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Association between serum uric acid to high density lipoprotein-cholesterol ratio and arterial stiffness in a Japanese population

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Abstract

Uric acid (UA) and HDL-cholesterol (HDL-C) level are closely associated to the cardiovascular disease (CVD) morbidity. The UA/HDL-C ratio (UHR), a new parameter combination of serum UA and HDL-C, attracts attention for its association with metabolic and inflammatory conditions. There may exists the association between UHR and arterial stiffness. This study aims to explore the association between the UHR and brachial-ankle PWV (baPWV) and to determine whether or not UHR has effect on arterial stiffness. The present study included a total of 912 Japanese (592 men and 320 women), aged from 24 to 84, received a health medical checkup programme with an automatic waveform analyzer to measure baPWV and various standardized questionnaires in a medical center of Japan. Non-linear regression and threshold effect analysis were conducted to explore the association between UHR and baPWV. It was found that UHR was positively correlated with baPWV after adjusting for multiple confounders. A non-linear relationship (with a inflection point was 14.25) was found between UHR and baPWV. Subgroup analyses showed that the significant association between UHR and baPWV only existed in females group, no fatty liver group and normal BMI groups. This study revealed the nonlinear relationship between UHR and baPWV. A significant correlation between UHR and baPWV existed in females but not in males. Fatty liver status, BMI, and menopausal status may affect the above association.

Abbreviations: ABI = ankle–brachial index, ALT = alanine aminotransferase, AST = aspartate transaminase, baPWV = brachial–ankle PWV, CVD = cardiovascular disease, eGFR = glomerular filtration rate, HDL-C = high-density lipoprotein cholesterol, NAFLD = nonalcoholic fatty liver disease, TC = total cholesterol, UA = uric acid, UHR = UA/HDL-C ratio, γ-GGT = γ-glutamyltranspeptidase.

Keywords: arterial stiffness, baPWV, high density lipoprotein-cholesterol, serum uric acid, UHR

1. Introduction

Cardiovascular disease (CVD) is a group of heart and blood vessel disorders and is the leading cause of death and morbidity worldwide, causing about one-third of all deaths globally and imposing a major public health burden over the past several decades. Arterial stiffness is associated with cardiovascular risk factors, atherosclerotic disease,[1,2] and increased cardiovascular mortality and can be used as powerful determinant for the assessment of cardiovascular risk. Among the various evaluation indicators for arterial stiffness, the brachial–ankle PWV (baPWV) is one of the most representative and noninvasive screening tools applied in clinical practice and is automatically measured using simple separate cuff for each of the 4 limbs by an oscillometric method.[3,4] A meta-analysis demonstrated that high levels of baPWV are closely correlated with increased risk of developing CVD.[5]

Uric acid (UA) is a highly insoluble waste product of endogenous and exogenous purine metabolism in humans, and two-thirds of UA is eliminated by renal excretion. UA is closely associated to various metabolic diseases because it serves as selective antioxidant and free radical scavenger in physiologic conditions, such as gout, hypertriglyceridemia, and diabetes mellitus.[6,7] Dyslipidemia plays an important role on the pathogenesis of CVD. Increased serum concentrations of low-density lipoprotein cholesterol (LDL-C) and triglycerides are recognized as risk factors for CVD, whereas increased high-density lipoprotein cholesterol (HDL-C)

HW, YB, XG, and JZ equally contributed to the study.

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The datasets generated during and/or analyzed during the current study are publicly available.

The original study had been approved the Medical Health Checkup Center at Murakami Memorial Hospital, Gifu, Japan.

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is considered to show pleiotropic effects on protecting the cardiovascular system, including reverse cholesterol transport to reduce atherosclerotic burden, anti-inflammation, antioxidation, and vasodilation.[8,9] Low HDL-C and high UA show association with increased risk of CVD and mortality in the general population. The combination of serum UA and HDL-C is proposed as a better predictor of CVD mortality than the single parameter. As one of the combinations, the UA/HDL-C ratio (UHR) has recently attracted attention for its association with metabolic and inflammatory conditions. Evidence showed that increased UHR is suggested to be related to metabolic syndrome,[10] thyroiditis,[11] and hepatic steatosis.[12] UHR can also be used as a strong predictor of diabetes control and metabolic syndrome in patients with diabetes.[13] Studies from different groups of China reported that UHR can serve as a reliable predictor of nonalcoholic fatty liver disease (NAFLD) onset in nonobese[14] or lean Chinese people for UHR level was associated with a significantly increased risk of NAFLD.[15] Elevated UHR levels can be associated with poor blood pressure control. Thus, Aktas and Khalid[16] proposed that the assessment of UHR may be useful in patients with hypertension.

Despite these interesting observations, studies investigating the association between UHR and arterial stiffness are scarce. This study aims to explore the association between UHR and baPWV and determine whether UHR affects arterial stiffness based on previously published data.

2. Materials and methods

This study was a secondary analysis of a cross-sectional study conducted at the Medical Health Checkup Center of Murakami Memorial Hospital (Gifu City, Japan) by Takuya from 2004 to 2012. Raw data were freely available for download and analysis from the "DATADRYAD" database (www.Datadryad.org) without infringing on the authors' rights for intellectual property or other rights and related ownership of these data were waived by the authors of the original study. We made a definitive statement when we cited the Dryad data package in accordance with the Dryad database policy (Dryad data package: Fukuda T, Hamaguchi M, Kojima T, Ohshima Y, Ohbora A, Kato T, Nakamura N, Fukui M (2014) Data from: Association between serum γ-glutamyltranspeptidase and atherosclerosis: a population-based cross-sectional study. Dryad Digital Repository. Dryad | Data – Association between serum γ-glutamyltranspeptidase and atherosclerosis: a population-based cross-sectional study. https://datadryad.org/stash/dataset/doi:10.5061/dryad.m484p.

In accordance with Takuya's description,[17] this study reviewed the medical records of 1445 participants who participated in the Japan medical health checkup program at Murakami Memorial Hospital and obtained informed consent from all participants in accordance with the Declaration of Helsinki. A total of 912 participants were received after excluding the following: participants who received medication, including oral contraceptives and hormone replacement therapy; participants who were positive to hepatitis B antigen and/or hepatitis C antibody; pregnant women; and participants with ankle–brachial index (ABI) less than 0.95.

As previously described, the variables included in the database, including γ-glutamyltranspeptidase (γ-GGT), fasting plasma glucose, triglycerides, HDL-C, LDL-C, total cholesterol (TC), alanine aminotransferase (ALT), aspartate transaminase (AST), and UA, were obtained from plasma and serum samples of participants in the fasting state (8 hours fasting). UHR was calculated as serum UA levels (in mg/dL) divided by HDL-C levels (in mg/dL). Weight and height were measured to calculate BMI as weight in kilograms divided by height in meters squared. The Japanese Society of Nephrology equation: eGFR = $194 \times Cr^{-1.094} \times age^{-0.287}$ (mL/min/1.73 m^2) was applied to calculate the estimated glomerular filtration rate (eGFR) for men. The eGFR for women was the eGFR for men multiplied by a correction factor of 0.739. The results of abdominal ultrasonography were applied to diagnose fatty liver by gastroenterologist by 4 criteria (i.e., hepatorenal echo contrast, vascular blurring, deep attenuation, and liver brightness) without reference to other test results of the participants.

Authors provide a detailed description for the measurement of baPWV in the original study. In brief, ECG electrodes on wrists and heart sound microphone on the left edge of the sternal border were placed on subjects, who stayed in the supine position in a quiet room with temperature around 25°C after resting for 5 minutes. Cuffs were wrapped around the arms and ankles and connected with a plethysmographic sensor and an oscillometric pressure sensor, which could determine the volume pulse form and blood pressure, respectively. The path lengths from the suprasternal notch to the ankle (La) and from the suprasternal notch to the brachium (Lb) were then calculated on the basis of the participant's height, and the delay time from the ascending point of the brachial waveform to the ascending point of each ankle wave form (DTba) was automatically obtained. The authors calculated baPWV (in cm/s) by the pulse wave propagation distance (Lb–La) divided by the pulse wave propagation time (DTba).

A standardized questionnaire for lifestyle factors was applied to acquire information about alcohol consumption, smoking status, and frequency of participation in sports. The total amount of alcohol consumed per week was calculated in grams, and smoking status was categorized into nonsmoker or ex-smoker and current smoker. Regular exercisers were participants who performed any kind of sport regularly at least once a week. Postmenopausal status was defined as more than a year after the cessation of menses.

2.1. Statistical analysis

All statistical analyses were conducted using the commercial statistical software package R (http://www.R-project.org, The R Foundation) and EmpowerStats (http://www.empowerstats.com, X&Y Solutions, Inc., Boston, MA). We analyzed the baseline characteristics of all subjects, which grouped UHR in tertiles. The normality of the data distribution was evaluated using Shapiro–Wilk normality test and kolmogorow–Smirnov normality test in this study. The continuous variables which passed the normality test are expressed as means ± SD while the continuous variables which didn't passed the normality test are expressed by median (P25, P75) (γGGP and TG). Differences between means and proportions among different groups were determined by one-way ANOVA (normal distribution) and Kruskal–Wallis H (non-normal distribution distribution) test. The categorical variables were expressed as percentages (%) or frequency, the differences of which analyzed by chi-square test. Multiple regression analyses were applied to estimate the independent association between UHR levels and baPWV. Three models adjusted for different degrees were used to provide statistical inference. Generalized additive models and smooth curve fitting were performed to identify nonlinear relationships between UHR levels and baPWV. Additionally, subgroup analyses were applied under stratified linear regression models. *P* value < .05 indicated a significant difference.

3. Results

3.1. Population characteristics

A total of 1445 participants were included during the study period, and 433 participants (284 men and 149 women) were excluded because they were receiving medication. In addition, 16 men and 10 women were excluded as they tested positive to the hepatitis B antigen and/or positive antihepatitis C antibody. Another 68 women were excluded for receiving hormone replacement therapy (66), taking an oral contraceptive (1), and being on gestational age (1). Additionally, 6 (5 men and 1 woman) participants were excluded due to ABIs

< 0.95. Finally, 912 participants (including 592 men and 320 women) were analyzed.

Table 1 summarizes the baseline demographic and clinical characteristics of participants subclassified on the basis of UHR tertiles. The gender distribution, TC level, and postmenopausal status did not differ among 3 subclassified groups. Being female and young age were associated with increased UHR levels. Participants with high UHR levels tended to have high BMI, BP, AST, ALT, γ-GGT, FBS, UA, TC, LDL3, and baPWV. Moreover, an inverse association existed among HDL-C, eGFR, exercise intensity, and smoking status and between amount of alcohol consumption and UHR levels. Besides, obese people (BMI > 26 kg/m^2) and individuals with fatty liver tended to have high UHR levels.

3.2. Association between UHR and baPWV

The effect sizes of association between UHR and baPWV are listed in Table 2. In the crude unadjusted model, a positive association was observed between UHR and baPWV. Similar results were found in models 2 (adjustment for age and sex; β = 6.16, 95% CI = 2.65–9.67) and 3 (adjustment for sex, age, BMI, SBP, DBP, ALT, AST, γ-GTP, and fatty liver status; β = 4.03, 95% CI: 0.76–7.30). We also performed UHR as a tertile categorical variable to explore the sensitivity analysis, it was found the same trend (*P* for trend was 0.002).

In the subgroup analyses stratified by gender, fatty liver status, amount of alcohol consumption, and BMI, the association between UHR and baPWV was no longer significant among males, individuals with fatty liver, medium and high alcohol consumption groups, and lean and obese groups.

3.3. Analyses of nonlinear relationship

We also conducted generalized additive models and smooth curve fittings to evaluate the associations between UHR and baPWV in the total model and different subgroups. A nonlinear relationship was found between UHR and baPWV. The smooth

Table 1

Baseline characteristics of participants.

UHR (tertiles)	T1	T2	T3	*P* value	*P* value*
N	304	304	304		
Age (yr, mean ± SD)	51.78 ± 9.26	51.18 ± 9.43	50.43 ± 10.00	.222	.223
BMI (kg/m^2, mean ± SD)	21.70 ± 2.58	23.11 ± 2.95	24.57 ± 3.14	<.001	<.001
SBP (mm Hg, mean ± SD)	115.33 ± 13.83	120.99 ± 14.90	124.42 ± 14.74	<.001	<.001
DBP (mm Hg, mean ± SD)	71.83 ± 9.24	76.99 ± 9.72	79.60 ± 9.50	<.001	<.001
AST (IU/L, mean ± SD)	19.01 ± 5.98	20.97 ± 8.85	22.57 ± 8.73	<.001	<.001
ALT (IU/L, mean ± SD)	16.74 ± 6.49	22.43 ± 14.26	28.88 ± 17.17	<.001	<.001
γGGP (IU/L, median (25P, 75P))	14.00 (11.00, 18.25)	19.00 (14.00, 31.00)	23.00 (17.00, 33.25)	<.001	<.001
Fasting glucose (mg/dL, mean ± SD)	94.78 ± 17.05	98.24 ± 12.16	101.13 ± 11.65	<.001	<.001
Uric acid (mg/dL, mean ± SD)	3.98 ± 0.90	5.35 ± 0.88	6.44 ± 1.04	<.001	<.001
TC (mg/dL, mean ± SD)	212.04 ± 35.70	207.70 ± 35.98	209.72 ± 36.21	.331	.258
TG (mg/dL, median (25P, 75P))	56.50 (40.00–76.25)	77.00 (55.00–111.25)	125.00 (88.75–182.25)	<.001	<.001
HDL-C (mg/dL, mean ± SD)	66.62 ± 13.25	53.22 ± 8.95	40.77 ± 7.03	<.001	<.001
LDL-C (mg/dL, mean ± SD)	121.92 ± 31.14	128.24 ± 31.19	134.01 ± 31.67	<.001	<.001
UHR (%)	6.08 ± 1.26	10.12 ± 1.15	16.15 ± 3.49	<.001	<.001
eGFR(mL/min/1.73 m^2, mean ± SD)	73.86 ± 12.96	70.65 ± 10.79	66.73 ± 11.22	<.001	<.001
baPWV (cm/s, mean ± SD)	1368.21 ± 206.99	1415.10 ± 225.54	1463.94 ± 289.84	<.001	<.001
Sex (n, %)					
Male	70 (23.03)	234 (76.97)	288 (94.74)	<.001	–
Female	234 (76.97)	70 (23.03)	16 (5.26)		
Current smoking (n, %)					
None	273 (89.80)	234 (76.97)	208 (68.42)	<.001	–
Current	31 (10.20)	70 (23.03)	96 (31.58)		
Ex-smoking (n, %)					
No	226 (74.34)	138 (45.39)	97 (31.91)	<.001	–
Yes	78 (25.66)	166 (54.61)	207 (68.09)		
Regular exercise (>1 wk) (n, %)					
No	222 (75.00)	238 (79.33)	259 (86.33)	.002	–
Yes	74 (25.00)	62 (20.67)	41 (13.67)		
Fatty liver (n, %)					
None	271 (89.44)	235 (77.30)	140 (46.05)	<.001	–
Yes	32 (10.56)	69 (22.70)	164 (53.95)		
Menopausal status (n, %)					
Post-menopausal	103 (44.02)	29 (41.43)	6 (37.50)	.833	–
No	131 (55.98)	41 (58.57)	10 (62.50)		
Alcohol consumption (n, %)					
<80 (g/wk)	253 (84.05)	199 (65.68)	197 (66.78)	<.001	–
≥80, <180 (g/wk)	24 (7.97)	55 (18.15)	45 (15.25)		
≥180 (g/wk)	24 (7.97)	49 (16.17)	53 (17.97)		
BMI					
<19 (kg/m^2, mean ± SD)	40 (13.16)	16 (5.26)	6 (1.97)	<.001	–
≥19, <26 (kg/m^2, mean ± SD)	244 (80.26)	238 (78.29)	218 (71.71)		
≥26 (kg/m^2, mean ± SD)	20 (6.58)	50 (16.45)	80 (26.32)		

ALT = alanine aminotransferase, AST = aspartate transaminase, baPWV = brachial-ankle pulse wave velocity, BMI = body mass index, DBP = diastole pressure, eGFR = estimated glomerular filtration rate, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, SBP = systolic pressure, TC = total cholesterol, TG = triglyceride, UHR = uric acid to high-density lipoprotein cholesterol ratio, γGGT = γ-glutamyltranspeptidase.

P value* was calculated by Kruskal-Wallis H test.

Table 2

Relationship between UHR and baPWV in different models.

Exposure	Non-adjusted model β (95% CI)	Adjust I model β (95% CI)	Adjust II model β (95% CI)
UHR	6.56 (3.19, 9.93) 0.0001	6.16 (2.65, 9.67) 0.0006	4.03 (0.76, 7.30) 0.0159
UHR (tertiles)			
T1	Reference	Reference	Reference
T2	46.89 (8.20, 85.59) 0.0177	40.95 (2.40, 79.50) 0.0376	26.43 (–6.57, 59.43) 0.1168
T3	95.73 (57.04, 134.43) < 0.0001	95.14 (52.86, 137.42) < 0.0001	59.48 (21.34, 97.62) 0.0023
P for trend	<.001	<.001	.002
Gender			
Male	2.60 (–1.91, 7.11) 0.2584	4.03 (0.10, 7.96) 0.0446	2.53 (–1.04, 6.10) 0.1650
Female	20.88 (10.81, 30.95) < 0.0001	16.43 (8.10, 24.75) 0.0001	11.77 (3.59, 19.95) 0.0051
Fatty liver			
None	7.33 (2.74, 11.92) 0.0018	3.14 (–1.70, 7.98) 0.2047	4.80 (0.49, 9.11) 0.0295
Yes	–3.23 (–9.49, 3.03) 0.3126	2.08 (–3.94, 8.10) 0.4987	2.75 (–2.44, 7.93) 0.2998
Alcohol consumption			
<80 (g/wk)	8.68 (4.64, 12.72) < 0.0001	9.02 (4.70, 13.34) < 0.0001	6.70 (2.68, 10.71) 0.0011
≥80, <180 (g/wk)	0.40 (–10.34, 11.15) 0.9417	0.71 (–9.27, 10.69) 0.8894	3.79 (–6.05, 13.63) 0.4523
≥180 (g/wk)	–2.34 (–10.98, 6.30) 0.5966	–3.96 (–12.32, 4.40) 0.3548	–6.64 (–14.54, 1.26) 0.1024
BMI			
<19 (kg/m^2)	14.20 (–2.49, 30.89) 0.1006	2.60 (–16.07, 21.27) 0.7860	8.61 (–8.98, 26.19) 0.3419
≥19, <26 (kg/m^2)	8.12 (3.85, 12.40) 0.0002	6.65 (2.18, 11.12) 0.0037	4.77 (0.74, 8.80) 0.0206
≥26 (kg/m^2)	–0.92 (–7.24, 5.40) 0.7748	2.20 (–4.22, 8.62) 0.5035	2.36 (–3.39, 8.12) 0.4224

Crude model: we did not adjust other covariants.

Minimally adjusted model: we adjusted age and sex.

Fully adjusted model: we adjusted sex; age; BMI; SBP; DBP; ALT; AST; γ-GTP; fatty liver status.

ALT = alanine aminotransferase, AST = aspartate transaminase, baPWV = brachial-ankle pulse wave velocity, BMI = body mass index, CI = confidence interval, DBP = diastole pressure, Ref = reference, SBP = systolic pressure, UHR = uric acid to high-density lipoprotein cholesterol ratio.

curve is presented in Figure 1. The inflection point (14.25) was obtained using a two-piecewise linear regression model. For UHR < 14.25%, every 1% increase in UHR was associated with 9.4 cm/s increase in baPWV (95% CI = 4.24–14.56). By comparison, for individuals with UHR > 14.25 mg/dL, a 1% increase in UHR was associated with a 3.1 cm/s decrease in baPWV (95% CI = –9.40 to 3.11). The similar threshold effect of UHR on baPWV was also found in no fatty liver group, premenopausal state group, and nonobese group. Detailed information are presented in Table 3 and Figure 2.

3.4. Interaction analyses

As shown in Table 4, interactions were significant for sex (*P* for interaction = .0327), smoking status (*P* for interaction were .0452 and .0292 for current smoker and ex-smoker, respectively), alcohol consumption (*P* for interaction = .0103), and menopausal status for female subjects (*P* for interaction = .0111), whereas interactions were not statistically significant for exercise status, fatty liver, and BMI (*P* for interaction = .6190, .5343, and .7205, respectively).

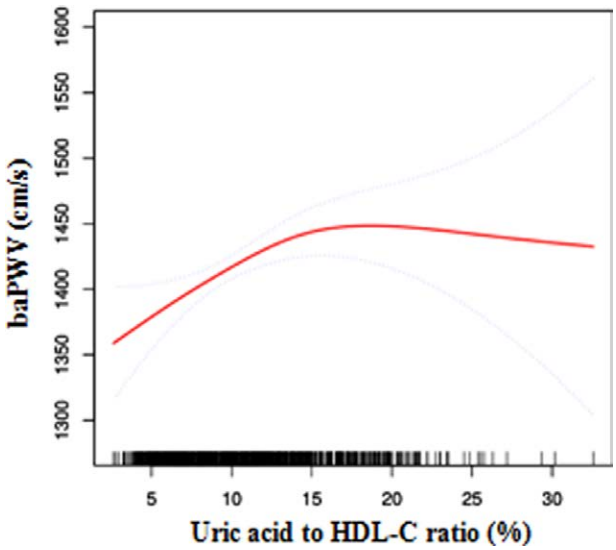

Figure 1. The non-linear relationship between Uric acid to HDL-C ratio and baPWV. The relationship between AST/ALT and baPWV. Adjusting for sex; age; BMI; SBP; DBP; ALT; AST; γ-GTP; Fatty liver status. (The area between 2 blue dotted lines is expressed as a 95% CI. Each point shows the magnitude of UHR and is connected to form a continuous line). ALT = alanine aminotransferase, AST = aspartate transaminase, baPWV = brachial–ankle PWV, BMI = body mass index, DBP = diastole pressure, HDL-C = high-density lipoprotein cholesterol, SBP = systolic pressure, UHR = UA/HDL-C ratio.

4. Discussion

In this study, previous data are used to evaluate the associations between UHR and baPWV in a Japanese population. To the best of our knowledge, this study is the first population-based cohort study that has evaluated associations between UHR and arterial stiffness. Results revealed a nonlinear relationship between UHR and baPWV, which follows a nearly inverse U-shaped curve with an inflection point (14.25%). UHR is positively associated with baPWV on the left of the inflection point but is not statistically significant on the right side of the inflection point. Specifically, we found a significant correlation between UHR and baPWV in females but not in males. Other subgroup analyses showed that a significant relationship between UHR and baPWV exists in nonfatty liver, low alcohol consumption, and normal weight (19 kg/m^2 ≤ BMI ≤ 26 kg/m^2) groups. Inverse U-shaped curves are also observed in nonfatty liver, nonmenopausal status, and nonobese groups.

UHR is a recently introduced physiological indicator that has attracted considerable attention in current research due to its potential impact on physiological processes and the onset of diseases. A study conducted on the Turkish population revealed a significant correlation between UHR and several key indicators of diabetic kidney injury, leading to the proposal of UHR as a diagnostic tool for this condition.[18]

Table 3

Threshold effect analysis of UHR on baPWV by using two-piecewise linear regression.

	Adjusted ß (95% CI), *P* value
Fitting by standard linear model	4.03 (0.76, 7.30) .0159
Fitting by two-piecewise linear model	
Inflection point	14.25
<14.25 (%)	9.40 (4.24, 14.56) .0004
>14.25 (%)	−3.14 (−9.40, 3.11) .3249
Log likelihood ratio	0.008
No Fatty Liver	
Fitting by standard linear model	4.80 (0.49, 9.11) .0295
Fitting by two-piecewise linear model	
Inflection point	15.99
<15.99(%)	9.01 (3.60, 14.42) .0012
>15.99(%)	−14.63 (−30.42, 1.16) .0699
Log likelihood ratio	0.012
	−1.70 (−12.09, 8.70) .7496
POSR.MENOPAUSAL.STATE	
Fitting by standard linear model	−1.70 (−12.09, 8.70) .7496
Fitting by two-piecewise linear model	
Inflection point	5.27
<5.27(%)	59.12 (4.44, 113.79) .0360
>5.27(%)	−9.96 (−22.54, 2.61) .1229
Log likelihood ratio	0.021
BMI < 19	
Fitting by standard linear model	8.61 (−8.98, 26.19) .3419
Fitting by two-piecewise linear model	
Inflection point	6.83
<6.83 (%)	44.87 (−0.52, 90.27) .0585
>6.83 (%)	−0.86 (−21.31, 19.59) .9345
Log likelihood ratio	0.060
BMI ≥ 19, <26	
Fitting by standard linear model	4.77 (0.74, 8.80) .0206
Fitting by two-piecewise linear model	
Inflection point	15.95
<15.95(%)	9.17 (3.85, 14.49) .0008
>15.95(%)	−8.95 (−20.55, 2.65) .1310
Log likelihood ratio	0.013

Adjusted: Sex; age; BMI; SBP; DBP; ALT; AST; γ-GTP; fatty liver status.

ALT = alanine aminotransferase, AST = aspartate transaminase, baPWV = brachial-ankle pulse wave velocity, BMI = body mass index, CI = confidence interval, DBP = diastole pressure, SBP = systolic pressure, UHR = uric acid to high-density lipoprotein cholesterol ratio.

In a separate investigation, Chinese researchers focused their efforts on UHR and discovered a connection between visceral adiposity and elevated UHR levels in patients with type 2 diabetes.[19] Additionally, there is emerging evidence suggesting a potential association between UHR and the regulation of ALT levels in Chinese children and adolescents with short stature.[20]

UHR is a marker combining UA and HDL-C. Thus, increased UHR is caused by either decreased serum HDL cholesterol, increased serum UA, or both. UA and HDL-C differ between males and females. Hyperuricemia is UA ≥ 6 mg/dL for women and UA ≥ 8 mg/dL for men, whereas low HDL-C is defined as HDL-C < 40 mg/dL for men or HDL-C < 50 mg/dL for women. Thus, UHR is different between males and females, and we found that UHR and baPWV in men are significantly higher than those in women and that a significantly positive correlation between UHR and baPWV only exists in women. The underlying definitive mechanism of such gender-specific differences remains unknown. Sex hormones for different hormonal milieu may affect the well-regulated balance of 2 main extracellular matrix proteins of the arterial wall, i.e., collagen and elastin, whose dysregulation leads to stiffening of the arterial wall.[21] Estrogen is shown to affect arterial wall remodeling directly by decreasing collagen deposition and increasing elastin production in human arteries.[22] Besides, sex differences relate to the type and levels of sex hormones in vascular biology, and tissue and cellular differences that are responsible for sex-specific responses to various stimuli also exist. For instance, men have less arterial estrogen receptors than women although the human aorta has estrogen and progesterone receptors.[23] Different nitric oxide-mediated vasodilatory effects of estrogen between genders are also observed based on the report that intracoronary injections of estradiol improve endothelial function and coronary flow in women but not in men.[24] Furthermore, sex differences in measures of arterial pulsatility and stiffness are present. The truth that women have shorter aortic length and faster wave travel time also results in achieving the reflected pressure wave in the cardiac cycle fast and increasing baPWV.[25]

Further analysis based on the menopause status of women found a nearly inverse U-shaped relationship between UHR and baPWV with an inflection point in the nonmenopausal status group and irregular UHR–baPWV relationship in the menopausal group. A complex relationship between HDL-C and menopause has been reported, and UA is proposed as an independent predictor of cardiovascular events in postmenopausal women. Moreover, it was multiple and intricate that hormonal and metabolic alterations occur with menopause. The incidence of CVD increases disproportionately in women after menopause, and women who undergo menopause earlier shows poor cardiovascular outcomes.[26,27] The elevation of blood pressure caused by arterial stiffness in women may play a role on the mechanisms underlying the loss of cardiovascular protection with menopause.[28] Furthermore, severe symptoms in menopause are associated with remarkable arterial stiffness, and the association between mortality and arterial stiffness in females is double that in males.[29] Thus, menopause should be considered when evaluating the association between UHR and arterial stiffness.

Fatty liver is the most prevalent chronic liver disease in the world. In recent years, the association between UHR and fatty liver has attracted increasing attention. Zhang et al proposed that UHR is significantly associated with NAFLD and may serve as a novel and reliable marker for NAFLD in lean adults, whereas another study from a Chinese team demonstrated that high UHR values are independently associated with increased risk for NAFLD occurrence in nonobese Chinese individuals with normal blood lipid levels.[14,15] A Japanese study demonstrated the significant association of fatty liver index, a surrogate marker of fatty liver, with baPWV.[30] A recent cross-sectional study conducted on NHANES revealed a significant positive correlation between UHR and the severity of hepatic steatosis, but not fibrosis. The findings demonstrated that elevated UHR levels were independently associated with an increased risk of NAFLD and the severity of liver steatosis.[31] Above reports indicated that an association between UHR and baPWV may exist in fatty liver population. However, our subgroup analysis results showed that the significantly positive correlation between UHR and baPWV only exists in nonfatty liver group but not in the fatty liver group. Our inconsistent results may be due to limited sample size. Further studies are required to validate these findings.

The association between obesity and CVD has been well established, and vascular dysfunction has also been proposed as one of the important factors linking these 2 pathological states. However, conclusions about the relationship between obesity and arterial stiffness are inconsistent. For example, Rodrigues et al reported that BMI is not independently associated with increased aortic stiffness in a Brazilian population.[32] Additionally, Tang et al[33] found that the arterial stiffness measured as baPWV increases with BMI in a middle-aged healthy Chinese population. Our study suggested that BMI has a significant effect on the association between UHR and baPWV. A significantly positive correlation is observed between UHR and baPWV in the normal weight group but not in the lean or obesity group. Given that BMI is associated with UA and adult BMI is negatively related to HDL-C, BMI is speculated to be associated with baPWV. However, the complex mechanism

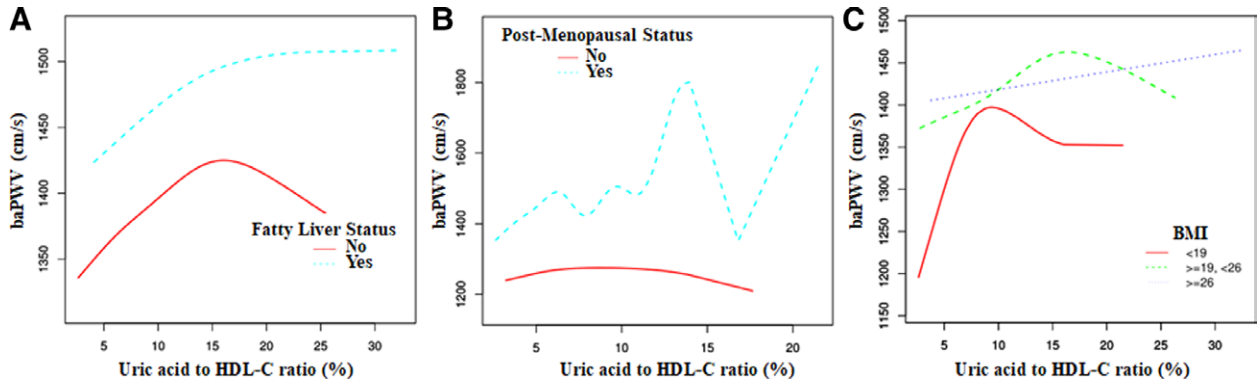

Figure 2. The association between serum Uric acid to HDL-C ratio and baPWV according to different subgroup. A. Fatty liver status B. Post-menopausal status. C. BMI. Adjusting for sex; age; BMI; SBP; DBP; ALT; AST; γ-GTP; Fatty liver status. ALT = alanine aminotransferase, AST = aspartate transaminase, baPWV = brachial–ankle PWV, BMI = body mass index, DBP = diastole pressure, HDL-C = high-density lipoprotein cholesterol, SBP = systolic pressure.

Table 4

Effect size of UHR on baPWV in prespecified and exploratory subgroup.

Characteristic	No of participants	Effect size (95% CI) *P*	*P* for interaction
Sex			
Male	592	2.34 (−1.21, 5.89) .1970	.0327
Female	320	11.97 (3.79, 20.15) .0042	
Current smoker			
No	715	5.94 (2.06, 9.81) .0028	.0452
Yes	197	−1.41 (−7.57, 4.75) .6540	
Ex-smoking			
No	462	8.38 (3.21, 13.54) .0015	.0292
Yes	450	1.18 (−2.94, 5.30) .5744	
Regular exercise (>1 wk)			
No	719	3.65 (0.02, 7.29) .0493	.6190
Yes	177	1.60 (−5.77, 8.97) .6706	
Fatty liver			
No	646	4.90 (0.56, 9.23) .0270	.5343
Yes	265	2.87 (−2.01, 7.75) .2495	
Menopausal status			
Postmenopausal	138	−2.13 (−15.18, 10.92) .7495	.0111
No	182	19.00 (8.50, 29.50) .0005	
Alcohol consumption			
<80 (g/wk)	649	6.89 (2.85, 10.92) .0009	.0103
≥80, <180 (g/wk)	124	2.69 (−6.54, 11.93) .5676	
≥180 (g/wk)	126	−6.29 (−13.97, 1.40) .1093	
BMI			
<19 (kg/m^2, mean ± SD)	62	8.61 (−9.69, 26.90) .3566	.7205
≥19, <26 (kg/m^2, mean ± SD)	700	4.77 (0.82, 8.73) .0183	
≥26 (kg/m^2, mean ± SD)	150	2.36 (−3.93, 8.66) .4621	

Adjusted: Sex; age; BMI; SBP; DBP; ALT; AST; γ-GTP; fatty liver status.

ALT = alanine aminotransferase, AST = aspartate transaminase, baPWV = brachial-ankle pulse wave velocity, BMI = body mass index, CI = confidence interval, DBP = diastole pressure, SBP = systolic pressure, UHR = uric acid to high-density lipoprotein cholesterol ratio.

underlying how BMI affects the association between UHR and baPWV is beyond the scope of this study. Based on the second analysis research design, future research should focus on these issues.

This study has limitations. First, this study was cross-sectional and provided limited evidence of associations between exposure and outcome but could not confirm causality. Second, raw data were obtained from a single Japanese population. Thus, applying the results to other ethnic groups should be done with caution. Finally, this study had a small sample size.

In summary, this study revealed a nonlinear relationship between UHR and baPWV. UHR is positively associated with baPWV on the left of the inflection point (14.25%) but is not statistically significant on the right side of the inflection point. Significant correlation between UHR and baPWV exists in females but not in males. Fatty liver status, BMI, and menopausal status may affect the above association. The clinical translation of the study results holds potential implications for UHR as a useful tool, which may contribute to advancements in related medical knowledge and practice.

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