Original Research

Sex-specific in the relationship between hyperuricemia and pulse pressure in non-diabetic Korean adults: the 2017 Korean National Health and Nutrition Examination Survey

Kyu Su Lee[1], Jae Min Lee[2], Chang Gi Kong[3], Cho Hee Park[4], Hyun Yoon[5],*

[1]Department of Radiological Science, Hanlyo University, 57764 Gwangyangsi, South Korea
[2]Department of Emergency Medical Technology, Gwangju Health University, 62287 Gwangsan-gu, South Korea
[3]Department of Radiology, Cheomdan Hospital, 62274 Gwangsan-gu, South Korea
[4]Department of global Medical Beauty, Konyang University, 32992 Nonsan-si, South Korea
[5]Department of Biomedical Laboratory Science, Wonkwang Health Science University, 54538 Iksan-si, South Korea
*Correspondence: yh9074@yahoo.co.kr (Hyun Yoon)

Abstract

Background and objective: The present study assesses the relationship between hyperuricemia and pulse pressure (PP) in non-diabetic Korean adults. **Material and methods**: Data from 5122 subjects (2251 men and 2871 women) in the seventh Korean National Health and Nutrition Examination Survey (KNHANES VII-2, 2017) were analyzed. **Results**: Systolic blood pressure (SBP) and PP were significant factors determining the odds ratios (ORs) for hyperuricemia (uric acid ≥ 7.0 mg/dL in men or ≥ 6.0 mg/dL in women) in men and the overall population. In women, SBP, diastolic blood pressure (DBP), and PP were not significant factors determining the OR for hyperuricemia. After adjusting for related variables, the OR of hyperuricemia was significantly higher in the high PP group (PP >60.0 mmHg) for men (OR, 1.760; 95% confidence interval [CI], 1.152–2.688) and the overall population (OR, 1.557; 95% CI, 1.132–2.140) compared with the normal PP group, but this trend was not seen in women (OR, 1.060; 95% CI, 0.646–1.740). **Conclusions**: Hyperuricemia was positively associated with PP in non-diabetic Korean men but not in women.

Keywords: Uric acid; Pulse pressure; Systolic blood pressure; Gender difference; Non-diabetic population

1. Introduction

High systolic blood pressure (SBP) affects cardiac structure and function and is associated with chronic left ventricular (LV) overload and ventricular remodeling [1,2]. In addition, some studies suggest that low diastolic blood pressure (DBP) is associated with coronary events and myocardial damage [3,4]. Pulse pressure (PP) is the difference between SBP and DBP. An elevated PP is a strong risk factor for LV hypertrophy, atrial fibrillation, and arterial stiffness [5–7].

Uric acid (UA) is mainly formed in the liver and intestine and is the end product of purine metabolism [8]. Hyperuricemia, defined as a serum UA concentration of ≥ 7.0 mg/dL in men and ≥ 6.0 mg/dL in women [9], is an independent risk factor for cardiovascular disease and is associated with diabetes, metabolic syndrome, hypertension, and chronic kidney disease in high-risk populations [10–12]. Additionally, some studies have demonstrated a relationship between carotid–femoral pulse wave velocity (PWV) and the development or progression of arterial stiffness and changes in the structural properties of the large artery wall in subjects with hyperuricemia [13–15].

To our best knowledge, there are no prior studies on the relationship between hyperuricemia and PP by gender in the non-diabetic Korean population. Therefore, we investigated this relationship using data from the seventh Korean National Health and Nutrition Examination Survey (KNHANES VII-2, 2017), a representative cross-sectional survey of the Korean population.

2. Methods

2.1 Study subjects

This study was based on data from the KNHANES VII–2 (2017), which are the most recent data for blood pressure and UA. The KNHANES is a cross-sectional survey conducted nationwide by the Division of Korean National Health and Welfare. The KNHANES VII–2 (2017) was performed from January 2017 to December 2017. Participants provided written informed consent to participate in this survey, and we received the data in anonymized form. In the KNHANES VII-1, 8127 individuals over age 1 were sampled for the survey. Among them, of the 6458 subjects who participated in the KNHANES VII-2, we limited the analyses to adults aged ≥ 20 years. We excluded participants 821 subjects whose data were missing for important analytic variables, such as UA, SBP, DBP, and various blood chemistry tests. Thereafter, we excluded those individuals with missing values or who suffered from diabetes (this included 515 subjects diagnosed with type 1 or 2 diabetes mellitus or with fasting blood glucose level ≥ 126 mg/dL, or treatment for hyperglycemia). Finally, 5122 sub-

jects (2251 men and 2871 women) were included in the statistical analysis (Fig. 1). This study was performed in accordance with the tenets of the Declaration of Helsinki. All survey participants agreed with the use of epidemiological research to identify risk factors and death causes of chronic diseases. Participants' records and information in the KNHANES were anonymous and de-identified prior to analysis. Further information can be found in "The KNHANES VII-2 (2017) Sample", which is available on the KNHANES website. The official website of KNHANES (http://knhanes.cdc.go.kr) is currently operating an English-language information homepage. The data of the respective year are available to everyone free of charge. If the applicant completes a simple subscription process and provides his/her email address on the official website of KNHANES, the data of the respective year can be downloaded free of charge. If additional information is required, the readers may contact the department responsible for the storage of data directly (Su Yeon Park, sun4070@korea.kr). As the data of KNHANES VII-2 are available to the public after removing personal identifiers and being anonymized, the Institutional Review Board (IRB) of Namseoul University determined that this study was exempt from requiring their approval (IRB No, 1041479-HR-201804-007).

2.2 General characteristics and blood chemistry

Research subjects were classified by sex (men and women), smoking (non-smoker or ex-smoker or current smoker), alcohol drinking (yes or no), and regular exercise (yes or no). Anthropometric measurements included measurement of body mass index (BMI), waist circumference (WC), SBP, and DBP. Blood chemistries included measurements of total cholesterol (TC), triglycerides (TGs), high density lipoprotein cholesterol (HDL-C), fasting blood glucose (FBG), blood urea nitrogen (BUN), creatinine (Crea), high sensitivity C reactive protein (CRP), and UA.

2.3 Hyperuricemia and pulse pressure

Hyperuricemia was classified as UA of over 7.0 mg/dL and 6.0 mg/dL for men and women [9]. SBP and DBP were measured by a nurse using a sphygmomanometer (Baumanometer, Wall Unit 33, USA) after the participants rested for over 20 minutes. SBP and DBP were measured twice on the right and left arm, and the average of the two values was calculated. PP was calculated as the difference between SBP and DBP. As a definitive cutoff value for high PP was not found in the literature, a high PP was classified when the PP was >60 mmHg [16].

2.4 Statistical analysis

The collected data were statistically analyzed using SPSS WIN version 18.0 (SPSS Inc., Chicago, IL, USA). The distributions of the participant characteristics were converted into percentages, and the successive data were presented as averages with standard deviations. The distribu-

tion and average difference in clinical characteristics according to normouricemia and hyperuricemia were calculated using a chi-square (χ^2) and an independent t-test. In the case of logistic regression for odds ratio of hyperuricemia, the 4 models constructed were: (1) non-adjusted; (2) adjusted for smoking, drinking, and regular exercising or gender; (3) further adjusted for BMI, WC, TC, TGs, HDL-C, BUN, Crea, FBG, and hs CRP or gender; (4) further adjusted for age or gender. The significance level for all of the statistical data was set as $p < 0.05$.

3. Results

3.1 Clinical characteristics of research subjects

The clinical characteristics of the research subjects are shown in Table 1. Among the 5122 subjects, the incidence of high PP was 574 (11.2%), and the incidence of hyperuricemia was 608 (11.9%). SBP, DBP, BMI, WC, TGs, FBG, BUN, Crea, hs CRP, and UA were higher in men than in women, TC and HDL-C were lower in men than in women, and PP was not significant. The incidence of both a high PP and hyperuricemia was higher in men than in women.

3.2 Clinical characteristics of subjects according to normouricemia and hyperuricemia groups in men, women, and the overall population

The clinical characteristics of the subjects according to the normouricemia and hyperuricemia groups are shown in Table 2. In the overall population, SBP and DBP were higher in the hyperuricemia group than in the normouricemia group, but age and PP were not significant. For both sexes, SBP, DBP, and age were higher in the hyperuricemia group than in the normouricemia group, whereas PP was significant for women only.

3.3 Logistic regression analyses for the independent factors determining hyperuricemia in men, women, and the overall population

Logistic regression analyses for the independent factors determining hyperuricemia are shown in Tables 3,4. SBP and PP, but not DBP, were significant factors determining the odds ratios (ORs) for hyperuricemia in men and the overall population (Table 3). In women, SBP, DBP, and PP were not significant factors determining the OR for hyperuricemia (Table 4).

3.4 Comparisons of hyperuricemia and high PP in men, women, and the overall population

Comparisons of the ORs of hyperuricemia according to high PP are shown in Table 5. After adjusting for related variables (except for age), the ORs of hyperuricemia in men and the overall population with normal and high PP were not significant (Model 3). However, after further adjusting for age, the ORs of hyperuricemia in men (OR, 1.460; 95% confidence interval [CI], 1.152–2.688) and the overall
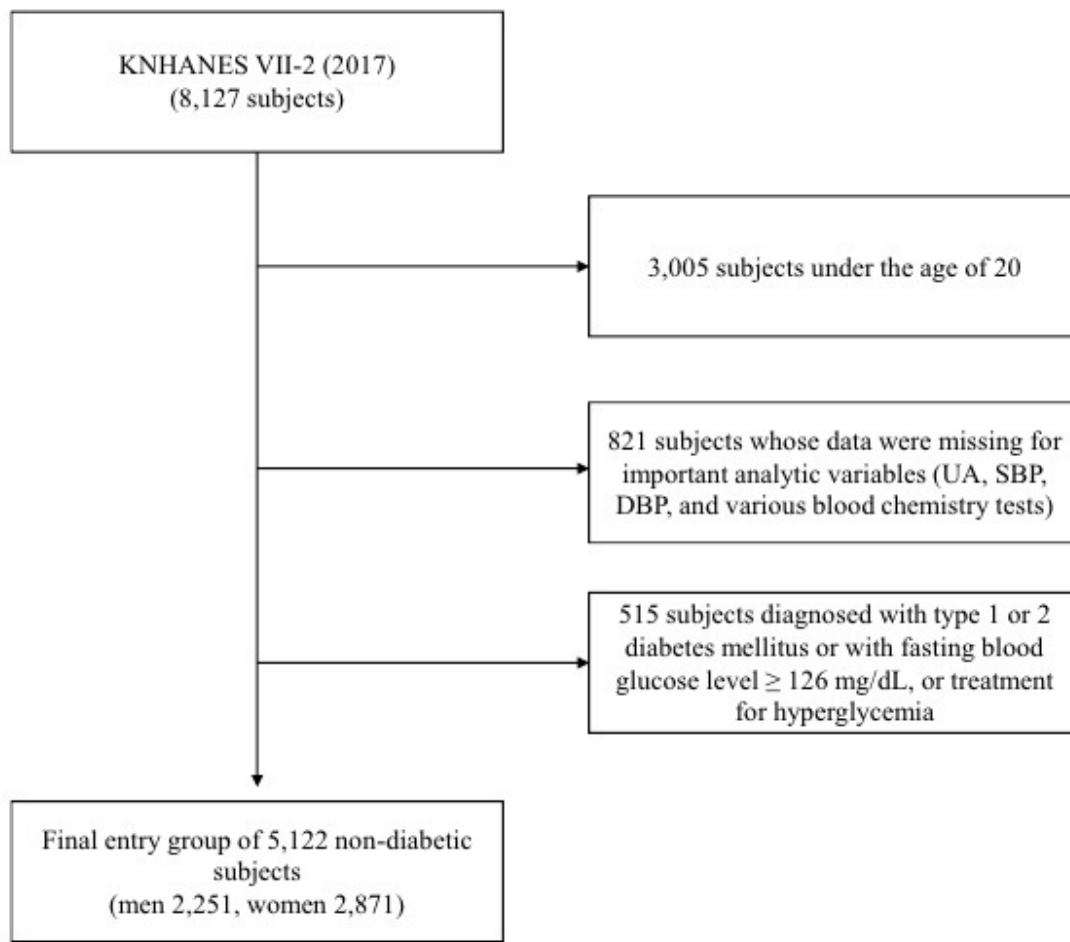
Fig. 1. Flowchart showing criteria for subject selection.

population (OR, 1.557; 95% CI, 1.132–2.140) were significantly higher for those with high PP than those with normal PP (Model 4). In women, after adjusting for related variables (including age), the OR of hyperuricemia in the normal PP and high PP group was not significant (OR, 1.060; 95% CI, 0.646–1.740).

4. Discussion

The present study investigated the association between hyperuricemia and PP by gender in non-diabetic Korean adults using data from the KNHANES VII-2 (2017). After adjustment for conventional risk factors, such as age, hyperuricemia was positively associated with PP in men but not in women.

UA, produced by the metabolism of purine nucleotides, tends to accumulate in the human body [17]. Hyperuricemia is a strong risk factor for atherosclerotic cardiovascular disease. Wu *et al*. [18] positively associated hyperuricemia with clustering of chronic vascular disease risk factors, such as obesity, dyslipidemia, and hypertension, in Chinese adults. In the Generation 3 Framingham Heart Study, serum UA was independently associated with carotid-femoral PWV and carotid-radial PWV, suggesting

a role for UA in increasing arterial stiffness [19]. In other studies, hyperuricemia was found to be an independent predictor of hypertension [20], arteriosclerosis [21], and the development of LV hypertrophy [22].

Serum UA can cause arteriosclerosis and LV hypertrophy by directly stimulating the renin-angiotensin system, reducing endothelial nitric oxide bioavailability, and inducing oxidative stress due to the generation of oxidants or NADPH during UA production by xanthine oxidoreductase. In turn, activation of the vascular renin-angiotensin system can lead to irreversible vasoconstriction and remodeling of the intrarenal vasculature [23,24]. Moreover, hyperuricemia can increase the endothelin-1 level and myocardial oxidative stress, inducing ventricular remodeling and LV hypertrophy [25]. Therefore, some studies argued that inhibitors of UA production, such as allopurinol, suppress LV hypertrophy and LV dysfunction [26,27].

In the presented study, after adjusting for related variables (excluding age), hyperuricemia was not associated with high PP in men, women, and the overall population. However, after further adjusting for age, hyperuricemia was positively associated with PP in men and the overall population but not in women. Age is associated with hype-

Table 1. General clinical characteristics (n (%), Mean ± SD).

Variables	Category	Overall (n = 5122)	Men (n = 2251)	Women (n = 2871)	p
Age (years)		51 ± 16	50 ± 16	51 ± 16	0.075
	<40	1428 (27.9)	662 (29.4)	766 (26.7)	0.095
	40–59	2040 (39.8)	880 (39.1)	1160 (40.4)	
	≥60	1654 (32.3)	709 (31.5)	945 (32.9)	
Drinking	Current drinker	2855 (55.7)	1620 (72.0)	1235 (43.0)	<0.001
Smoking	Current smoker	911 (17.8)	783 (34.8)	128 (4.5)	<0.001
Exercising	Regular exerciser	306 (6.0)	177 (7.9)	129 (4.5)	<0.001
SBP (mmHg)		119 ± 17	121 ± 15	117 ± 18	<0.001
DBP (mmHg)		76 ± 10.	78 ± 10	74 ± 10	<0.001
PP (mmHg)		43 ± 13	43 ± 13	43 ± 14	0.254
	Normal PP	4548 (88.8)	2036 (90.4)	2512 (87.5)	0.001
	High PP	574 (11.2)	215 (9.6)	359 (12.5)	
BMI (kg/m^2)		23.8 ± 3.5	24.3 ± 3.2	23.4 ± 3.6	<0.001
WC (cm)		81.4 ± 9.9	85.7 ± 8.9	78.1 ± 9.6	<0.001
TC (mg/dL)		194 ± 37	193 ± 37	196 ± 38	0.004
TGs (mg/dL)		131 ± 101	156 ± 123	111 ± 72	<0.001
HDL-C (mg/dL)		52 ± 12	47 ± 11	55 ± 12	<0.001
FBG (mg/dL)		95.5 ± 10.3	97.3 ± 10.6	94.1 ± 9.9	<0.001
BUN (mg/dL)		14.3 ± 4.4	14.9 ± 4.4	13.8 ± 4.3	<0.001
Crea (mg/dL)		0.8 ± 0.3	1.0 ± 0.3	0.7 ± 0.2	<0.001
hs CRP (mg/L)		1.1 ± 1.7	1.3 ± 1.9	1.0 ± 1.5	<0.001
UA (mg/dL)		5.1 ± 1.4	5.9 ± 1.3	4.4 ± 1.0	<0.001
	Normouricemia	4514 (88.1)	1813 (80.5)	2701 (94.1)	<0.001
	Hyperuricemia	608 (11.9)	438 (19.5)	170 (5.9)	

SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; High PP, PP ≥60 mmHg; BMI, body mass index; WC, waist circumference; TC, total Cholesterol; TGs, triglycerides; HDL-C, high density lipoprotein cholesterol; FBG, fasting blood glucose; BUN, blood urea nitrogen; Crea, creatinine; hs-CRP, high sensitivity C reactive protein; UA, uric acid; Hyperuricemia, UA ≥7.0 mg/dL in men or UA ≥6.0 mg/dL in women.

ruricemia and sexual hormones in both men and women. In our results, age was higher in the hyperuricemia group than in the normouricemia group for women but lower for men. Kurahashi et al. [28] observed a dose-response association between the onset of hyperuricemia and testosterone dose received by females undergoing testosterone replacement therapy, and a positive correlation between serum UA and creatinine levels. The up-regulation of UA was attributed, at least in part, to the rapid increase in purine production associated with the increase in muscle mass. Hak et al. [29] explained the increase in serum UA in women from the United States (US) by menopause and other age-related factors. Estrogen and progestogen therapy in post-menopausal women can dramatically lower serum UA levels [30]. Mumford et al. [31] revealed an inverse association between UA level and estrogen and progesterone in US women.

The association between UA and atherosclerosis and LV hypertrophy in men and women can differ by coun-try, race, and other potential confounding factors, such as obesity, hypertension, chronic kidney disease, and diabetes mellitus. According to Zangana, high UA level is positively linked to both LV mass and abnormal LV geometry among hypertensive adults in Iraq; and this effect is greater in men than in women [32]. In another study, an elevated serum UA level was positively associated with higher cardio-ankle vascular index risk in Chinese women but not in men [33]. Matsumura et al. [34] described serum UA as an independent factor for LV hypertrophy in hypertensive Japanese women ($p = 0.027$) but not in men ($p = 0.29$). In contrast, the Baltimore Longitudinal Study of Aging disclosed a positive correlation between serum UA level and PWV in US men but not in women [35]. In Chinese adults who underwent health screening, Kuo et al. [36] associated hyperuricemia with co-existing arterial stiffness, measured by abnormal brachial-ankle PWV, in men (OR, 2.72; 95% CI, 1.53–4.85) but not in women (OR, 1.14; 95% CI, 0.89–1.47). In addition, Kurata et al. [37] found a posi-

Table 2. General clinical characteristics according to uric acid in men and women (n (%), Mean ± SD).

Variables	Overall (n = 5122)			Men (n = 2251)			Women (n = 2871)		
	Normouricemia	Hyperuricemia	p	Normouricemia	Hyperuricemia	p	Normouricemia	Hyperuricemia	p
	(n = 4514)	(n = 608)		(n = 1813)	(n = 438)		(n = 2701)	(n = 170)	
UA (mg/dL)	4.7 ± 1.0	7.5 ± 0.9	<0.001	5.5 ± 0.9	7.8 ± 0.8	<0.001	4.2 ± 0.8	6.6 ± 0.7	<0.001
Age (years)	51 ± 16	48 ± 17	0.918	51 ± 16	45 ± 16	<0.001	50 ± 16	55 ± 18	<0.001
SBP (mmHg)	118 ± 17	123 ± 17	<0.001	120 ± 15	123 ± 15	<0.001	117 ± 18	123 ± 22	<0.001
DBP (mmHg)	75 ± 10	79 ± 12	<0.001	77 ± 10	80 ± 11	<0.001	74 ± 9	75 ± 12	0.013
PP (mmHg)	43 ± 13	44 ± 14	0.081	43 ± 13	42 ± 12	0.616	43 ± 14	47 ± 18	<0.001
High PP	501 (11.1)	73 (12.0)	0.494	175 (9.7)	40 (9.1)	0.786	326 (12.1)	33 (19.4)	0.008
BMI (kg/m^2)	23.6 ± 3.34	25.5 ± 3.8	<0.001	24.0 ± 3.0	25.6 ± 3.8	<0.001	23.3 ± 3.5	25.3 ± 3.8	<0.001
WC (cm)	80.66 ± 9.8	87.2 ± 9.8	<0.001	85.0 ± 8.5	88.6 ± 9.6	<0.001	77.8 ± 9.5	83.4 ± 9.4	<0.001
TC (mg/dL)	194 ± 37	200 ± 40	<0.001	191 ± 36	201 ± 39	<0.001	196 ± 37	197 ± 41	0.528
TGs (mg/dL)	123 ± 89	187 ± 151	<0.001	144 ± 107	203 ± 166	<0.001	109 ± 71	144 ± 88	<0.001
HDL-C (mg/dL)	52 ± 13	46 ± 11	<0.001	48 ± 11	44 ± 9	<0.001	55 ± 12	50 ± 12	<0.001
FBG (mg/dL)	95.3 ± 10.2	97.3 ± 11.0	0.036	97.3 ± 10.5	97.2 ± 10.9	0.832	93.9 ± 9.8	97.4 ± 11.3	<0.001
BUN (mg/dL)	14.1 ± 4.2	15.6 ± 5.6	<0.001	14.9 ± 4.4	15.1 ± 4.6	0.304	13.6 ± 4.0	16.8 ± 7.5	<0.001
Crea (mg/dL)	0.8 ± 0.3	1.0 ± 0.3	<0.001	0.95 ± 0.29	1.0 ± 0.3	<0.001	0.7 ± 0.0	0.9 ± 0.3	<0.001
hs CRP (mg/L)	1.1 ± 1.7	1.4 ± 1.8	<0.001	1.3 ± 1.9	1.4 ± 1.9	0.277	1.0 ± 1.5	1.5 ± 1.7	<0.001

Hyperuricemia, UA ≥7.0 mg/dL in men or UA ≥6.0 mg/dL in women.

Table 3. Comparisons of hyperuricemia and systolic and diastolic blood pressure.

Variables	Hyperuricemia (UA ≥7.0 mg/dL in men or ≥6.0 mg/dL in women)								
	Overall (n = 5122)			Men (n = 2251)			Women (n = 2871)		
	Exp (B)	95% CI	p	Exp (B)	95% CI	p	Exp (B)	95% CI	p
Women	0.679	0.500–0.922	0.013			None			
Age (years)	0.976	0.969–0.984	<0.001	0.973	0.964–0.982	<0.001	0.988	0.973–1.004	0.129
Current drinker	1.459	1.178–1.806	0.001	1.532	1.163–2.019	0.002	1.484	1.038–2.120	0.030
Current smoker	1.008	0.881–1.154	0.904	0.987	0.853–1.143	0.865	1.198	0.859–1.671	0.287
Regular exerciser	1.080	0.762–1.533	0.664	1.038	0.698–1.544	0.854	1.161	0.552–2.442	0.693
BMI (kg/m^2)	1.062	1.004–1.124	0.035	1.066	0.991–1.148	0.087	1.059	0.967–1.160	0.215
WC (cm)	1.015	0.993–1.038	0.174	1.007	0.980–1.035	0.605	1.021	0.984–1.061	0.272
TC (mg/dL)	1.004	1.002–1.007	0.001	1.006	1.003–1.010	<0.001	1.002	0.997–1.006	0.499
TGs (mg/dL)	1.002	1.001–1.002	0.001	1.001	1.000–1.002	0.006	1.001	0.999–1.003	0.177
HDL-C (mg/dL)	0.970	0.960–0.980	<0.001	0.968	0.955–0.981	<0.001	0.974	0.957–0.992	0.004
FBG (mg/dL)	0.999	0.989–1.008	0.759	0.993	0.982–1.005	0.238	1.012	0.995–1.029	0.157
BUN (mg/dL)	1.055	1.029–1.081	<0.001	1.022	0.991–1.054	0.162	1.108	1.064–1.154	<0.001
Crea (mg/dL)	3.613	2.082–6.271	<0.001	3.581	1.789–7.133	<0.001	3.284	1.331–10.982	0.013
hs CRP (mg/L)	1.026	0.978–1.077	0.294	1.004	0.946–1.065	0.898	1.087	0.998–1.184	0.055
SBP (mmHg)	1.014	1.006–1.022	<0.001	1.018	1.007–1.028	0.001	1.002	0.989–1.016	0.726
DBP (mmHg)	1.000	0.988–1.012	0.981	1.000	0.986–1.015	0.969	1.002	0.980–1.024	0.868

Hyperuricemia, UA ≥7.0 mg/dL in men or ≥6.0 mg/dL in women.

tive correlation between LV (LV mass and wall thickness) and serum UA level in Japanese hypertensive men but not in women, suggesting a link between elevated UA level and concentric hypertrophy in men. In our study of non-diabetic Korean adults, the association between hyperuricemia and PP differed between the sexes. As far as we know, there are no prior studies of gender differences in the relation-

ship between hyperuricemia and PP in non-diabetic populations. However, when evaluating the relationship between serum UA and PWV in healthy Brazilian adults, Baena *et al.* [38] described a positive association between serum UA and PWV in men (*p* = 0.01) but not in women (*p* = 0.10).

Currently, the exact reason for the gender difference in the association of UA with PP remains unclear. How-

Table 4. Comparisons of hyperuricemia and pulse pressure.

Variables	Overall (n = 5122)			Men (n = 2251)			Women (n = 2871)		
	Exp (B)	95% CI	p	Exp (B)	95% CI	p	Exp (B)	95% CI	p
Women	0.648	0.478–0.878	0.005		None				
Age (years)	0.976	0.969–0.984	<0.001	0.974	0.965–0.983	<0.001	0.988	0.973–1.003	0.127
Current drinker	1.489	1.203–1.843	<0.001	1.565	1.189–2.059	0.001	1.496	1.048–2.134	0.026
Current smoker	1.001	0.875–1.145	0.987	0.997	0.844–1.130	0.751	1.201	0.861–1.675	0.281
Regular exerciser	1.070	0.754–1.518	0.706	1.024	0.668–1.524	0.906	1.161	0.552–2.442	0.695
BMI (kg/m^2)	1.073	1.014–1.134	0.014	1.079	1.003–1.161	0.040	1.062	0.971–1.162	0.188
WC (cm)	1.015	0.993–1.037	0.183	1.007	0.980–1.035	0.607	1.021	0.983–1.060	0.279
TC (mg/dL)	1.005	1.002–1.008	<0.001	1.007	1.003–1.010	<0.001	1.002	0.997–1.006	0.459
TGs (mg/dL)	1.002	1.001–1.003	<0.001	1.002	1.001–1.003	0.001	1.001	0.999–1.003	0.168
HDL-C (mg/dL)	0.971	0.961–0.981	<0.001	0.970	0.958–0.983	<0.001	0.974	0.957–0.992	0.004
FBG (mg/dL)	1.000	0.990–1.009	0.947	0.995	0.984–1.007	0.399	1.012	0.996–1.029	0.148
BUN (mg/dL)	1.052	1.026–1.078	<0.001	1.016	0.985–1.048	0.312	1.108	1.063–1.154	<0.001
Crea (mg/dL)	3.677	2.120–6.379	<0.001	3.774	1.897–7.506	<0.001	3.767	1.317–10.775	0.013
hs CRP (mg/L)	1.027	0.978–1.078	0.286	1.005	0.948–1.066	0.869	1.087	0.998–1.185	0.055
PP (mmHg)	1.014	1.006–1.022	0.001	1.016	1.005–1.026	0.003	1.003	0.990–1.016	0.693

Hyperuricemia, UA ≥7.0 mg/dL in men or UA ≥6.0 mg/dL in women.

Table 5. Comparisons of hyperuricemia and high pulse pressure.

Gender	Category	Hyperuricemia (UA ≥7.0 mg/dL in men or UA ≥6.0 mg/dL in women)			
		Model 1	Model 2	Model 3	Model 4
Overall (n = 5122) *	Normal PP	1	1	1	1
	High PP	1.093 (0.841–1.420)	1.305 (0.994–1.712)	1.170 (0.870–1.574)	1.557 (1.132–2.140)
	p	0.482	0.072	0.286	0.005
Men (n = 2251)**	Normal PP	1	1	1	1
	High PP	0.941 (0.656–1.349)	1.009 (0.701–1.453)	1.247 (0.839–1.853)	1.760 (1.152–2.688)
	p	0.774	0.937	0.264	0.006
Women (n = 2871)**	Normal PP	1	1	1	1
	High PP	1.755 (1.179–2.611)	1.827 (1.217–2.741)	0.938 (0.589–1.493)	1.060 (0.646–1.740)
	p	0.006	0.004	0.810	0.823

High PP, PP ≥60 mmHg.

*Model 1, non-adjusted; Model 2, further adjusted for gender, smoking, drinking, and regular exercising; Model 3, Model 2 further adjusted for BMI, WC, TC, TGs, HDL-C, BUN, Crea, FBG, and hs CRP; Model 4, Model 3 further adjusted for age.

**Model 1, non-adjusted; Model 2, further adjusted for smoking, drinking, and regular exercising; Model 3, Model 2 further adjusted for BMI, WC, TC, TGs, HDL-C, BUN, Crea, FBG, and hs CRP; Model 4, Model 3 further adjusted for age.

ever, there are several potential explanations. First, despite smaller carotid arteries in women than men, women are much less likely to develop atherosclerosis than men. However, postmenopausal women, especially those with an autoimmune disease, are at an increased risk of developing atherosclerosis [39]. In this regard, Fairweather suggested that differences in sex hormones alter the immune response during atherosclerosis [40]. Cytokines, enzymes, and other mediators, such as mast cells and macrophages, produced due to elevated innate immune activation in men, allow remodeling of the blood vessel wall, a key process

in the pathogenesis of atherosclerosis; in contrast, estrogen promotes more antibodies and auto-antibodies against oxidized low-density lipoprotein in the form of immune complexes, which coupled with the smaller size of vessels, leads to atherosclerosis in women [40]. In the National Heart, Lung, and Blood Institute Family Heart Study in the US, a positive interaction was reported between serum UA and carotid atherosclerotic plaques in men (p = 0.002) but not in women (p = 0.08) [41]. Second, PP, the difference between SBP and DBP, is a known predictor of arteriosclerosis and LV hypertrophy [42]. If SBP increases and DBP decreases,

or SBP increases and DBP does not increase, then PP increases. An increase in SBP is associated with chronic LV overload, which enhances myocardial wall stress and oxygen demand [43]. Pérez-Lahiguera *et al.* [44] reported that both SBP ($p = 0.001$) and PP ($p = 0.001$) were positively associated with the LV mass index in Spanish adults, but DBP ($p = 0.070$) was not significant. In the study by Lin *et al.* [45], hyperuricemia was an independent risk factor of increased SBP in Chinese men but not in women. In terms of arithmetic methods, PP increases when SBP increases and DBP decreases; SBP does not increase, and DBP decreases; and SBP increases and DBP does not increase. One reason for the increased PP in hyperuricemia is that hyperuricemia is associated with an increase in SBP in men and the overall population (without an increase in DBP, i.e., the third case scenario mentioned above) but not in women (Tables 3,4). In our study, SBP but not DBP was an independent risk factor for hyperuricemia in men; for this reason, PP was also an independent risk factor. In contrast, SBP, DBP, and, thereby PP, were not independent risk factors for hyperuricemia in women.

The present study has some limitations. First, medications for antihypertensive therapy constitute important determinants of PP. However, most of the subjects in the KNHANES VII-2 study did not answer the question about antihypertensive drugs. Therefore, we could not use antihypertensive drugs as an adjustment variable for analyzing the association between hyperuricemia and PP. In addition, antihypertensive drugs constitute determinants of the relationship between hyperuricemia and PP. However, the use of UA inhibitors was not investigated in the KNHANES VII-2 study. Therefore, antihypertensive drugs and UA inhibitors should be included as adjustment variables for exploring the link between PP and hyperuricemia in future studies. Second, because KNHANES VII-2 is a cross-sectional study, there is a limitation to establishing a causal relationship between hyperuricemia and PP by gender among Korean non-diabetic adults. However, this is the first study to report the relationship between hyperuricemia and PP among Korean non-diabetic adults. More accurate results might be obtained by performing a cohort study.

5. Conclusions

The present study investigated the association between UA and PP in a non-diabetic Korean population using data from the KNHANES VII-2. Hyperuricemia was positively associated with PP in men but not in women. Our results may provide fundamental data linking UA with arterial stiffness and cardiovascular disease.

Author contributions

HY and JML contributed to conception and design. CGK and CHP contributed to data acquisition, analysis and interpretation. HY and KSL were a major contributor in writing the manuscript. All authors read and approved the final manuscript.

References

[1] Ioannou CV, Morel DR, Katsamouris AN, Katranitsa S, Startchik I, Kalangos A, *et al.* Left ventricular hypertrophy induced by reduced aortic compliance. Journal of Vascular Research. 2009; 46: 417–425.

[2] White WB. Systolic versus diastolic blood pressure versus pulse pressure. Current Cardiology Reports. 2002; 4: 463–467.

[3] McEvoy JW, Chen Y, Rawlings A, Hoogeveen RC, Ballantyne CM, Blumenthal RS, *et al.* Diastolic Blood Pressure, Subclinical Myocardial Damage, and Cardiac Events. Journal of the American College of Cardiology. 2016; 68: 1713–1722.

[4] Vidal-Petiot E, Ford I, Greenlaw N, Ferrari R, Fox KM, Tardif J, *et al.* Cardiovascular event rates and mortality according to achieved systolic and diastolic blood pressure in patients with stable coronary artery disease: an international cohort study. Lancet. 2016; 388: 2142–2152.

[5] Mitchell GF, Vasan RS, Keyes MJ, Parise H, Wang TJ, Larson MG, *et al.* Pulse Pressure and Risk of New-Onset Atrial Fibrillation. Journal of the American Medical Association. 2007; 297: 709–715.

[6] Pääkkö TJW, Perkiömäki JS, Kesäniemi YA, Ylitalo AS, Lumme JA, Huikuri HV, *et al.* Increasing ambulatory pulse pressure predicts the development of left ventricular hypertrophy during long-term follow-up. Journal of Human Hypertension. 2018; 38: 180–189.

[7] Said MA, Eppinga RN, Lipsic E, Verweij N, van der Harst P. Relationship of Arterial Stiffness Index and Pulse Pressure with Cardiovascular Disease and Mortality. Journal of the American Heart Association. 2018; 7: e007621.

[8] George J, Struthers AD. Role of urate, xanthine oxidase and the effects of allopurinol in vascular oxidative stress. Vascular Health Risk Management. 2009; 5: 265–272.

[9] Lin KC, Lin HY, Chou P. Community based epidemiological study on hyperuricemia and gout in Kin-Hu, Kinmen. The Journal of Rheumatology. 2000; 27: 1045–1050.

[10] Feig DI, Kang D, Johnson RJ. Uric acid and cardiovascular risk. the New England Journal of Medicine. 2008; 359: 1811–1821.

[11] Liu W, Hung C, Chen S, Yeh S, Lin M, Chiu Y, *et al.* Association of hyperuricemia with renal outcomes, cardiovascular disease, and mortality. Clinical Journal of the American Society of Nephrology. 2012; 7: 541–548.

[12] Sánchez-Lozada LG, Soto V, Tapia E, Avila-Casado C, Sautin YY, Nakagawa T, *et al.* Role of oxidative stress in the renal abnormalities induced by experimental hyperuricemia. American

Journal of Physiology-Renal Physiology. 2008; 295: F1134–F1141.

[13] Chen X, Li Y, Sheng C, Huang Q, Zheng Y, Wang J. Association of serum uric acid with aortic stiffness and pressure in a Chinese workplace setting. American Journal of Hypertension. 2010; 23: 387–392.

[14] Choi HY, Kim S, Choi AR, Kim SG, Kim H, Lee JE, et al. Hyperuricemia and risk of increased arterial stiffness in healthy women based on health screening in Korean population. PLoS ONE. 2017; 12: e0180406.

[15] Ramirez-Sandoval JC, Sanchez-Lozada LG, Madero M. Uric Acid, Vascular Stiffness, and Chronic Kidney Disease: is there a Link? Blood Purification. 2017; 43: 189–195.

[16] McEvoy JW, Chen Y, Rawlings A, Hoogeveen RC, Ballantyne CM, Blumenthal RS, et al. Diastolic Blood Pressure, Subclinical Myocardial Damage, and Cardiac Events: Implications for Blood Pressure Control. Journal of the American College of Cardiology. 2016; 68: 1713–1722.

[17] Caliceti C, Calabria D, Roda A, Cicero AFG. Fructose Intake, Serum Uric Acid, and Cardiometabolic Disorders: a Critical Review. Nutrients. 2017; 9: E395.

[18] Wu J, Qiu L, Cheng X, Xu T, Wu W, Zeng X, et al. Hyperuricemia and clustering of cardiovascular risk factors in the Chinese adult population. Scientific Reports. 2017; 7: 5456.

[19] Mehta T, Nuccio E, McFann K, Madero M, Sarnak MJ, Jalal D. Association of Uric Acid with Vascular Stiffness in the Framingham Heart Study. American Journal of Hypertension. 2015; 28: 877–883.

[20] Kuwabara M, Hisatome I, Niwa K, Hara S, Roncal-Jimenez CA, Bjornstad P, et al. Uric Acid is a Strong Risk Marker for Developing Hypertension from Prehypertension. Hypertension. 2018; 71: 78–86.

[21] Wakuda H, Uchida S, Ikeda M, Tabuchi M, Akahoshi Y, Shinozuka K, et al. Is hyperuricemia a risk factor for arteriosclerosis? Uric acid and arteriosclerosis in apolipoprotein e-deficient mice. Biological &Amp; Pharmaceutical Bulletin. 2014; 37: 1866–1871.

[22] Cuspidi C, Facchetti R, Bombelli M, Sala C, Tadic M, Grassi G, et al. Prevalence and correlates of new-onset left ventricular geometric abnormalities in a general population: the PAMELA study. Journal of Hypertension. 2016; 34: 1423–1431.

[23] Bavishi C, Messerli FH, Rimoldi SF. Serum Uric Acid in Primary Hypertension: from Innocent Bystander to Primum Movens? Hypertension. 2016; 67: 845–847.

[24] Mazzali M, Kanellis J, Han L, Feng L, Xia Y, Chen Q, et al. Hyperuricemia induces a primary renal arteriolopathy in rats by a blood pressure-independent mechanism. American Journal of Physiology Renal Physiology. 2002; 282: F991–F997.

[25] Chen C, Hsu Y, Lee T. Impact of elevated uric acid on ventricular remodeling in infarcted rats with experimental hyperuricemia. American Journal of Physiology Heart and Circulatory Physiology. 2011; 301: H1107–H1117.

[26] Kao MP, Ang DS, Gandy SJ, Nadir MA, Houston JG, Lang CC, et al. Allopurinol benefits left ventricular mass and endothelial dysfunction in chronic kidney disease. Journal of the American Society of Nephrology. 2011; 22: 1382–1389.

[27] Szwejkowski BR, Gandy SJ, Rekhraj S, Houston JG, Lang CC, Morris AD, et al. Allopurinol reduces left ventricular mass in patients with type 2 diabetes and left ventricular hypertrophy. Journal of the American College of Cardiology. 2013; 62: 2284–2293.

[28] Kurahashi H, Watanabe M, Sugimoto M, Ariyoshi Y, Mahmood S, Araki M, et al. Testosterone replacement elevates the serum uric acid levels in patients with female to male gender identity disorder. Endocrine Journal. 2013; 60: 1321–1327.

[29] Hak AE, Choi HK. Menopause, postmenopausal hormone use and serum uric acid levels in us women–the third National Health and Nutrition Examination Survey. Arthritis Research & Therapy. 2008; 10: R116.

[30] Jung JH, Song GG, Lee YH, Kim J, Hyun MH, Choi SJ. Serum uric acid levels and hormone therapy type: a retrospective cohort study of postmenopausal women. Menopause. 2018; 25: 77–81.

[31] Mumford SL, Dasharathy SS, Pollack AZ, Perkins NJ, Mattison DR, Cole SR, et al. Serum uric acid in relation to endogenous reproductive hormones during the menstrual cycle: findings from the BioCycle study. Human Reproduction. 2013; 28: 1853–1862.

[32] Zangana SN. The impact of gender on serum uric acid levels in hypertensive patients with left ventricular hypertrophy in Erbil city-Iraq. International Journal of Medical Research and Health Sciences. 2016; 2: 4–8.

[33] Zheng X, Wei Q, Long J, Gong L, Chen H, Luo R, et al. Gender-specific association of serum uric acid levels and cardio-ankle vascular index in Chinese adults. Lipids in Health and Disease. 2018; 17: 80.

[34] Matsumura K, Ohtsubo T, Oniki H, Fujii K, Iida M. Gender-related association of serum uric acid and left ventricular hypertrophy in hypertension. Circulation Journal. 2006; 70: 885–888.

[35] Canepa M, Viazzi F, Strait JB, Ameri P, Pontremoli R, Brunelli C, et al. Longitudinal Association between Serum Uric Acid and Arterial Stiffness: Results from the Baltimore Longitudinal Study of Aging. Hypertension. 2017; 69: 228–235.

[36] Kuo C, Yu K, Luo S, Ko Y, Wen M, Lin Y, et al. Role of uric acid in the link between arterial stiffness and cardiac hypertrophy: a cross-sectional study. Rheumatology. 2010; 49: 1189–1196.

[37] Kurata A, Shigematsu Y, Higaki J. Sex-related differences in relations of uric acid to left ventricular hypertrophy and remodeling in Japanese hypertensive patients. Hypertension Research. 2005; 28: 133–139.

[38] Baena CP, Lotufo PA, Mill JG, Cunha Rde S, Benseñor IJ. Serum Uric Acid and Pulse Wave Velocity Among Healthy Adults: Baseline Data From the Brazilian Longitudinal Study of Adult Health (ELSA-Brazil). American Journal of Hypertension. 2015; 28: 966–970.

[39] Fairweather D, Petri MA, Coronado MJ, Cooper LT. Autoimmune heart disease: role of sex hormones and autoantibodies in disease pathogenesis. Expert Review of Clinical Immunology. 2012; 8: 269–284.

[40] Fairweather D. Sex differences in inflammation during atherosclerosis. Clinical Medicine Insights. Cardiology. 2015; 8: S49–S59.

[41] Neogi T, Ellison RC, Hunt S, Terkeltaub R, Felson DT, Zhang Y. Serum uric acid is associated with carotid plaques: the National Heart, Lung, and Blood Institute Family Heart Study. The Journal of Rheumatology. 2009; 36: 378–384.

[42] Pääkkö TJW, Perkiömäki JS, Kesäniemi YA, Ylitalo AS, Lumme JA, Huikuri HV, et al. Increasing ambulatory pulse pressure predicts the development of left ventricular hypertrophy during long-term follow-up. Journal of Human Hypertension. 2018; 32: 180–189.

[43] White WB. Systolic versus diastolic blood pressure versus pulse pressure. Current Cardiology Reports. 2002; 4: 463–467.

[44] Pérez-Lahiguera FJ, Rodilla E, Costa JA, Gonzalez C, Martín J, Pascual JM. Relationship of central and peripheral blood pressure to left ventricular mass in hypertensive patients. Revista Espanola De Cardiologia. 2012; 65: 1094–1100.

[45] Lin X, Wang X, Li X, Song L, Meng Z, Yang Q, et al. Gender- and Age-Specific Differences in the Association of Hyperuricemia and Hypertension: a Cross-Sectional Study. International Journal of Endocrinology. 2019; 2019: 7545137.