
Body mass index, kg/m^2	23.6	23.8	23.7	23.6	0.865
Current drinker, %	42	52	54	55	0.003
Current smoker, %	28	25	25	24	0.646
Diabetes mellitus, %	8.7	9.0	11.1	9.5	0.733
Serum triglycerides (TG), mg/dl	123	124	129	127	0.786
Serum HDL-cholesterol (HDL), mg/dl	54.9	54.3	55.0	54.1	0.832
Serum aspartate aminotransferase (AST), IU/L	25	26	25	24	0.106
Serum γ-glutamyltranspeptidase (γ-GTP), IU/L	41.8	44.3	47.9	43.8	0.553
Serum uric acid, mg/dl	5.8	6.1	6.2	6.2	0.002
Serum creatinine, mg/dl	0.83	0.89	0.90	0.92	<0.001
Estimated glomerular filtration rate (JCKD; mL/min/1.73m^2)	77.1	71.0	69.0	68.3	<0.001
Estimated glomerular filtration rate (Horio; mL/min)	84.8	85.5	87.5	93.7	<0.001

Age: mean ± standard deviation. p: p factor. Height quartiles: <158.8cm, 158.8-163.0cm, 163.1-167.9cm, >167.9cm

Table 2. Odd ratios (ORs) and 95% confidence intervals (CI) for hyperuricemia in relation to body height for all subjects

	Height quartiles					1 SD increment in height
	Q1 (low)	Q2	Q3	Q4 (high)	P for trend	
Hyperuricemia						
All subjects						
No. at risk	339	344	328	339		
No. of cases (percentage)	72 (21)	95 (28)	98 (30)	103 (30)		
Model 1	1.00	1.42 (1.00-2.03)	1.60 (1.12-2.30)	1.66 (1.44-2.41)	0.007	1.26 (1.11-1.44)
Model 2	1.00	1.40 (0.98-2.02)	1.60 (1.10-2.32)	1.61 (1.09-2.36)	0.015	1.24 (1.08-1.43)
Mode .3	1.00	1.25 (0.86-1.83)	1.41 (0.95-2.08)	1.39 (0.93-2.08)	0.096	1.17 (1.01-1.35)

Model 1 : Adjusted for age. Model 2: Age + other CVD risk factors (systolic blood pressure, antihypertensive medication use, antihyperlipidemic agent use, body mass index, smoking, alcohol intake, diabetes mellitus, serum triglycerides, serum HDL cholesterol, serum aspartate aminotransferase (AST), and serum γ-glutamyltranspeptidase (γ-GTP)). Model 3 : Model 2 + serum creatinine. Hyperuricemia defined as serum uric acid level >7.0mg/dL. Height quartiles: <158.8cm, 158.8-163.0cm, 163.1-167.9cm, and >167.9cm.

Table 3. Odd ratios (ORs) and 95% confidence intervals (CI) for hyperuricemia in relation to body height for all subjects

	Height quartiles					1 SD increment in height
	Q1 (low)	Q2	Q3	Q4 (high)	P for trend	
Hyperuricemia						
Non-overweight (25kg/m^2>BMI)						
No. at risk	243	225	224	223		
No. of cases (percentage)	39 (16)	53 (24)	58 (26)	60 (27)		
Model 1	1.00	1.67 (1.05-2.66)	1.98 (1.24-3.16)	2.17 (1.34-3.53)	0.002	1.39 (1.17-1.64)
Mode .2	1.00	1.70 (1.05-2.76)	1.98 (1.20-3.24)	2.12 (1.27-3.54)	0.004	1.35 (1.12-1.61)
Model 3	1.00	1.57 (0.95-2.61)	1.82 (1.09-3.04)	1.86 (1.10-3.16)	0.023	1.26 (1.05-1.52)
Overweight (BMI $\geq$ 25kg/m^2)						
No. at risk	96	119	104	116		
No. of cases (percentages)	33 (34)	42 (35)	40 (39)	43 (37)		
Model 1	1.00	1.04 (0.59-1.82)	1.16 (0.65-2.08)	1.07 (0.58-1.94)	0.762	1.09 (0.87-1.36)
Model 2	1.00	1.02 (0.57-1.84)	1.07 (0.58-1.97)	0.95 (0.51-1.79)	0.916	1.05 (0.83-1.33)
Model 3	1.00	0.83 (0.45-1.54)	0.84 (0.44-1.59)	0.81 (0.43-1.56)	0.578	1.01 (0.79-1.29)

Model 1 : Adjusted for age. Model 2: Age + other CVD risk factors (systolic blood pressure, antihypertensive medication use, antihyperlipidemic agent use, body mass index, smoking, alcohol intake, diabetes mellitus, serum triglycerides, serum HDL cholesterol, serum aspartate aminotransferase (AST), and serum γ-glutamyltranspeptidase (γ-GTP)). Model 3 : Model 2 + serum creatinine. Hyperuricemia : serum uric acid level >7.0mg/dL. Height quartiles: <158.8cm, 158.8-163.0cm, 163.1-167.9cm, >167.9cm

4.Discussion

Major findings of the study presented here were that body height showed positive associations with the risk of hyperuricemia for Japanese men, especially non-overweight men. Being overweight was found to be a confounding factor for the subjects of this study.

Arastair et al. detected a significantly positive association between height and serum uric acid for healthy mixed sex subjects (27 men and 30 women). This study also performed a sex-specific analysis and found that this association did not reach significance for either men or women. The correlation coefficients for serum uric acid concentration and body height were r=0.47 (P<0.001) for all subjects, r=0.08 (P>0.1) for men, and r=0.15 (P>0.1) for women.[16]

However, women might not be suitable subjects for such an investigation because menopause is independently associated with higher serum uric acid levels[17] and also height is confounded by vertebral compression fractures, which are mainly caused by postmenopausal osteoporosis.[18] We therefore limited our study to men. Furthermore, the prevalence of hyperuricemia was reported to be higher for obese than non-obese individuals.[9,10] A study taking BMI status, besides obesity, into account was also needed, however, and our study showed significant positive associations between body height and hyperuricemia for men, and that this asso-

ciation was limited to non-overweight participants.

Several studies have reported that positive associations exist between body height and risk of death from several organ-specific malignancies such as melanoma and cancer of the pancreas, breast, ovary, prostate and colorectum.[3-7] Other studies reported that risk of cancer was higher for subjects with higher uric acid levels.[8,19] In this connection, it has been hypothesized that, because taller people have larger organs, they have more cells at risk of malignant transformation and/or proliferation.[20] Since uric acid is the final product of purine metabolism in human beings, cell proliferation is related to uric acid production. These mechanisms thus may explain why taller people show higher levels of uric acid.

Since height is regarded as a surrogate marker of childhood social and physical conditions[1,2] while BMI may reflect primarily current physical conditions, a detailed analysis of persons with lower BMI may elucidate a potential effect of childhood conditions. A previous of ours, The Circulatory Risk in Community Study (CIRCS), determined that height was inversely associated with risk of stroke among middle-aged Japanese men and women and that inverse association was limited to persons with lower BMI, which suggests that childhood social and physical conditions may contribute to the development of stroke in adulthood.[21] On the other hand, the prevalence of hyperuricemia is reportedly higher among obese than non-obese individuals.[9,10] And our present study determined significant positive association between height and hyperuricemia especially among participants with non-overweight which also suggests that childhood social and physical conditions may contribute to the development of hyperurimia in adulthood.

These studies support our hypothesis that body height is positively associated with risk of hyperurimia especially for non-overweight.

However, other studies have reported that height was inversely associated with incidence of or mortality from cardiovascular disease,[22,23] while several studies found a positive association between serum uric acid and cardiovascular disease.[24-26] Nevertheless, many of these reports indicated that hyperuricemia may not constitute an independent risk factor for most cardiovascular diseases.[24,25]

Potential limitations of this study warrant consideration. Because we did not have access to creatinine clearance data and estimated GFR is not an effective tool for evaluating kidney function for a comparison of associations with various body heights, we could not perform an analysis adjusted for precise renal function. However, our analysis showed statistically significant associations even after further adjustments for serum creatinine, but because this study was cross sectional, we could not establish any causal relationships.

In conclusion, we established that body height is positively associated with risk of hyperuricemia (serum uric acid>7.0mg/dl) for general Japanese men, especially for non-overweight ($25kg/m^2$>BMI) men which suggests that childhood social and physical conditions may contribute to the development of hyoeruricemia in adulthood.

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