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Uric acid concentration as a risk marker for blood pressure progression and incident hypertension : A Chinese cohort study

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ABSTRACT

Objective. Little is known about serum uric acid (SUA) role for hypertension in the Asian countries with low cardiovascular events. We aimed to explore the relationship in a comprehensive Chinese cohort.

Methods. Participants in the Taiwanese Survey on Prevalences of Hypertension, Hyperglycemia, and Hyperlipidemia (TwSHHH) who were free of hypertension at baseline recruitment in 2002 (n=3257) were evaluated for the longitudinal association between baseline SUA and blood pressure progression (BPP) and incident hypertension.

Results. During a mean follow-up of 5.41 years, 1119 persons (34.3%) had experienced progression to a higher blood pressure stage and 496 persons (15.2%) had developed hypertension. In multivariate analyses, the adjusted hazard ratios (HRs) [95% confidence intervals (CIs)] comparing the highest and lowest SUA quartiles were 1.78 (1.11–2.02, P for trend .004) for BPP and 1.68 (1.23–2.04, P for trend .028) for incident hypertension. The positively graded relationships between SUA concentration and blood pressure outcomes were observed in both males and females. More interestingly, a statistically significant trend for increasing risk of BPP and incident hypertension across SUA quartiles was most pronounced in participants with abdominal obesity.

Conclusion. We concluded that SUA level was an independent predictor of blood pressure progression and incident hypertension in a Chinese population.

Abbreviations: BMI, body mass index; BPP, blood pressure progression; CI, confidence interval; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; JNC VI, the Sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; LDL-C, low-density lipoprotein cholesterol; MDRD, Modification of Diet in Renal Disease; NHIS, the National Health Interview Survey; SBP, systolic blood pressure; SD, standard deviation; SUA, serum uric acid; TwSHHH, the Taiwanese Survey on Prevalences of Hypertension, Hyperglycemia, and Hyperlipidemia.

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1. Introduction

Hypertension is an important worldwide public health challenge because of its high frequency and concomitant risks of cardiovascular and kidney disease [1]. A prior study in Taiwan reported a hypertension prevalence rate of 26% in adult males and 19% in adult females, using the definition of hypertension according to the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) [2]. In addition, along with its comorbidities, hypertension-related conditions have accounted for almost a third of the total causes of death in Taiwan in recent years [3]. Therefore, it is extremely important to identify individuals who are at risk for hypertension.

Serum uric acid (SUA) levels have been associated with increased risk of cardiovascular disease and metabolic syndrome [4–6]. Accumulating experimental evidence also suggests a pathogenic role for SUA in development of hypertension [7,8]. In animal models, hyperuricemia may predispose to hypertension by several mechanisms such as inflammatory and vascular changes in the renal microcirculation, activation of the renin–angiotensin system, and endothelial dysfunction [7]. Several epidemiological studies have observed that elevated uric acid levels in whites are associated with increased risk of developing hypertension [4]. However, data on the causative role of SUA in hypertension in Asians are limited. Additionally, previous studies have had limited ability to explore the relationship of SUA with hypertension across adiposity strata.

According to statistics from the Nutrition and Health Survey in Taiwan, the prevalences of hyperuricemia in men (SUA > 7.7 mg/dL) and women (SUA > 6.6 mg/dL) were as high as 26.1% and 17.0%, respectively [9]. The average SUA levels and prevalence of hyperuricemia were higher in the Chinese population in Taiwan as compared with those of other ethnic groups [9,10]. Accordingly, it is timely and crucial to understand the impact of SUA on hypertension risk in Taiwan. Therefore, we prospectively assessed the longitudinal relationship between SUA and blood pressure progression and incident hypertension and the modifying effect of adiposity on these associations in a nation-wide cohort study of the Chinese population in Taiwan.

2. Materials and methods

2.1. Study design and population

Data for this study came from the Taiwanese Survey on Prevalences of Hypertension, Hyperglycemia, and Hyperlipidemia (TwSHHH) that was conducted in 2002. The TwSHHH was a nation-wide cross-sectional survey to estimate the prevalences of hypertension, hyperglycemia, and dyslipidemia for noninstitutionalized people in Taiwan. Participants in the TwSHHH were drawn from a subsample of the National Health Interview Survey (NHIS) conducted by the National Health Research Institute and Bureau of Health Promotion in Taiwan in 2001 [11].

Because implementing a biomarker screening for all NHIS participants was not affordable, one-half of the NHIS chosen townships/districts were randomly selected for the TwSHHH. In total, 10,292 individuals were randomly selected for the TwSHHH. Of these 10,292 subjects, 7578 (73.6%) completed interviews and 6600 (64.1%) permitted blood pressure and other biomarker measurements. A subsequent follow-up program, named TwSHHH-II, was initiated in 2007 to estimate the incidences of hypertension, hyperglycemia, and dyslipidemia for people in Taiwan. A total of 6600 individuals who had completed questionnaire interviews and blood pressure and other biomarker measurements in the TwSHHH were enrolled in the TwSHHH-II. Subjects were excluded for the following reasons: refusal to participate (n=1095), death (n=242), and inability to make contact (n=581). Accordingly, there were 4682 individuals including in the TwSHHH-II, resulting in a response rate of 70.9%. Differences in sex and age distributions were not statistically significant between participants and nonparticipants in the TwSHHH-II. The protocols for the TwSHHH and TwSHHH-II were approved by the Institutional Review Board at the Bureau of Health Promotion, Department of Health, Executive Yuan in Taiwan. Written informed consent was obtained from all participants in the TwSHHH and TwSHHH-II.

2.2. Data collection and measurements

At study entry, participants underwent questionnaire interviews and anthropometric measurements by well-trained nurses under a standardized protocol. Anthropometric measurements, including body weight, height, and waist circumference, were taken from each participant. Body mass index (BMI) was calculated as weight (in kg) divided by height^2 (in m^2). Arterial blood pressure was also taken from each participant using a random-zero mercury column sphygmomanometer in the TwSHHH and an electric sphygmomanometer (BP3AC1-1, Microlife Cooperation, Berneck, Switzerland) in the TwSHHH-II. The electric sphygmomanometer has been validated according to the international protocol published by the European Society of Hypertension [12]. In addition, we evaluated the performance of blood pressure measurements for both a calibrated mercury sphygmomanometer and the BP3AC1-1 electric sphygmomanometer based on a random sample of 20 participants (mean age±SD, 53±14 years; 11 men and 9 women). The average difference between the two device readings was 0.6±1.5 mm Hg and 0.3±1.4 mmHg for systolic blood pressure (SBP) and diastolic blood pressure (DBP), respectively. In the current study, well-trained nurses measured the SBP and DBP two times in the left arm of seated participants according to a standardized protocol. A third blood pressure measurement was made if the first two blood pressure readings differed by more than 10 mm Hg. The average of the two closest readings was calculated to determine the reported blood pressure for each participant.

A blood sample was collected into an EDTA anticoagulant tube for each participant after a 12-h overnight fast. Standard enzymatic methods were used to determine serum cholesterol and triglycerides. Electrophoresis was performed to measure high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) . SUA was assayed using the colorimetric uricase–peroxidase principle [13]. Plasma glucose was measured by the hexokinase glucose-6-

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phosphate dehydrogenase procedure. Further, serum creatinine was analyzed by uncompensated Jaffe method with alkaline picrate kinetic test [14]. The coefficients of variation of these measurements were approximately 5%. All biochemical tests were performed using automatic analyzers (TBA-200FR, Toshiba Corporation, Tokyo, Japan). All measurements were taken with blinded quality control specimens in the central laboratory.

In the present study, abdominal obesity was indicated by waist circumference ≥90 cm in men and ≥80 cm in women [15]. In addition, the simplified Modification of Diet in Renal Disease (MDRD) equation was used to estimate glomerular filtration rate (eGFR) as 186.3 × (serum creatinine in mg/dL)$^{-1.154}$ × age$^{-0.203}$ × (0.742 for women) [16]. Further, hypertension was defined according to the criteria set in the JNC VI: SBP ≥140 mm Hg, DBP ≥90 mm Hg, or use of antihypertensive medications [17].

For study purposes, study subjects with a diagnosis of hypertension or baseline blood pressure measurements ≥140/90 mm Hg (n=726), and those with missing data on SUA (n=3) were excluded. Given that increased serum concentrations of uric acid have been implicated in cardiometabolic disorders [4,18] and hypertension is a powerful risk factor for cardiorenal complications [19], participants with a diagnosis of cardiovascular disease (n=352), a diagnosis of diabetes or baseline fasting glucose ≥126 mg/dL (n=133), or a diagnosis of chronic kidney disease or baseline eGFR <60 mL/min/1.73m^2 (n=211), were excluded from the data analysis .The final analytic sample included 3257 participants [mean (±SD) age, 37.83 (±14.26) years; 45.4% males] (Fig. 1).

2.3. *Statistical analysis*

In this Chinese population, the average concentration of SUA was significantly higher in men compared with women (7.16 vs. 5.37 mg/dL, P<.001). We classified participants on the basis of sex-specific quartiles of SUA. For descriptive analyses across the quartile group of SUA, we used chi-square analyses for categorical variables and ANOVA for continuous traits.

The outcomes examined were progression of blood pressure and incidence of hypertension. At baseline recruitment in 2002, we classified eligible participants into three groups of

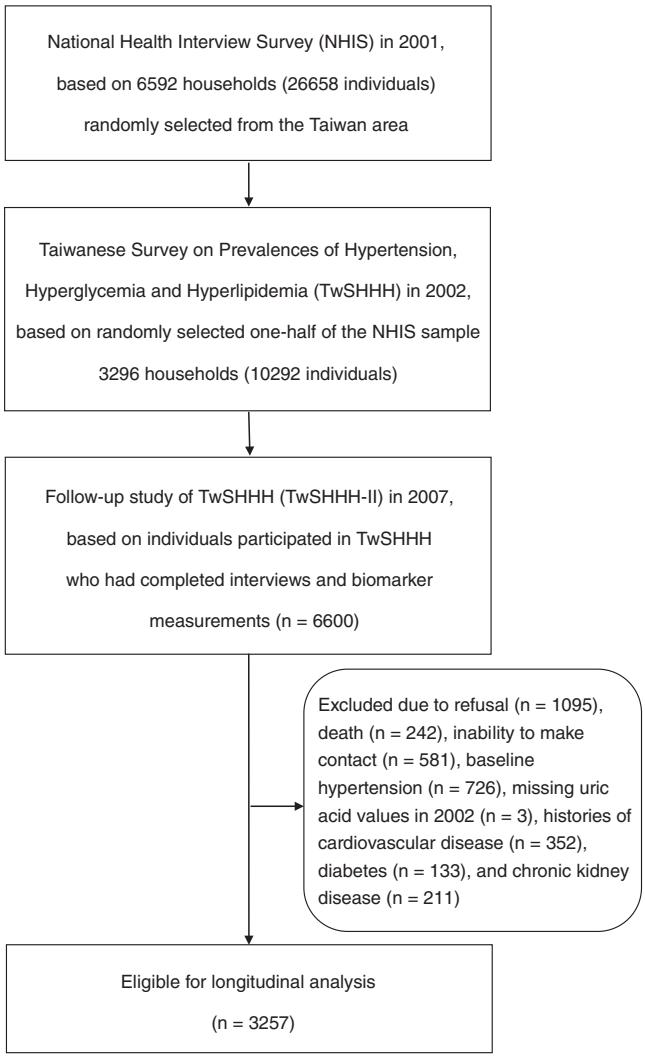

Fig. 1 – Flow chart of study participants in the Taiwanese Survey on Prevalences of Hypertension, Hyperglycemia, and Hyperlipidemia (TwSHHH) and a subsequent follow-up program (TwSHHH-II).

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Table 1 – Characteristics of study participants according to serum uric acid concentration at baseline enrollment in 2002, Taiwan (*n*=3257).

Quartile of serum uric acid (mg/dL)					
Characteristics	Q1	Q2	Q3	Q4	*P* value
Serum uric acid at baseline					
Men	<6.2	6.2–7.1	7.2–8.0	>8.0	
Women	<4.4	4.4–5.2	5.3–6.1	>6.1	
Clinical variables at baseline			Mean±SD		
Age, years	39.68±14.21	36.86±13.43	37.10±14.88	37.76±14.41	<.001
BMI [a], kg/m^2	21.95±2.90	22.56±3.43	23.05±3.54	24.39±4.20	<.001
WC [a], cm	75.47±9.56	76.00±10.82	77.86±10.16	80.56±11.44	<.001
SBP [a], mm Hg	107.64±11.72	107.82±11.70	109.18±12.20	111.02±11.44	<.001
DBP [a], mm Hg	70.46±8.45	70.55±8.64	71.64±8.53	73.23±8.29	<.001
Biochemical measures at baseline					
Total cholesterol, mg/dL	171.43±33.54	175.99±31.06	179.94±35.69	186.25±39.19	
HDL-C [a], mg/dL	56.11±14.28	56.76±13.44	55.51±14.52	54.45±15.44	<.001
LDL-C [a], mg/dL	106.68±24.48	109.89±23.93	113.03±26.31	117.42±27.90	.009
Triglycerides, mg/dL	95.61±49.26	102.30±59.65	118.63±75.72	136.98±86.11	<.001
Glucose, mg/dL	87.00±9.02	87.56±8.88	87.90±9.29	88.81±9.67	<.001
Creatinine, mg/dL	0.85±0.16	0.85±0.16	0.87±0.17	0.89±0.17	.001
eGFR [a], mL.min.1.73m^2	96.27±15.90	94.96±15.44	93.21±16.10	90.79±15.39	<.001
			No. (%)		
Blood pressure stage at baseline [b]					
Optimal	598 (75.3)	642 (74.0)	521 (67.1)	509 (62.2)	<.001
Normal	137 (17.3)	159 (18.3)	179 (23.0)	204 (24.9)	
High normal	59 (7.4)	67 (7.7)	77 (9.9)	105 (12.8)	
Blood pressure stage at follow-up [b]					
Optimal	490 (61.7)	563 (64.9)	398 (51.2)	373 (45.6)	<.001
Normal	180 (22.7)	163 (18.8)	181 (23.3)	224 (27.4)	
High normal	38 (4.8)	43 (5.0)	58 (7.5)	50 (6.1)	
Hypertension	86 (10.8)	99 (11.4)	140 (18.0)	171 (20.9)	

[a] BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate.
[b] Blood pressure stages at baseline and at follow-up were defined as optimal when SBP<120 mm Hg and DBP<80 mm Hg, normal when SBP 120–129 mm Hg or DBP 80–84 mm Hg, high normal when SBP 130–139 mm Hg or DBP 85–89 mm Hg, and hypertension at follow-up when SBP≧140 mm Hg or DBP≧90 mm Hg.

blood pressure measurements: optimal (SBP < 120 mm Hg and DBP < 80 mm Hg), normal (SBP 120–129 mm Hg or DBP 80–84 mm Hg), or high normal (SBP 130–139 mm Hg or DBP 85–89 mm Hg) blood pressure, as defined by the JNC VI [17]. If SBP and DBP belonged to different categories, the higher of the two readings was used to determine the blood pressure category. The progression of blood pressure during follow-up was defined by an increase of blood pressure ≥1 JNC VI stage [20]. In addition, the incidence of hypertension among non-hypertensive individuals at baseline recruitment in 2002 was measured at follow-up examination in 2007. Hazard ratios (HRs) calculated from the Cox proportional hazards model were used to investigate the relationships between baseline SUA and blood pressure outcomes at follow-up examinations and were adjusted for potential confounding covariates. To avoid collinearity between covariates (i.e., serum total cholesterol and LDL-C and HDL-C; serum creatinine and age, sex, and eGFR), potential confounding variables included in the model were age, sex, BMI (as a surrogate of general obesity), waist circumference (as an indicator of abdominal obesity), serum levels of total cholesterol, triglycerides, and creatinine, plasma glucose level, as well as SBP and DBP. The proportional hazards assumption was fulfilled for all factors used in the Cox model shown by parallel lines of −log[−log(survival)] versus log of follow-up time [21]. To test a linear trend across uric acid quartiles, we used the median uric acid concentration of each category as a continuous variable in the multivariate model. All of the analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA), and all of the statistical tests were 2-tailed with an α level of 0.05.

3. Results

Baseline characteristics of participants according to SUA concentration are shown in Table 1. Higher levels of SUA were significantly positively associated with BMI, waist circumference, blood pressure, serum levels of total cholesterol, LDL-C, triglycerides, and creatinine, as well as plasma glucose level. However, elevated levels of SUA were significantly negatively related to age, serum level of HDL-C, and eGFR.

At baseline recruitment in 2002, 2270 (69.7%) participants had optimal blood pressure, 679 (20.8%) had normal blood pressure, and 308 (9.4%) had higher normal blood pressure. During a mean follow-up of 5.41 (±0.19) years, 1119 (34.3%) individuals had experienced progression to a higher blood pressure stage and 496 (15.2%) subjects had developed hypertension. As shown in Table 1, higher levels of SUA

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Table 2 – Hazard ratios (HRs) of blood pressure (BP) progression according to baseline serum uric acid quartile.

Uric acid quartile, mg/dL	No. at risk	BP increase≧1 JNC VI stage No. (%)	HR (95% CI [a])	Adjusted HR [b] (95% CI)
Total				
Q1 (<5.0)	826	181 (21.9)	1.00 (reference)	1.00 (reference)
Q2 (5.0–6.0)	811	260 (32.1)	1.46 (1.21–1.76)	1.25 (1.02–1.54)
Q3 (6.1–7.2)	790	295 (37.3)	1.86 (1.54–2.24)	1.41 (1.14–1.75)
Q4 (>7.2)	830	383 (46.1)	2.20 (1.84–2.62)	1.78 (1.11–2.02)
				P_{trend}: .004
Male				
Q1 (<6.2)	392	157 (40.1)	1.00 (reference)	1.00 (reference)
Q2 (6.2–7.1)	375	138 (36.8)	1.02 (0.80–1.26)	1.01 (0.72–1.21)
Q3 (7.2–8.0)	346	163 (47.1)	1.25 (1.03–1.59)	1.15 (0.91–1.45)
Q4 (>8.0)	367	176 (48.0)	1.28 (1.04–1.42)	1.19 (1.01–1.31)
				P_{trend}: .038
Female				
Q1 (<4.4)	402	84 (20.9)	1.00 (reference)	1.00 (reference)
Q2 (4.4–5.2)	493	96 (19.5)	0.88 (0.65–1.17)	0.78 (0.54–1.04)
Q3 (5.3–6.1)	431	140 (32.5)	1.54 (1.18–2.02)	1.19 (1.01–1.54)
Q4 (>6.1)	451	165 (36.6)	1.86 (1.43–2.42)	1.26 (1.04–1.72)
				P_{trend}: .024

[a] CI, confidence interval.
[b] Hazard ratios were adjusted for sex (for the total), age, body mass index, waist circumference, total cholesterol, triglycerides, glucose, systolic and diastolic blood pressures, and serum creatinine levels measured at baseline recruitment.

were significantly associated with higher proportions of participants with high normal blood pressure at baseline and hypertension at follow-up. More specifically, at the follow-up examination, the risk of progression to a higher blood pressure group was significantly increased across SUA quartiles (Table 2). After adjustment for potential confounding covariates, participants in the highest SUA quartile had a significantly elevated risk of blood pressure progression than those in the lowest quartile (adjusted HR 1.78, 95% CI 1.11–2.02, *P* for trend .004). This positive gradient for the risk of blood pressure progression across quartiles of SUA was observed in both men and women.

In assessing whether the risk of hypertension was dependent on SUA, we found that there was a statistically significant trend for increasing incidence of hypertension across SUA quartiles (Table 3). After adjustment for potential

Table 3 – Incidence of hypertension in relation to baseline serum uric acid quartile.

Uric acid quartile, mg/dL	No. at risk	Incident hypertension No. (%)	HR (95% CI [a])	Adjusted HR [b] (95% CI)
Total				
Q1 (<5.0)	826	75 (9.1)	1.00 (reference)	1.00 (reference)
Q2 (5.0–6.0)	811	104 (12.8)	1.41 (0.85–1.90)	1.05 (0.76–1.46)
Q3 (6.1–7.2)	790	132 (16.7)	2.01 (1.51–2.66)	1.24 (1.12–1.78)
Q4 (>7.2)	830	185 (22.3)	2.56 (1.96–3.35)	1.68 (1.23–2.04)
				P_{trend}: .028
Per 1 SD increment in SUA				1.21 (1.05–1.38)
Male				
Q1 (<6.2)	392	51 (13.0)	1.00 (reference)	1.00 (reference)
Q2 (6.2–7.1)	375	56 (14.9)	1.26 (0.86–1.84)	1.14 (0.67–1.78)
Q3 (7.2–8.0)	346	76 (22.0)	1.75 (1.29–2.62)	1.21 (1.00–1.91)
Q4 (>8.0)	367	87 (23.7)	1.84 (1.24–2.48)	1.41 (1.08–1.92)
				P_{trend}: .028
Per 1 SD increment in SUA				1.17 (1.02–1.36)
Female				
Q1 (<4.4)	402	35 (8.7)	1.00 (reference)	1.00 (reference)
Q2 (4.4–5.2)	493	43 (8.7)	0.95 (0.61–1.48)	0.77 (0.47–1.27)
Q3 (5.3–6.1)	431	64 (14.8)	1.70 (1.13–2.57)	1.18 (1.02–1.67)
Q4 (>6.1)	451	84 (18.6)	2.27 (1.53–3.37)	1.64 (1.23–2.03)
				P_{trend}: .036
Per 1 SD increment in SUA				1.15 (1.04–1.33)

[a] CI, confidence interval.
[b] Hazard ratios were adjusted for sex (for the total), age, body mass index, waist circumference, total cholesterol, triglycerides, glucose, systolic and diastolic blood pressures, and serum creatinine levels measured at baseline recruitment.

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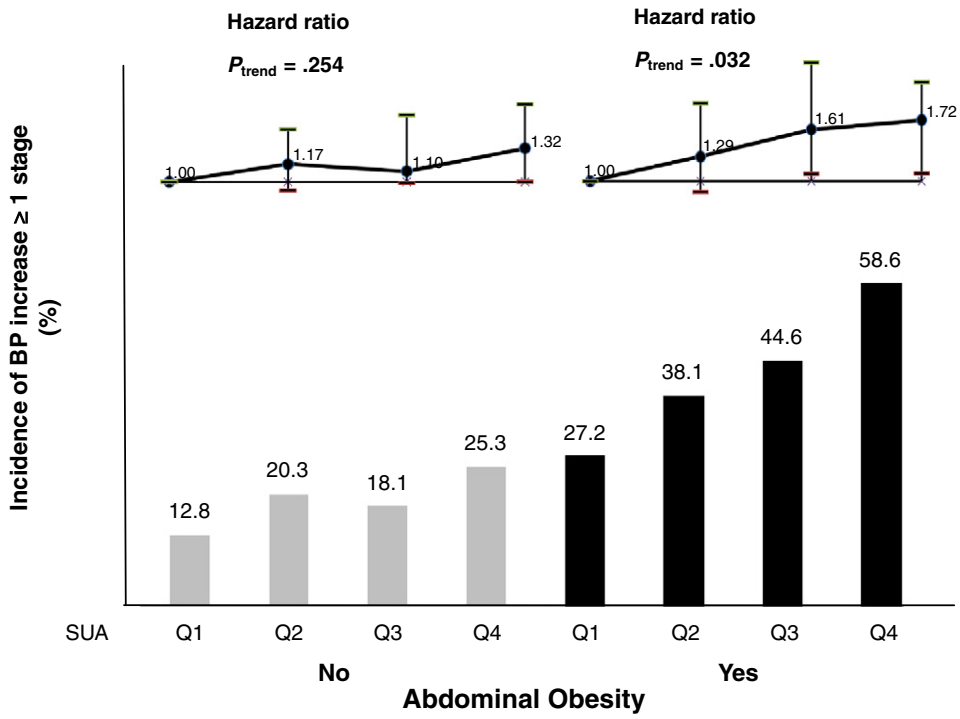

Fig. 2 – Incidences and hazard ratios(HRs) of blood pressure increase of ≥ one JNC VI stage in relation to serum uric acid (SUA) quartile, stratified by the presence or absence of abdominal obesity (defined by waist circumference ≥ 90 cm in men and ≥ 80 cm in women). Hazard ratios were adjusted for sex, age, body mass index, total cholesterol, triglycerides, glucose, systolic and diastolic blood pressures, and serum creatinine levels measured at baseline recruitment.

confounding variables, participants in the highest quartile had a greater risk of incident hypertension than those in the lowest quartile (adjusted HR 1.68, 95% CI 1.23–2.04, *P* for trend .028). This positively graded relationship between SUA concentration and the risk of hypertension was noted in both males and females. Furthermore, the results of multivariate analysis disclosed that a one-standard deviation (SD) increase in SUA was significantly associated with 21% increased risk of developing hypertension ($P < .001$, Table 3). This enhanced risk of incident hypertension associated with one-SD increment in SUA was observed in both men and women (Table 3).

Given that abdominal obesity is an important risk factor of cardiovascular diseases and a strong predictor of metabolic disorders in Taiwan [22,23], we performed an analysis to assess the potential modifying effect of abdominal obesity on the relationships between SUA and blood pressure outcomes. As shown in Fig. 2 and Fig. 3, after adjustment for potential confounding factors, a statistically significant trend for increasing risk of blood pressure progression (Fig. 2) and incident hypertension (Fig. 3) across SUA quartiles was more robust in participants with abdominal obesity (*P* values for trend test were .032 and .024, respectively) than in those without abdominal obesity (*P* values for trend test were .254 and .062, respectively).

4. Discussion

Our data clearly demonstrated that SUA was significantly positively associated with blood pressure progression and incident hypertension during follow-up in this comprehensive Chinese cohort in Taiwan. Associations were consistent for analyses relating SUA to blood pressure progression and incidence of hypertension. In addition, results of models using SUA as a continuous variable were also consistent with analyses assessing trend across quartiles.

Our principal findings relating SUA to blood pressure outcomes at short-term follow-up were in agreement with previous reports [24–33]. Our data were also consistent with results of previous meta-analysis showing a 55% increased risk of hypertension in those in the highest category of uric acid compared with those in the lowest [31]. However, the association derived from analysis using SUA as a continuous variable was stronger in our study (a 20% increased risk of incident hypertension per SD increment in SUA) compared with previous studies. For example, in the Atherosclerosis Risk in Communities study, a 1 SD increment in SUA was associated with a 7% greater risk of incident hypertension over 9 years of follow-up [30]. In another study of Framingham participants, an SD increment in SUA was in relation to a 10%–15% increased risk of hypertension incidence [29]. Thus, the prognostic significance of SUA with hypertension may vary by ethnicity.

Evidence from animal models has helped elucidate possible mechanisms whereby an elevated SUA may lead to hypertension. It has been known that uric acid may function as antioxidant that may prevent oxidant-induced cardiac and renal toxicity [34]. Nevertheless, uric acid is also a prooxidant that can increase oxygen radicals in circulation, which may, in turn, promote the lipid oxidation, leading to vascular endothelial dysfunction, inflammation, decreased nitric oxide

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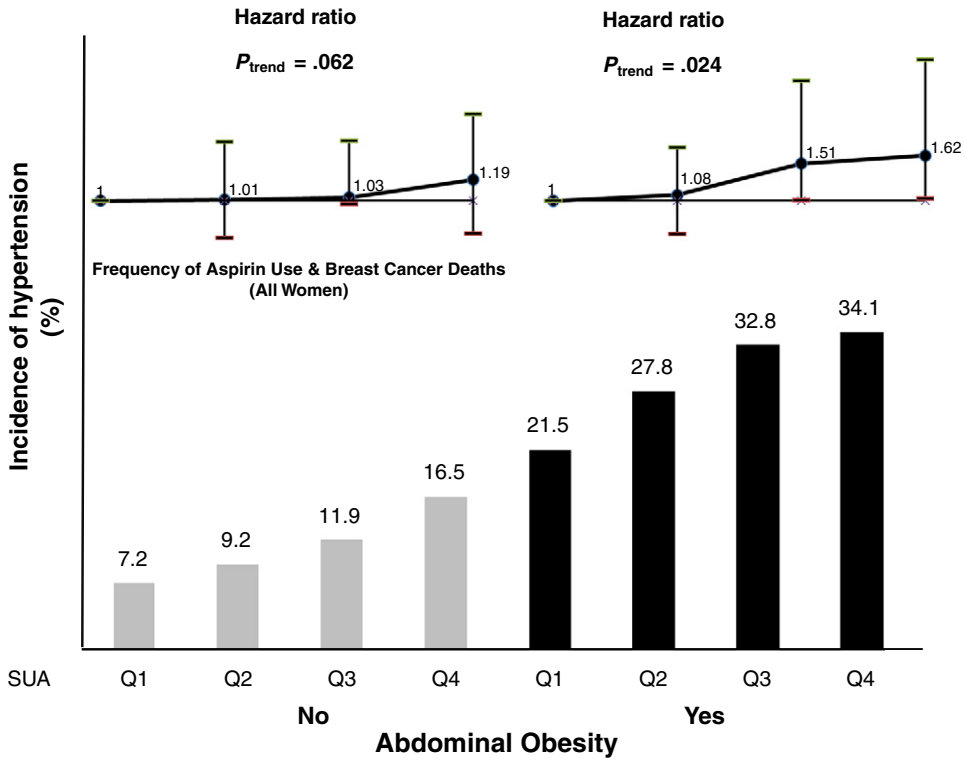

Fig. 3 – Incidences and hazard ratios (HRs) of incident hypertension (defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or use of antihypertensive medications) in relation to serum uric acid (SUA) quartile, stratified by the pressence or absence of abdominal obesity (defined by waist circumference ≥ 90 cm in men and ≥ 80 cm in women). Hazard ratios were adjusted for the same covariates as Fig. 2.

production, atherosclerosis, and thrombogenesis [5,35]. In animal models, the proinflammatory and proliferative effects of uric acid influence vascular smooth muscle cells [30]. In addition, hyperuricemia activates the renin–angiotensin system, which increases sodium resorption [4]. Hypertension develops thereafter in relation to intrarenal vascular disease. The observation that experimental hyperuricemia causes vascular inflammation, intrarenal vascular disease, and hypertension in animal models may also provide the long-sought pathogenic mechanism by which uric acid could cause cardiovascular disease in humans [4,35].

The present study provides an interesting data that female participants with SUA levels below the current definition of hyperuricemia were at increased risk for blood pressure progression and incident hypertension. These findings possibly suggest that there is no threshold of effect of SUA on hypertension. Further, it has been shown that the SUA concentration is more strongly associated with adverse effects in women than in men [5,36]. The SUA level was significantly associated with impaired endothelial function and increased levels of C-reactive protein in females but not in males [36]. Taken together, these study results represent that females may be more susceptible to uric acid-associated disorders than males.

More interestingly, in the current study, a significant trend for increasing risk of BP outcomes across SUA quartiles was most prominent in individuals with abdominal obesity. This observation was consistent with previous reports that joint exposure to elevated levels of SUA and abdominal obesity significantly increased the risk of incident hypertension [31]. Indeed, abdominal obesity is the major determinant of hyperinsulinemia/insulin resistance [37], which may enhance the reabsorption of uric acid, accompanied by decreased sodium and potassium excretion. Thus, abdominal obesity may function as a common precursor of hyperinsulinemia and hyperuricemia and strengthen the association of hyperuricemia with hypertension.

It is important to acknowledge the relative merits and weaknesses of the present study. The strengths of the study included samples representative of Chinese adult populations in Taiwan and prospective design. Moreover, the pattern of association for blood pressure progression across SUA quartiles was consistent when modeling the alternative outcome of hypertension incidence, strengthening the viewpoint that uric acid plays a pathogenic role in hypertension. On the other hand, the results of the present study need to be interpreted within the context of some limitations. Although our analyses made adjustments for important confounders, there remains the possibility that the observed relationship was secondary to residual confounding. Adequate evidence is available to link salt intake with an increased risk of hypertension [38]. However, data on salt intake were not obtained from study subjects in this study; the potential confounding effect of salt intake on the relationship of SUA with blood pressure outcomes, therefore, cannot be controlled for in the present study. In addition, SUA has been strongly associated with

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urinary microalbumin, a marker of early vascular damage and renal dysfunction in pre-hypertensive individuals [39]. In the absence of information on urinary albumin, we are unable to evaluate the potential confounding effect of preclinical proteinuria on the associations we observed.

In summary, baseline SUA level was an independent predictor of blood pressure progression and hypertension incidence during short-term follow-up in our community-based sample of non-hypertensive individuals. Previous studies have reported that hyperuricemia acts as an independent risk factor for cardiovascular and all-cause mortality in patients with hypertension in Taiwan [40,41]. These observations are of biological importance because they support the notion that uric acid plays a continuous role in the pathogenesis of cardiovascular disease.

Author contributions

Tsan Yang prepared the manuscript; Chi-Hong Chu, Chyi-Huey Bai, San-Lin You, and Yu-Ching Chou assisted the data collection; Lee-Ching Hwang, Kuo-Liong Chien, Ta-Chen Su, and Chin-Hsiao Tseng advised the interpretation of questionnaire data and laboratory assays;, and Chien-An Sun planned the study. All authors commented on the draft, contributed to the interpretation of the findings and approved the manuscript.

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Conflict of interest

The authors declare no conflict of interest.

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