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Differential Association of Vitamin D Deficiency With Albuminuria by Sex in the Korean General Population: A Cross-sectional Study of the Korea National Health and Nutrition Examination Survey 2011-2012

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Objectives: Albuminuria has emerged as a biomarker for several medical conditions, and vitamin D has received attention due to its associations with various disorders. We evaluated the association between low serum vitamin D levels and prevalent albuminuria by sex in the Korean general population.

Methods: We analyzed 9823 participants (4401 males, 5422 females) from the Korea National Health and Nutrition Examination Survey 2011-2012 (KNHANES V-2), and categorized them as having a normal range of vitamin D levels, vitamin D insufficiency, or vitamin D deficiency. A multivariable logistic regression model was used to compare the risk of albuminuria across these groups. Stratified analyses were conducted by smoking status, obesity, and renal function.

Results: Albuminuria was found in 325 of the 4401 male participants (7.4%) and in 455 of the 5422 female participants (8.4%). Among the males, vitamin D deficiency was associated with an odds ratio (OR) for albuminuria of 1.78 (95% confidence interval [CI], 1.07 to 2.97, $p<0.05$). However, such an association was not found in females. The association was stronger in male current smokers (OR, 3.54; 95% CI, 1.47 to 8.50; $p=0.005$).

Conclusions: The findings of this study suggest that sex differences exist in the association between serum vitamin D deficiency and albuminuria. Additionally, we observed that the association was stronger in current smokers than in the overall male population, but was not seen in non-smokers. Therefore, different approaches by sex and smoking status might be needed when considering using vitamin D as a biomarker for renal function.

Key words: Vitamin D deficiency, Albuminuria, Sex factors, Smoking, Korea

INTRODUCTION

Albuminuria is not only a prognostic marker for renal disease, but also a significant predictor of cardiovascular disease and all-cause mortality [1,2]. Because of its broad range of implications, albuminuria itself has been targeted as a therapeutic goal to prevent the progression of certain medical conditions [1-3]. It was reported that 6.2% of the general population had albuminuria in Korea, while 29.9% of the subjects with micro-

albuminuria had intact renal function [3]. Albuminuria is normally defined by levels of the urinary albumin/creatinine ratio (UACR) over 30 mg/g. Albuminuria in individuals without kidney disease may occur due to systemic endothelial dysfunction in the kidney.

Vitamin D has recently received attention from medical researchers due to its associations with various non-osteoskeletal disorders [4-9]. Those medical conditions include hypertension, diabetes mellitus, obesity, cardiovascular disease, cancers, infections, and autoimmune diseases [4,6,10,11]. Serum 25-hydroxyvitamin D production from cutaneous sources has decreased since people started engaging more in indoor jobs. Despite its important roles in the human body, only 13.2% of males and 6.7% of females in the Korean adult population were reported to have sufficient levels of vitamin D [12]. Another study reported that 49.9% of males and 67.4% of females in the Korean general population had insufficient or deficient levels of serum vitamin D, which is a much higher rate than has been observed in Western countries. Moreover, vitamin D deficiency was more prevalent in young adults in Korea [13].

Over the years, many studies have demonstrated a significant link between serum vitamin D deficiency and albuminuria [10, 14,15]. However, it is still controversial whether vitamin D replacement therapy could delay the progress of chronic kidney disease or reduce the incidence of albuminuria [16]. Some studies in Korea showed that vitamin D deficiency was associated with the estimated glomerular filtration rate (eGFR) in healthy adults, while others showed that severe vitamin D deficiency could result in increased UACR levels among individuals with normo-albuminuria [17,18].

However, to our knowledge, the association between vitamin D deficiency and albuminuria in the general population in Korea has not yet been investigated. Moreover, since sex has strong effects on the prevalence of albuminuria and on vitamin D metabolism [2,19], it is necessary to explore whether sex has confounding effects or interaction effects on the association between these 2 variables. The aim of our study was to assess the association between low serum vitamin D levels and albuminuria separately by sex in the Korean general population.

METHODS

Data Source and Study Population

The Korea National Health and Nutrition Examination Survey (KNHANES) is a nationwide population-based cross-sec-

tional survey. Detailed information about the survey has been presented elsewhere [20]. As data on urinary albumin levels were first collected in 2011, we used data from the KNHANES V-2, which contains samples from 2011-2012. A standardized questionnaire was given to all participants to collect information on socio-demographic variables, family history, medical history, and other health-related variables. Among 12 729 members of the adult population, participants who had missing data on key variables such as serum vitamin D (n=1264), the UACR (n=840), and other parameters were excluded, and 10 164 participants remained. We additionally excluded 79 pregnant females, 213 cancer patients, and 40 chronic renal failure patients, because those health states could strongly affect the association [15]. We also excluded 9 individuals with no diagnosis of chronic renal failure who nonetheless had a UACR over 3000 mg/g, indicating nephrotic-range albuminuria, which is known to affect vitamin D metabolism [15]. A final total of 9823 subjects were analyzed in this study. Informed consent for participation in the KNHANES V-2 was granted by all subjects, so we did not need to obtain separate consent for this study.

Definition of Albuminuria and Vitamin D Deficiency

We used the UACR (mg/g) to determine whether a participant had albuminuria. Albuminuria was considered to be present in individuals with a UACR $\geq$ 30 mg/g and absent in others [21]. Based on previous studies, vitamin D deficiency was defined as serum 25(OH)D levels less than 12 ng/mL, vitamin D insufficiency as 12-20 ng/mL, and the normal range as over 20 ng/mL [9,15,22].

Definition of Covariates

Participants were classified according to body mass index (BMI) as low body weight (<18.5 kg/m^2), normal (18.5-25.0 kg/m^2), or obese ($\geq$ 25.0 kg/m^2). The place of residence of participants was categorized based on their address; those who had a final address unit of 'dong' were classified as residing in an urban area, while those who had a final address unit of 'eup' or 'myeon' were classified as residing in a rural area. The latitude of participants' places of residence varied from 33.36 to 37.57 degrees north, so we additionally categorized them by geometric tertiles as south, middle, or north. We defined white-collar workers as those who worked as managers, professionals, office workers, and indoor service providers; blue-collar

workers as those who worked in agriculture, forestry, fishery, machinery, and as general laborers; and others as those who fell into other occupational categories, including homemakers and students. The eGFR was calculated from age, sex, and serum creatinine concentration using the Chronic Kidney Disease Epidemiology Collaboration equation: eGFR (mL/min/1.73 m^2) $= 141 \times \min$ (SCr/κ, 1)$^\alpha \times \max$ (SCr/κ, 1)$^{-1.209} \times 0.993^{Age} \times 1.018$ if female, where SCr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males,

min indicates the minimum value of SCr/κ or 1, and max indicates the maximum value of SCr/κ or 1 [23]. A decreased eGFR was defined as an eGFR$<$60 mL/min/1.73 m^2. Those who stated on the questionnaire that they smoked at the present time were categorized as current smokers and the others as nonsmokers. Current drinkers were defined in this study as those who drank at least once a month. We defined regular walking as walking at least 30 minutes a day on 5 days a week on average. Participants were asked about the average amount of

Table 1. General characteristics by vitamin D status[1] in each sex

Characteristics	Male				Female			
	Normal (n=1511)	Vitamin D insufficiency (n=2352)	Vitamin D deficiency (n=538)	*p*-value	Normal (n=1289)	Vitamin D insufficiency (n=2993)	Vitamin D deficiency (n=1140)	*p*-value
Age (y)	55.2±14.8	49.3±16.0	46.6±16.7	<0.001	58.6±14.6	50.9±15.6	48.1±16.6	<0.001
Body mass index (kg/m^2)	23.9±2.9	24.2±3.2	23.9±3.4	<0.001	23.8±3.3	23.7±3.6	23.1±3.6	<0.001
Rural area	474 (31.4)	392 (16.7)	64 (11.9)	<0.001	384 (29.8)	578 (19.3)	157 (13.8)	<0.001
Latitude				<0.001				<0.001
Northern	590 (39.1)	1269 (54.0)	353 (65.6)		524 (40.7)	1484 (49.6)	704 (61.8)	
Middle	757 (50.1)	982 (41.8)	165 (30.7)		629 (48.8)	1327 (44.3)	397 (34.8)	
Southern	164 (10.9)	101 (4.3)	20 (3.7)		136 (10.6)	182 (6.1)	39 (3.4)	
Occupation				<0.001				<0.001
White-collar	447 (29.6)	992 (42.2)	229 (42.6)		254 (19.7)	887 (29.6)	384 (33.7)	
Blue-collar	711 (47.1)	816 (34.7)	144 (26.8)		357 (27.7)	559 (18.7)	147 (12.9)	
Other (students, homemakers, etc.)	353 (23.4)	544 (23.1)	165 (30.7)		678 (52.6)	1547 (51.7)	609 (53.4)	
eGFR (mL/min/1.73 m^2)[2]	86.9±15.0	91.3±16.0	94.5±17.5	<0.001	88.6±16.5	95.7±17.0	99.2±17.8	<0.001
Albuminuria[3]	122 (8.1)	158 (6.7)	45 (8.4)		130 (10.1)	231 (7.7)	94 (8.3)	
Systolic blood pressure (mmHg)	122.7±16.4	121.3±15.0	120.5±15.4	0.004	121.7±18.4	117.6±17.7	117.1±18.3	<0.001
Diastolic blood pressure (mmHg)	77.9±10.7	78.7±10.4	78.5±11.2	0.09	74.4±9.5	73.9±9.7	74.0±9.8	0.19
Total cholesterol (mg/dL)	187.9±34.1	189.1±35.9	185.5±37.0	0.10	196.3±36.3	193.4±37.4	190.7±36.9	0.001
Triglycerides (mg/dL)	141.0±101.1	157.3±135.9	164.2±115.4	<0.001	119.7±68.5	117.7±87.3	120.6±99.1	0.55
Current medication								
Hypertension	352 (23.3)	461 (19.6)	92 (17.1)	0.002	403 (31.3)	624 (20.9)	221 (19.4)	<0.001
Diabetes mellitus	149 (9.9)	178 (7.6)	48 (8.9)	0.04	118 (9.2)	182 (6.1)	79 (6.9)	0.001
Dyslipidemia	98 (6.5)	132 (5.6)	28 (5.2)	0.42	137 (10.6)	211 (7.1)	82 (7.2)	<0.001
Current smoker[4]	562 (37.2)	952 (40.5)	265 (49.3)	<0.001	44 (3.4)	165 (5.5)	72 (6.3)	0.003
Current drinker[5]	1081 (71.5)	1759 (74.8)	385 (71.6)	0.05	391 (30.3)	1155 (38.6)	384 (33.7)	<0.001
Regular walking[6]	656 (43.4)	907 (38.6)	221 (41.1)	0.01	448 (34.8)	1058 (35.4)	363 (31.8)	0.10
Sun exposure[7]	392 (25.9)	314 (13.4)	62 (11.5)	<0.001	206 (16.0)	239 (8.0)	50 (4.4)	<0.001

Values are presented as mean±standard deviation or number (%).
eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.
[1]Vitamin D insufficiency was defined as serum vitamin D levels of 12-20 ng/dL; Vitamin D deficiency was defined as serum vitamin D levels of ≤12 ng/dL.
[2]Calculated using the CKD-EPI equation. eGFR (mL/min/1.73 m^2)$=141 \times \min$ (SCr/κ, 1)$^\alpha \times \max$ (SCr/κ, 1)$^{-1.209} \times 0.993^{Age} \times 1.018$ if female, where SCr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum value of SCr/κ or 1, and max indicates the maximum value of SCr/κ or 1.
[3]Urinary albumin/creatinine ratio ≥30 mg/g.
[4]Indicates those who reported smoking at the present time.
[5]Indicates those who reported drinking at least once a month at the present time.
[6]Indicates those who walked continuously for at least 30 min/d, 5 d/wk.
[7]Indicates the proportion of those who were exposed to sunlight for more than 5 hr/d.

time that they were exposed to direct sunlight each day. Sun exposure was defined in this study as being exposed to direct sunlight for more than 5 hours a day on average.

Statistical Analysis

Differences in general characteristics by vitamin D status were evaluated using the chi-square test and one-way analysis of variance in each sex. Logistic regression analyses were employed to investigate the associations between vitamin D deficiency and the prevalence of albuminuria. We analyzed the association in the total population and also separately by sex. We adjusted for age, BMI, rural area, latitude, and occupation in model 1, and sex was also adjusted for in the estimation for the total population. Medical factors such as the eGFR, systolic blood pressure, diastolic blood pressure, total cholesterol, triglyceride levels, and current medication for hypertension, diabetes mellitus, and dyslipidemia were added to model 2. In the final model, lifestyle factors such as smoking status, drinking status, regular walking, and sun exposure were additionally adjusted for. We analyzed the association stratified by smoking status, decreased eGFR, and obesity, since those variables showed significant differences in the univariate analysis by vitamin D status and are known to be possible effect modifiers.

To test the robustness of our study, we repeated the analysis with a redefinition of vitamin D deficiency as less than 10 ng/mL and vitamin D insufficiency as 10-20 ng/mL as a sensitivity analysis. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

The general characteristics of the 9823 total participants are shown in Table 1 separately by sex (4401 males and 5422 females). Among the total population, 5345 individuals (54.4%) were classified as having vitamin D insufficiency, and 1678 (17.1%) had vitamin D deficiency (males: 538, 12.2%; females: 1140, 21.0%). The mean eGFR was higher in the vitamin D deficiency group than in the normal-range group in both males and females (94.5 ± 17.5 vs. 86.9 ± 15.0 mL/min/1.73 m^2 in males; 99.2 ± 17.8 vs. 88.6 ± 16.5 mL/min/1.73 m^2 in female). Among male participants, albuminuria was likewise more common in the vitamin D deficiency group than in the normal-range group (8.4 vs. 8.1%). However, among the female participants, it was more common in the normal-range group (8.3 vs. 10.1%). Systolic blood pressure was the lowest in the vitamin D deficiency group in both sexes. The total cholesterol level significantly

Table 2. Risks of albuminuria according to vitamin D status[1] in each sex

Vitamin D status	Total (n)	Albuminuria (n)	Unadjusted model OR (95% CI)	p-value	Adjusted model 1[2] OR (95% CI)	p-value	Adjusted model 2[3] OR (95% CI)	p-value	Adjusted model 3[4] OR (95% CI)	p-value
Total										
Normal	2800	252	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Vitamin D insufficiency	5345	389	0.74 (0.60, 0.92)	0.006	0.99 (0.79, 1.24)	0.91	1.01 (0.80, 1.28)	0.94	1.01 (0.80, 1.27)	0.96
Vitamin D deficiency	1678	139	0.96 (0.72, 1.28)	0.79	1.49 (1.09, 2.04)	0.01	1.47 (1.06, 2.04)	0.02	1.46 (1.06, 2.02)	0.02
Male										
Normal	1511	122	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Vitamin D insufficiency	2352	158	0.78 (0.58, 1.06)	0.11	1.10 (0.79, 1.54)	0.57	1.12 (0.80, 1.58)	0.50	1.11 (0.79, 1.55)	0.55
Vitamin D deficiency	538	45	1.06 (0.67, 1.66)	0.81	1.87 (1.13, 3.11)	0.01	1.82 (1.10, 3.02)	0.02	1.78 (1.07, 2.97)	0.03
Female										
Normal	1289	130	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Vitamin D insufficiency	2993	231	0.65 (0.49, 0.88)	0.005	0.89 (0.65, 1.22)	0.48	0.90 (0.65, 1.25)	0.52	0.90 (0.65, 1.24)	0.51
Vitamin D deficiency	1140	94	0.78 (0.55, 1.10)	0.15	1.25 (0.85, 1.85)	0.25	1.20 (0.80, 1.80)	0.37	1.19 (0.79, 1.78)	0.41

OR, odds ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate.

[1]Vitamin D insufficiency was defined as serum vitamin D levels of 12-20 ng/dL; Vitamin D deficiency was defined as serum vitamin D levels of $\leq$12 ng/dL.

[2]Adjusted for age, body mass index, rural area, latitude, and occupation + sex (for the estimate in the total population).

[3]Adjusted for age, body mass index, rural area, latitude, occupation, eGFR, systolic blood pressure, diastolic blood pressure, total cholesterol, triglycerides, and medication (hypertension, diabetes mellitus, dyslipidemia) + sex (for the estimate in the total population).

[4]Adjusted for age, body mass index, rural area, latitude, occupation, eGFR, systolic blood pressure, diastolic blood pressure, total cholesterol, triglycerides, and medication (hypertension, diabetes mellitus, dyslipidemia), smoking status, drinking status, regular walking, and sun exposure + sex (for the estimate in the total population).

Table 3. Risks of albuminuria according to vitamin D status[1] by smoking status

Vitamin D status	Non-smokers[2]				Current smokers[3]			
	Total (n)	Albuminuria (n)	OR (95% CI)	*p*-value	Total (n)	Albuminuria (n)	OR (95% CI)	*p*-value
Total								
Normal	2194	210	1.00 (reference)		606	42	1.00 (reference)	
Vitamin D insufficiency	4228	314	0.86 (0.66, 1.12)	0.26	1117	75	1.75 (0.93, 3.27)	0.08
Vitamin D deficiency	1341	114	1.18 (0.82, 1.69)	0.38	337	25	3.19 (1.42, 7.19)	0.005
Male								
Normal	949	83	1.00 (reference)		552	39	1.00 (reference)	
Vitamin D insufficiency	1400	98	0.86 (0.58, 1.26)	0.43	952	60	1.75 (0.89, 3.45)	0.10
Vitamin D deficiency	273	25	1.10 (0.60, 2.00)	0.77	265	20	3.54 (1.47, 8.50)	0.005
Female								
Normal	1245	127	1.00 (reference)		44	3	1.00 (reference)	
Vitamin D insufficiency	2828	216	0.86 (0.62, 1.21)	0.39	165	15	3.84 (0.90, 16.38)	0.07
Vitamin D deficiency	1068	89	1.15 (0.75, 1.75)	0.52	72	5	4.47 (0.88, 22.64)	0.07

All analyses herein presented were adjusted for age, body mass index, rural area, latitude, occupation, eGFR, systolic blood pressure, diastolic blood pressure, total cholesterol, triglycerides, medication (hypertension, diabetes mellitus, dyslipidemia), drinking status, regular walking, and sun exposure + sex (for the estimate in the total population).
OR, odds ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate.
[1]Vitamin D insufficiency was defined as serum vitamin D levels of 12-20 ng/dL; Vitamin D deficiency was defined as serum vitamin D levels of ≤12 ng/dL.
[2]Indicates those who did not smoke at the present time.
[3]Indicates those who smoked at the present time.

decreased as vitamin D levels decreased in the female population, but not in the male population. In contrast, triglyceride levels increased as vitamin D levels decreased in males, but not in females. The proportion of current smokers was higher in the vitamin D deficiency group than in other vitamin D status groups in both males and females, whereas the proportion of those who were exposed to direct sunlight for more than 5 hours a day was higher in the normal vitamin D range group in both sexes.

Among the total population, 780 individuals (7.9%) (males: 325, 7.4%; females: 455, 8.4%) had albuminuria. Table 2 shows the risks of albuminuria according to vitamin D status. In the fully adjusted model, vitamin D deficiency conferred an odds ratio (OR) for albuminuria of 1.46 (95% confidence interval [CI], 1.06 to 2.02; *p*<0.05). In the male population, individuals with vitamin D deficiency did not show a significantly higher risk of albuminuria in the unadjusted model. However, when possible confounders were adjusted for, they showed a higher risk of albuminuria than the reference group (those with vitamin D levels in the normal range), with an OR of 1.78 (95% CI, 1.07 to 2.97; *p*<0.05) in the fully adjusted model. Those associations were not observed in the female population. In the sensitivity analysis, the association in males remained marginally significant (Table S1).

When stratified by smoking status (Table 3), the association was only present in current smokers (OR, 3.19; 95% CI, 1.42 to 7.19 in the total population and OR, 3.54; 95% CI, 1.47 to 8.50 in the male population). In Tables S2 and S3, the results of stratification by eGFR and obesity are shown. An association between vitamin D deficiency and albuminuria was also observed in individuals with normal renal function (normal eGFR), but it disappeared in those with a decreased eGFR. When stratified by obesity, the normal-weight population showed a similar association in the total population and among male participants.

DISCUSSION

The main finding of this study is that vitamin D deficiency had a significant association with prevalent albuminuria in Korea, especially among males. Additionally, the association between vitamin D deficiency and albuminuria disappeared in non-smokers.

Some previous studies demonstrated an association of vitamin D deficiency with prevalent albuminuria [10,14,15,17,18]. Furthermore, some experimental studies have been conducted to investigate whether supplementation of vitamin D could improve albuminuria [24-26]. As a possible mechanism, it was

suggested that albuminuria could be caused by several conditions—such as renin-angiotensin-aldosterone system activation, increased blood pressure, and impaired glucose metabolism—and that those conditions can result from podocyte loss and glomerulosclerosis, which could be caused by vitamin D deficiency [15,24,27,28]. Conversely, albuminuria could cause vitamin D deficiency. The megalin and cubilin receptors actively reabsorb vitamin D in the proximal tubule of the kidney. It is possible that additional filtered albumin could interfere with the reabsorption of vitamin D, resulting in vitamin D deficiency [29].

Unlike other previous studies, we observed that sex modified the association between vitamin D deficiency and albuminuria. The interaction of sex on the association was observed even in subgroup analyses stratified by smoking status, eGFR, and obesity. Further studies may be required to explain the precise mechanism, but the following considerations could be possible explanations.

First, the different proportions of sex hormones by sex might be a reason for this trend. Some studies have proposed that estrogen protects females from the progression of renal function decline [30,31]. In contrast, androgens have been observed to cause males to experience a rapid decline of renal function compared to females [32]. It was reported that androgens activated the renin-angiotensin system, which could cause endothelial injury, and that testosterone could cause salt and water retention, possibly contributing to vascular injuries [33]. Several previous studies have suggested that vitamin D responsiveness also differs by the proportions of sexual hormones [19,34]. Not only the proportions, but androgens themselves, were suggested to have a significant association with vitamin D metabolism [35]. Second, anatomical differences by sex, such as the distribution of adiposity or responsiveness of the vasculature, could affect the mechanism through which vitamin D and albuminuria are associated. The higher proportion of adipose tissue in female versus male bodies was suggested to be a factor contributing to lower vitamin D concentrations [36]. The prevalence of vitamin D deficiency was reported to be higher in females than in males [7], and almost double in the Korean population [13], as was found in our study (12.2 vs. 21.0% in males and females, respectively). In contrast, albuminuria has been reported to be more prevalent in males than in females [37]. This could be because the renal vasculature in males is more sensitive in some ways than the renal vasculature in females [30]. Similarly, the response of renal vessels to

deficient levels of vitamin D could differ by sex.

The unique results of our study could also be attributable to ethnic and racial differences. Most previous studies were conducted in Caucasian populations, and UACR levels are affected by ethnicity and culturally-associated lifestyle factors (e.g., the more frequent ingestion of animal protein in Western cultures). The prevalence of albuminuria (7.9%) in this study was lower than was reported in a previous study in the US (11.6%) [15], and the occurrence of nephropathy is known to be affected by race [37]. Vitamin D metabolism also could differ by race and culture [21]. Some observational studies showed that vitamin D deficiency was more prevalent in the Korean population than in the Caucasian population (17.1% in our study, 3.7% in another study from the US) [13,15]. This could be due to differences in skin pigmentation or cultural practices, such as vitamin D supplementation, sunscreen application, and the use of sunglasses [13].

Smoking status also showed an effect modification in our subgroup analysis. If a male participant was a current smoker, the association between vitamin D deficiency and albuminuria was much stronger, whereas the association disappeared in non-smokers. Even in the female population, the prevalence of albuminuria was much higher among smokers. Trials have investigated whether vitamin D supplementation could prevent albuminuria progression [25,26], but we would instead suggest based on our observations that smoking cessation might work better.

Some limitations and strengths of our study should be considered. First, since this was a cross-sectional study, it was impossible to infer causal or temporal relationships. Second, some of the participants might have been taking antihypertensive medications, which could affect albuminuria. However, we did not consider the effects of the subtype of antihypertensive agents (e.g., angiotensin-converting enzyme inhibitors). Third, there could have been additional possible confounders involving behavioral factors that affect vitamin D deficiency, such as dietary habits, sunscreen use, or clothing, which we could not analyze [12]. Our study also had important strengths. This study analyzed KNHANES data, which represent the general population of Korea with a large sample size. Moreover, unlike other studies, we analyzed the association separately by sex and investigated the association in an Asian population.

We conclude that sex differences exist in the association between serum vitamin D deficiency and increased urinary albumin excretion. Low levels of vitamin D had a significant corre-

lation with prevalent albuminuria in the Korean male population, but not in females. Additionally, we also observed that the association was stronger in current smokers than in the total population, but was not seen in non-smokers. These findings suggest that different approaches by sex and smoking status might be needed when considering the use of vitamin D as a biomarker for renal function.

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CONFLICT OF INTEREST

The authors have no conflicts of interest associated with the material presented in this paper.

SUPPLEMENTARY MATERIALS

Supplementary Material 1: Table S1 is available at https://www.jpmph.org/.
Supplementary Material 2: Table S2 is available at https://www.jpmph.org/.
Supplementary Material 3: Table S3 is available at https://www.jpmph.org/.

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