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Association between Urine Albumin-to-Creatinine Ratio within the Normal Range and Incident Hypertension in Men and Women

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Purpose: There have been few studies on gender difference in the impact of a urine albumin-to-creatinine ratio (UACR) within the normal range on the risk of hypertension. We evaluated whether the association between the UACR below the microalbuminuria range and the incident risk of hypertension is different between men and women.

Materials and Methods: A total of 1173 individuals (442 men and 731 women) aged 40 to 70 years without hypertension was examined at baseline (2005–2008) and followed (2008–2011). We defined the UACR as the amount of albumin (mg/dL) divided by creatinine (g/dL) in randomly voided urine. The subjects were classified according to UACR tertile.

Results: During an average of 2.6 years of follow-up, 57 men (12.9%) and 66 women (9.0%) developed hypertension. In multivariable-adjusted models, the odds ratio for new-onset hypertension comparing the highest and lowest tertiles of UACR was 1.83 [95% confidence interval (CI) 0.85–3.94] in men and 2.69 (95% CI 1.27–5.73) in women. In stratified analyses by menopausal status, higher tertiles of UACR were associated with an increased risk of incident hypertension in postmenopausal women.

Conclusion: Higher normal UACR levels were associated with an increased risk of incident hypertension in women. The UACR could have a clinical role in predicting the development of hypertension.

Key Words: Albuminuria, hypertension, prospective study

INTRODUCTION

Hypertension is one of the most influential risk factors for mortality worldwide.[1,2] Epidemiological studies have reported that hypertension is strongly associated with the risk of coronary heart disease, cerebrovascular disease, and chronic kidney disease.[3-5] However, there remains a lack of understanding of the determinants of hypertension.

Microalbuminuria is a diagnostic criterion for chronic kidney disease[6] and an independent predictor of hypertension, metabolic syndrome, type 2 diabetes and coronary heart disease.[7-9] Early diagnosis and appropriate management of microalbuminuria could reduce the burden of hypertension-related morbidity and mortality in the general population.[10] Urine albumin-to-creatinine ratio (UACR) calculation is a method by which an individual can be diagnosed with albuminuria. The method is easy and quite acceptable in large epidemiological studies.

Previous studies have reported that an increased UACR is associated with the development of hypertension.[11,12] Recently, several longitudinal studies have demonstrated that higher UACR values within the normal range can be used to predict the development of hypertension.[13-15] However, few studies have evaluated the gender difference in the association between a

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UACR below the microalbuminuria range and the risk of incident hypertension. We examined whether the association between a UACR in the normal range and the incident risk of hypertension differs by gender in a community-based prospective study.

MATERIALS AND METHODS

Study design and participants

Our study data were obtained from the Korean Genome and Epidemiology Study on Atherosclerosis Risk of Rural Areas in the Korean General Population (KoGES-ARIRANG), which is an ongoing prospective study conducted in Wonju and Pyeongchang, Korea.[16] A total of 5178 adults aged 40 to 70 years were included in the baseline survey (November 2005 to January 2008), of whom 3862 participants (74.6%) attended the first follow-up survey, which was carried out from April 2008 to January 2011. We excluded 863 subjects without baseline UACR measurements, 1658 subjects with hypertension at baseline, and 19 participants with a history or presence of cardiovascular disease. To include only subjects with a UACR within the normal range, we excluded those with a UACR of ≥30 mg/g (n=149).[17] Ultimately, 1173 individuals (442 men and 731 women) were included in the analysis (Fig. 1). The protocol for this study was approved by the Institutional Review Board of Wonju Severance Christian Hospital, and all participants provided written informed consent for the study.

Anthropometric and biochemical measurements

At baseline and at the first follow-up examination, study participants underwent a complete evaluation of medical history and answered a lifestyle questionnaire. Body weight and height were measured while participants wore light indoor clothing without shoes. Systolic and diastolic blood pressures were measured from the right arm using a standard mercury sphygmomanometer (Baumanometer, Copiague, NY, USA) after each participant had rested for 5 minutes. Two measurements were taken with at least 5-minute intervals, and the mean of the two blood pressure readings was used for the analyses. A suitable cuff size was chosen for each participant according to the mid-arm circumference. Muscle mass was measured via bioelectrical impedance analysis (Zeus 9.9, Jawon Medical Co., Ltd., Gyeongsan, Korea). Baseline data for past history of disease and current smoking and alcohol drinking status were collected using self-reported questionnaires. Subjects who answered "yes" to the question "Do you perform physical exercise regularly enough to make you sweat?" were placed in the regular exercise group.

Antecubital venous blood samples were collected from the participants after fasting for more than 12 hours or overnight. The fasting glucose and insulin levels were determined using a glucose oxidase-based assay and double-antibody radioimmunoassay (Biosource Europe SA, Nivelles, Belgium). Serum concentrations of high-density lipoprotein (HDL) and low-density lipoprotein cholesterol and triglyceride were determined using enzymatic methods (Advia 1650; Siemens, Tarrytown, NY, USA). High-sensitivity C-reactive protein (hs-CRP) was analyzed using the Denka Seiken assay (Tokyo, Japan). The estimated glomerular filtration rate (GFR) was calculated using the Modification of Diet in Renal Disease equation:[18]

$$\text{Estimated GFR} = 186 \times [\text{Serum Creatinine (in mg/dL)}]^{-1.154} \times [\text{Age (in years)}]^{-0.203} \times [0.742 \text{ (if female)}]$$

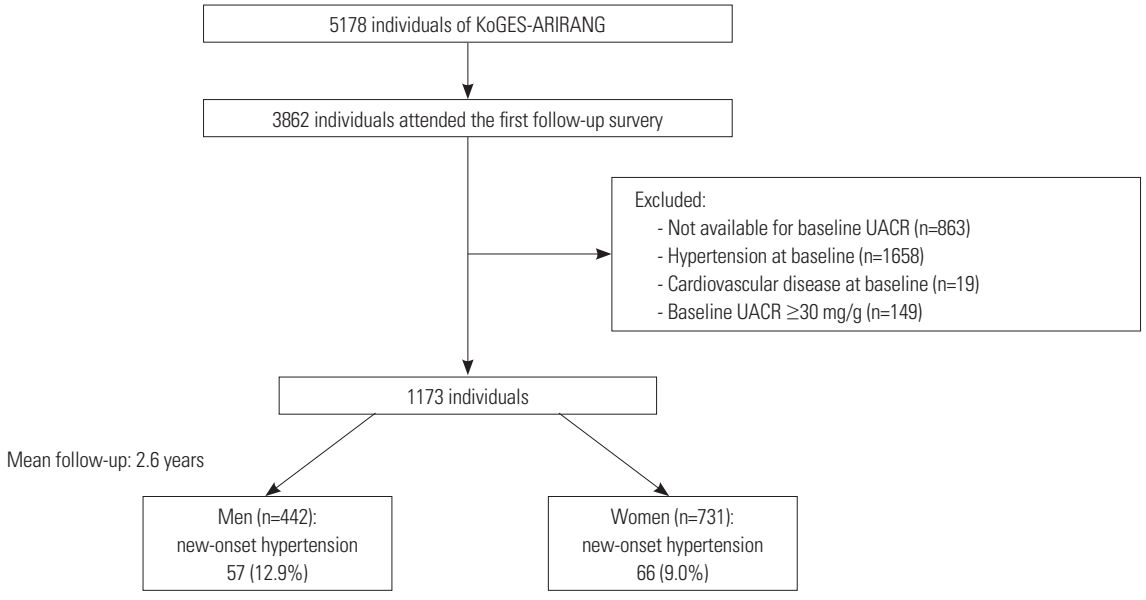

Fig. 1. Flowchart of study population. UACR, urine albumin-to-creatinine ratio; KoGES-ARIRANG, Korean Genome and Epidemiology Study on Atherosclerosis Risk of Rural Areas in the Korean General Population.

Urine albumin (mg/dL) and creatinine (g/dL) were measured from randomly voided urine. The UACR was defined as the amount of urine albumin divided by creatinine levels in urine. We defined the presence of microalbuminuria as a UACR between 30 and 300 mg/g and overt proteinuria as a UACR of greater than 300 mg/g.[17] The intra-assay and inter-assay coefficients of variation of urinary albumin were 1.1% and 1.2% and were 0.5% and 1.4% for urinary creatinine, respectively.

Definition of hypertension

Based on the Eighth Joint National Committee guidelines,[19] hypertension was defined as a systolic blood pressure of at least 140 mm Hg or a diastolic blood pressure of at least 90 mm Hg, or current usage of antihypertensive agents.

Statistical analysis

Data are expressed as means with standard deviations, medians with interquartile ranges, or frequencies with percentages. All analyses were performed separately for men and women and for menopausal status in women. The study population was divided into gender-specific tertiles of UACR values. The cutoff points of the UACR tertiles were 5.38 and 9.37 mg/g for men and 6.17 and 11.64 mg/g for women. Multivariable logistic regression was used to evaluate the independent association between baseline UACR values and incident hypertension. The study utilized three models with progressive degrees of adjustment. First, we conducted an age-adjusted analysis. Second, we additionally adjusted for baseline body mass index, muscle mass, systolic blood pressure, history of diabetes mellitus, smoking, alcohol consumption, and regular exercise. Finally, we further adjusted for baseline fasting serum glucose, triglyceride, HDL cholesterol, hs-CRP, and estimated GFR. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated with respect to increasing tertiles of UACR levels. All statistical analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC, USA). *p* values of <0.05 were considered to be statistically significant.

RESULTS

During an average 2.6 years of follow-up, 57 men (12.9%) and 66 women (9.0%) developed new-onset hypertension. Table 1 shows the baseline characteristics of the 1173 study subjects separated by gender, with and without incident hypertension. In both men and women, baseline body mass index and systolic blood pressure were significantly higher in subjects with incident hypertension than in those without incident hypertension. Diastolic blood pressure, urine albumin, and UACR were significantly higher in women who developed hyperten-

Table 1. Baseline Characteristics of Study Subjects with and without Incident Hypertension

	Men			Women		
	Without incident hypertension	With incident hypertension	*p* value	Without incident hypertension	With incident hypertension	*p* value
n (%)	385 (87.1)	57 (12.9)		665 (91.0)	66 (9.0)	
Age, yrs	55.1±8.2	56.1±8.8	0.425	51.9±8.1	57.0±8.1	<0.001
Body mass index, kg/m^2	23.4±2.8	24.5±2.3	0.006	23.9±3.0	25.0±3.0	0.007
Muscle mass, kg	46.5±4.6	47.8±4.7	0.058	35.6±3.9	35.8±3.7	0.661
Systolic BP, mm Hg	116.0±9.8	120.9±9.1	<0.001	114.3±10.9	120.3±10.3	<0.001
Diastolic BP, mm Hg	74.6±6.8	75.9±6.2	0.184	72.9±7.6	75.3±6.5	0.013
Fasting glucose, mg/dL	95.4±21.6	95.3±12.4	0.953	89.5±10.9	90.9±10.3	0.308
HDL-cholesterol, mg/dL	45.1±10.9	45.2±11.7	0.939	48.6±10.3	46.6±9.7	0.145
LDL-cholesterol, mg/dL	113.0±31.7	117.5±28.2	0.306	117.0±30.6	124.1±29.0	0.072
Triglycerides, mg/dL	122.0 (82.0, 182.0)	123.0 (101.0, 179.0)	0.710*	98.0 (74.0, 138.0)	112.5 (82.0, 153.0)	0.054*
hs-CRP, mg/L	0.79 (0.41, 1.91)	0.59 (0.47, 1.50)	0.645*	0.53 (0.29, 1.19)	0.66 (0.41, 1.27)	0.055*
Urine albumin, mg/dL	0.79 (0.43, 1.38)	0.92 (0.50, 1.68)	0.235*	0.76 (0.43, 1.11)	0.82 (0.74, 1.17)	0.010*
Urine creatinine, g/dL	0.133 (0.094, 0.169)	0.127 (0.081, 0.165)	0.393*	0.094 (0.064, 0.128)	0.081 (0.062, 0.111)	0.139*
Urine albumin to creatinine ratio, mg/g	6.85 (3.90, 10.76)	7.81 (5.77, 11.98)	0.121*	8.50 (4.95, 13.15)	10.88 (7.14, 16.55)	0.002*
Estimated GFR	78.0 (72.1, 85.7)	79.7 (69.7, 86.1)	0.953*	75.1 (69.7, 80.7)	73.0 (65.9, 79.1)	0.190*
Current smokers (%)	168 (43.6)	22 (38.6)	0.566	7 (1.1)	0 (0.0)	0.861
Current drinkers (%)	235 (61.0)	40 (70.2)	0.237	174 (26.2)	15 (22.7)	0.645
Regular exercise (%)	101 (26.2)	15 (26.3)	1.000	185 (27.8)	11 (16.7)	0.071

BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; GFR, glomerular filtration rate; SD, standard deviation.
Values are expressed as mean (SD), number (%), or median (25th, 75th percentiles).
**p* value from Mann-Whitney U test.

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sion than in those who did not. Women with incident hypertension were older than those without incident hypertension at baseline. Additionally, baseline body mass index was significantly higher in subjects with incident hypertension than in those without incident hypertension in both premenopausal and postmenopausal women. Age, systolic and diastolic blood pressure, urine albumin, and UACR were significantly higher in postmenopausal women who developed hypertension than in those who did not (Table 2).

Multivariable logistic regression models were used to evaluate the independent association between baseline UACR tertiles and new-onset hypertension (Table 3). In men, the OR for incident hypertension in the highest UACR tertile was 1.83 (95% CI 0.85–3.94) compared to the lowest UACR tertile (P for trend= 0.124) after adjustment for age, baseline body mass index, muscle mass, systolic blood pressure, diabetes mellitus, smoking, alcohol consumption, regular exercise, fasting glucose, triglyceride, HDL cholesterol, hs-CRP, and GFR. In women, the OR for incident hypertension in the highest UACR tertile was 2.69 (95% CI 1.27–5.73) compared to the lowest UACR tertile (P for trend=0.014) after adjustment for confounding factors described above.

Table 4 presents the ORs for new-onset of hypertension according to baseline UACR tertiles and menopausal status in women. Women were divided into premenopausal and postmenopausal groups. Compared to the lowest UACR tertile, the ORs for incident hypertension in the highest UACR tertile were 0.70 (95% CI 0.15–3.28) in premenopausal women (P for trend= 0.718) and 3.93 (95% CI 1.53–10.11) in postmenopausal women (P for trend=0.006).

DISCUSSION

The present study demonstrated gender-specific associations between a UACR within the normal range and incident hypertension in a Korean elderly population. We observed that higher UACR levels within the normal range are associated with an increased risk of incident hypertension, and these relationships were more pronounced and significant in women, particularly postmenopausal women. The associations were independent of baseline age, body mass index, systolic blood pressure, smoking, regular exercise, fasting serum glucose, triglyceride, HDL cholesterol, and hs-CRP.

The exact mechanism for the association between the UACR and incidence of hypertension is unclear, although several possible explanations were discussed in previous studies. Glomerular endothelial dysfunction may be an underlying precursor of hypertension.[13] Microalbuminuria could be an indicator of microvascular endothelial injury and is also involved in

Table 2. Baseline Characteristics of Premenopausal and Postmenopausal Women

	Premenopausal women			Postmenopausal women		
	Without incident hypertension	With incident hypertension	*p* value	Without incident hypertension	With incident hypertension	*p* value
n (%)	286 (95.6)	13 (4.4)		369 (88.1)	50 (11.9)	
Age, yrs	45.6±3.7	46.5±3.2	0.391	56.8±7.1	60.3±6.1	0.001
Body mass index, kg/m^2	24.0±3.1	25.9±2.3	0.022	23.8±3.0	24.7±3.2	0.038
Muscle mass, kg	36.9±3.6	38.1±2.2	0.230	34.6±3.7	35.1±3.7	0.338
Systolic BP, mm Hg	113.2±10.7	118.1±8.5	0.107	115.3±11.0	121.3±10.3	<0.001
Diastolic BP, mm Hg	72.4±7.9	73.8±5.1	0.508	73.3±7.3	75.8±6.9	0.022
Fasting glucose, mg/dL	89.0±9.9	90.8±11.4	0.502	89.9±11.6	90.5±10.0	0.728
HDL-cholesterol, mg/dL	48.8±9.9	47.1±14.2	0.679	48.4±10.6	46.0±8.3	0.065
LDL-cholesterol, mg/dL	108.9±28.5	119.0±26.5	0.209	123.0±30.5	124.2±28.9	0.786
Triglycerides, mg/dL	86.0 (67.0, 14.0)	111.0 (83.0, 153.0)	0.052*	110.0 (81.0, 152.0)	111.5 (82.0, 150.0)	0.825*
hs-CRP, mg/L	0.39 (0.24, 0.98)	0.45 (0.39, 0.72)	0.315*	0.66 (0.36, 1.35)	0.90 (0.49, 1.68)	0.178*
Urine albumin, mg/dL	0.75 (0.44, 1.11)	0.79 (0.49, 0.85)	0.961*	0.76 (0.41, 1.10)	0.88 (0.76, 1.28)	0.007*
Urine creatinine, g/dL	0.105 (0.069, 0.135)	0.086 (0.068, 0.156)	0.991*	0.089 (0.063, 0.120)	0.078 (0.062, 0.107)	0.226*
Urine albumin to creatinine ratio, mg/g	7.83 (4.68, 12.24)	6.81 (4.87, 11.18)	0.753*	9.02 (5.26, 13.57)	12.25 (8.52, 18.60)	0.001*
Estimated GFR	77.8 (72.1, 83.2)	77.9 (67.6, 80.6)	0.366*	73.3 (67.8, 78.1)	72.6 (65.2, 78.1)	0.549*
Current smokers (%)	3 (1.0)	0 (0.0)	1.000	4 (1.1)	0 (0.0)	1.000
Current drinkers (%)	96 (33.6)	6 (46.2)	0.524	74 (20.1)	9 (18.0)	0.878
Regular exercise (%)	87 (30.4)	4 (30.8)	1.000	94 (25.5)	5 (10.0)	0.025

BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; GFR, glomerular filtration rate; SD, standard deviation.
Values are expressed as mean (SD), number (%), or median (25th, 75th percentiles).
**p* value from Mann-Whitney U test.

Table 3. OR for New-Onset Hypertension According to Baseline UACR Tertile

	UACR at baseline			
	Tertile 1	Tertile 2	Tertile 3	P for trend
Men				
UACR, mg/g	<5.38	5.38–9.36	≥9.37	
No. of subjects	147	147	148	
No. of new-onset hypertension	14 (9.5%)	20 (13.6%)	23 (15.5%)	
OR (95% CI) for new-onset hypertension				
Model 1	1.00	1.47 (0.71–3.04)	1.71 (0.84–3.48)	0.146
Model 2	1.00	1.58 (0.75–3.33)	1.66 (0.79–3.48)	0.187
Model 3	1.00	1.65 (0.78–3.50)	1.83 (0.85–3.94)	0.124
Women				
UACR, mg/g	<6.17	6.17–11.63	≥11.64	
No. of subjects	243	244	244	
No. of new-onset hypertension	11 (4.5%)	24 (9.8%)	31 (12.7%)	
OR (95% CI) for new-onset hypertension				
Model 1	1.00	2.20 (1.05–4.64)	2.62 (1.27–5.40)	0.008
Model 2	1.00	2.59 (1.20–5.57)	2.73 (1.29–5.78)	0.012
Model 3	1.00	2.57 (1.19–5.56)	2.69 (1.27–5.73)	0.014

UACR, urine albumin-to-creatinine ratio; OR, odds ratio; CI, confidence interval; BMI, body mass index; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; GFR, glomerular filtration rate.
Model 1: adjusted for age, Model 2: Model 1+additionally adjusted for baseline BMI, muscle mass, systolic blood pressure, diabetes mellitus, smoking, alcohol consumption, regular exercise, Model 3: Model 2+additionally adjusted for baseline fasting serum glucose, triglyceride, HDL cholesterol, hs-CRP, estimated GFR.

Table 4. OR for New-Onset Hypertension According to Baseline UACR Tertile and Menopausal Status

	UACR at baseline			
	Tertile 1	Tertile 2	Tertile 3	P for trend
Premenopausal women				
UACR, mg/g	<5.65	5.65–10.74	≥10.75	
No. of subjects	99	100	100	
No. of new-onset hypertension	4 (4.0%)	5 (5.0%)	4 (4.0%)	
OR (95% CI) for new-onset hypertension*	1.00	1.18 (0.27–5.20)	0.70 (0.15–3.28)	0.718
Postmenopausal women				
UACR, mg/g	<6.54	6.54–12.33	≥12.34	
No. of subjects	139	140	140	
No. of new-onset hypertension	7 (5.0%)	19 (13.6%)	24 (17.1%)	
OR (95% CI) for new-onset hypertension*	1.00	3.49 (1.33–9.17)	3.93 (1.53–10.11)	0.006

UACR, urine albumin-to-creatinine ratio; OR, odds ratio; CI, confidence interval; BMI, body mass index; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; GFR, glomerular filtration rate.
*Adjusted for baseline age, baseline BMI, muscle mass, systolic blood pressure, diabetes mellitus, smoking, alcohol consumption, regular exercise, fasting serum glucose, triglyceride, HDL cholesterol, hs-CRP, estimated GFR.

the progression of chronic kidney disease.[20,21] Several studies have explored the relationship between endothelial dysfunction, arterial stiffness, and blood pressure.[22,23] Elevation of UACR could also be associated with loss of vasorelaxation and vascular calcification in patients with microalbuminuria.[24,25] Additionally, the development of hypertension may be due to the upregulation of angiotensin-converting enzymes in proteinuric-conditions and the albumin-triggered activation of the intrarenal renin-angiotensin system.[26,27]

Recent studies have reported that high normal ranges of UACR are associated with the development of hypertension.[13-15,28] The Framingham Offspring Study and an Indo-Asian population study reported an association between a high normal level of albuminuria and the risk of hypertension for 2 and 2.9 years of follow-up, respectively.[13,15] However, separate analyses by gender were not performed in these previous studies. Our results showed that the ORs for men were lower than those for women and not significant in the association between UACR and incident hypertension. This gender difference could be attributed to the different levels and variations in UACR between men and women. Women have higher baseline UACR values than men due to lower muscle mass and less urinary excretion of creatinine.[29] The non-significant results in men may have also been due to the small sample size. Further studies are

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required to understand the profound pathophysiology of the gender difference in the effects of UACR on hypertension.

Menopausal status could also affect the relationship between UACR and incident hypertension. Our results showed that postmenopausal women had higher baseline UACR levels than premenopausal women. A previous study reported that the supplementation of estrogen in postmenopausal women lowers the UACR level and thereby lowers the risk of albuminuria.[30] In stratified analyses by menopausal status, postmenopausal women showed a significant association between UACR and incident hypertension. Our findings are consistent with those of the Nurses' Health Study.[31] One possible explanation might be the lower levels of estrogen in postmenopausal women. Previous studies reported that sex hormones, particularly estrogen, modulate mesangial expansion, matrix deposition, collagen synthesis, and activation of the renin-angiotensin system in the kidneys.[32-34] The lack of estrogen in postmenopausal women may lead to the progression of hypertension in relation to the UACR.

The strengths of our study include its prospective design, gender-separated analyses, and adjustment for possible confounding factors. However, the present study also had several limitations. First, the sample in the present study was taken from a single spot urine collection for analyzing UACR instead of 24-hour urinary albumin excretion, which may have led to improper diagnosis of albuminuria in certain participants. However, spot urine for analyzing UACR correlates well with total amounts of urinary albumin excretion in 24-hour urine and is generally used to detect decreased kidney function.[35,36] Second, bioelectrical impedance analysis is not generally considered as a reference method for evaluating muscle mass. However, a bioelectrical impedance analysis can provide a simple and rapid measurement of muscle mass for epidemiological studies. Third, the study was restricted to middle-aged and elderly Koreans living in rural areas. Generalization of the results may be limited. Fourth, we analyzed the follow-up data for only 2.6 years. Further studies with a longer follow-up period are needed.

In conclusion, the present study provides epidemiological evidence that a higher UACR within the normal range can independently predict the development of hypertension in women. UACR measurement may be an easy and non-invasive marker for predicting incident hypertension. Further studies are required to understand the gender-specific impact of UACR on the risk of hypertension.

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