

# Higher volume of water intake is associated with lower risk of albuminuria and chronic kidney disease

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## Abstract

Increased water intake correlated to lower vasopressin level and may benefit kidney function. However, results of previous studies were conflicted and inconclusive. We aimed to investigate the association between water intake and risk of chronic kidney disease (CKD) and albuminuria.

In this cross-sectional study, the study population were adult participants of 2011–2012 National Health and Nutrition Examination Survey (NHANES) whose estimated glomerular filtration rate (eGFR) were  $\geq 30$  ml/min/1.73 m<sup>2</sup>. Data of water intake were obtained from the NHANES 24-h dietary recall questionnaire. Participants were divided into three groups based on volume of water intake: <500 (low, n = 1589),  $\geq 500$  to <1200 (moderate, n = 1359), and  $\geq 1200$  ml/day (high, n = 1685). CKD was defined as eGFR <60 ml/min/1.73 m<sup>2</sup>, and albuminuria as albumin-to-creatinine ratio (ACR)  $\geq 30$  mg/g.

Our results showed that 377 out of 4633 participants had CKD; the prevalence inversely correlated to volume of water intake: 10.7% in low, 8.2% in moderate, and 5.6% in high intake groups ( $P < .001$ ). Prevalence of albuminuria was also lower in high (9.5%) compared with moderate (12.8%) and low intake groups (14.1%),  $P < .001$ . Additionally, water intake positively correlated to eGFR and negatively correlated to urinary ACR, as well as plasma and urine osmolality. Multivariable logistic regression showed that low water intake group had higher risk of CKD (OR 1.35, 95% CI 1.01–1.82) and albuminuria when compared to high water intake group (OR 1.42, 95% CI 1.13–1.79).

In conclusion, increased water intake was associated lower risk of CKD and albuminuria. Meticulous studies are needed to elucidate the underlying mechanisms.

**Abbreviations:** ACR = albumin-to-creatinine ratio, BMI = body mass index, CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, ESRD = end-stage renal disease, NHANES = National Health and Nutrition Examination Survey, UACR = urinary albumin-to-creatinine ratio.

**Keywords:** proteinuria, albuminuria, chronic kidney disease (CKD), plain water intake, osmolality, vasopressin

## 1. Introduction

Chronic kidney disease (CKD) is a global health burden, which affects 10–15% of the adult population worldwide and

substantially impaired quality of life and reduced life expectancy.<sup>[1–3]</sup> According to the United States Renal Data System (USRDS) 2018 Annual Data Report, 6.9% of the adult population in the United States (U.S.) had CKD stage 3–5, defined as estimated glomerular filtration rate (eGFR) of <60 ml/min/1.73 m<sup>2</sup>. In addition, the prevalence of albuminuria, defined as a urinary albumin-to-creatinine ratio (ACR) of  $\geq 30$  mg/g of creatinine, was 10.1%.<sup>[4]</sup>

Lifestyle modifications such as healthy dietary patterns and regular physical activity had been shown to correlate with lower risk of albuminuria and CKD.<sup>[5–7]</sup> The association between water intake and progression of CKD had also been investigated; however, the effect of increased water intake on attenuation of kidney function decline remained inconclusive. Studies showed that increased water intake was associated with reduced plasma levels of vasopressin,<sup>[8]</sup> which may be beneficial for the preservation of the kidney function.<sup>[9,10]</sup> In addition, plasma vasopressin level was also associated with increased urinary albumin excretion and microalbuminuria,<sup>[11,12]</sup> which is a cardinal manifestation of CKD and correlated with lower levels of kidney function.<sup>[4]</sup> Although observational studies showed that increased water intake was associated with lower risk of CKD,<sup>[13,14]</sup> a randomized control trial failed to demonstrate the beneficial effect of increased water intake on slowing the decline of kidney function.<sup>[15]</sup> In addition, while the correlation of water intake and CKD progression had been examined, the population-

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based study on the association between water intake and albuminuria is relatively lacking. Therefore, we conducted this population-based study to investigate the association between water intake and risk of albuminuria and CKD.

## 2. Methods

### 2.1. Study design and data source

This is a cross-sectional study. The study population were participants of 2011–2012 National Health and Nutrition Examination Survey (NHANES) in the United States (U.S.). The data were obtained from the website of National Center for Health Statistics/Centers for Disease Control and Prevention. NHANES constitutes a series of cross-sectional, multistage probability surveys for civilian noninstitutionalized population across the U.S.<sup>[16]</sup> The NHANES protocol was approved by the National Center for Health Statistics Ethics Review Board (Available from: <https://www.cdc.gov/nchs/nhanes/index.htm>).

### 2.2. Study population

We included adult participants ( $\geq 18$  years of age) of 2011–2012 NHANES, totaling 5864 individuals. After excluding participants who were pregnant ( $N=57$ ), those whose serum creatinine were missing ( $N=700$ ), those with an estimated glomerular filtration rate (eGFR) of  $<30$  ml/min/1.73 m<sup>2</sup> ( $N=48$ ) or who received dialysis in the past 12 months ( $N=3$ ), and whose data of water intake were missing ( $N=423$ ), the final analytic cohort included 4633 individuals (Fig. 1).

### 2.3. Definition of variables

The data of water intake were obtained from the 24-h dietary recall questionnaire in NHANES, which was completed via a 5-step structured interview to help respondents describe drinks and foods they consumed.<sup>[17]</sup> The multi-pass method was conducted by a trained interviewer. Due to lack of evidence about health outcomes of recommended daily water intake, we divided the participants into tertiles according to volume of water intake as

low ( $<500$  ml/day), moderate ( $\geq 500$  to  $<1200$  ml/day) and high-water intake ( $\geq 1200$  ml/day). The eGFR was calculated by isotope dilution mass spectrometry (IDMS) traceable Modification of Diet in Renal Disease (MDRD) Study equation [GFR =  $175 \times (\text{standardized serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times 0.742$  (if the subject is a woman)  $\times 1.212$  (if the subject is black)]. An eGFR of  $< 60$  ml/min/1.73 m<sup>2</sup> was defined as CKD, and albuminuria was defined by albumin-to-creatinine ratio (ACR) of  $\geq 30$  mg/g. Histories of diabetes mellitus and hypertension were defined as self-reporting diagnosis with the disease or taking medications.

### 2.4. Statistical analysis

Continuous variables were presented as mean  $\pm$  standard deviation and were tested by Student's *t* tests when appropriately. Categorical variables were presented as numbers (percent) and were compared by  $\chi^2$  tests. Tests were two-tailed with a significance level of .05. Spearman correlation was conducted to explore the relationship between volume of water intake and eGFR as well as ACR, plasma and urine osmolality. Logistic regression analysis was performed to explore the association between water intake and CKD as well as albuminuria. In the multivariable logistic regression model for exploring the association between water intake and CKD, we adjusted for age, sex, race/ethnicity, body mass index (BMI), as well as self-reported diabetes and hypertension. In the model for albuminuria, we adjusted for age, sex, race/ethnicity, body mass index (BMI), eGFR, as well as self-reported diabetes and hypertension. Additionally, we stratified our regression analysis for albuminuria by eGFR  $< 60$  and  $\geq 60$  ml/min/1.73 m<sup>2</sup>. Data were presented as odds ratio (OR) and 95% confidence interval (CI). Statistical analysis was performed using SAS version 9.4.

## 3. Results

Our results showed that individuals with high water intake was younger ( $P < .001$ ), while there was no difference in sex between the three groups ( $P = .06$ ) (Table 1). We also showed that the prevalence of diabetes as well as hypertension were not significantly different between the three groups (both  $P > .05$ ). Of note, our results showed that individuals with higher volume of water intake had higher eGFR ( $P < .001$ ) and lower urinary ACR ( $P < .01$ ); additionally, the plasma and urine osmolality were significantly lower in the high intake group when compared to those with moderate and low water intake (both  $P < .001$ ). When using Spearman's correlation analysis, our results showed that the volume of water intake positively correlated to eGFR ( $r_s = 0.06$ ,  $P < .001$ ) and negatively correlated to urinary ACR ( $r_s = -0.04$ ,  $P = .01$ ), although the correlations were weak (Fig. 2A & B). In addition, water intake was also weakly negatively associated with plasma ( $r_s = -0.06$ ,  $P < .001$ ) and urine osmolality ( $r_s = -0.11$ ,  $P < .001$ ) (Fig. 2C & D).

Among 4633 participants, our results showed that 377 (8.1%) individuals had CKD. The prevalence of CKD was graded higher with groups of decreased water intake (Fig. 3). Additionally, among 4597 individuals of whom urinary ACR data were available (ACR data in 36 individuals were missing), we showed that 553 (12.0%) individuals had ACR  $\geq 30$  mg/g. The prevalence of albuminuria was lower in the high-water intake groups, while the difference between low and moderate intake group was not significant (Figure 3).

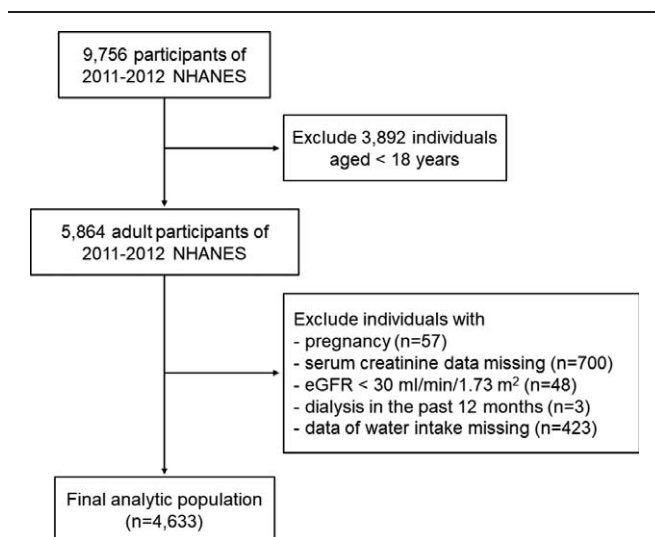


Figure 1. Flow diagram of the study population selection.

**Table 1**  
**Characteristics of the participants by volume of daily water intake.**

	Total N = 4,633	Low N = 1589 (34.3%)	Moderate N = 1359 (29.3%)	High N = 1685 (36.4%)	P-value
Age, years	46.78 (18.39)	48.87 (19.20)	47.91 (18.56)	43.91 (17.06)	<.001
Male	2350 (50.72%)	837 (52.67%)	656 (48.27%)	857 (50.86%)	.06
Ethnicity					<.001
Hispanic	936 (20.20%)	307 (19.32%)	275 (20.24%)	354 (21.01%)	
White	1780 (38.42%)	649 (40.84%)	489 (35.98%)	642 (38.10%)	
Black	1195 (25.79%)	438 (27.56%)	367 (27.01%)	390 (23.15%)	
Asian	577 (12.45%)	151 (9.50%)	191 (14.05%)	235 (13.95%)	
Other	145 (3.13%)	44 (2.77%)	37 (2.72%)	64 (3.80%)	
Diabetes	560 (12.09%)	197 (12.40%)	164 (12.07%)	199 (11.81%)	.88
Hypertension	1569 (33.87%)	568 (35.75%)	466 (34.29%)	535 (31.75%)	.05
Smoking					<.001
Current	892 (19.25%)	386 (24.29%)	208 (15.31%)	298 (17.69%)	
Prior	1021 (22.04%)	340 (21.40%)	297 (21.85%)	384 (22.79%)	
Never	2720 (58.71%)	863 (54.31%)	854 (62.84%)	1003 (59.53%)	
BW, kg	80.97 (21.28)	80.32 (21.40)	79.60 (20.64)	82.68 (21.57)	<.001
Height, cm	167.68 (10.05)	167.70 (9.84)	167.08 (10.29)	168.15 (10.04)	.01
BMI, kg/m <sup>2</sup>	28.72 (6.85)	28.49 (7.02)	28.44 (6.54)	29.16 (6.92)	.004
SBP, mmHg	122.74 (17.68)	123.71 (18.50)	123.17 (18.01)	121.47 (16.53)	<.001
DBP, mmHg	70.56 (12.71)	70.20 (12.39)	70.53 (13.18)	70.92 (12.63)	.28
BUN, mg/dL	12.62 (4.87)	12.82 (5.10)	12.74 (4.98)	12.35 (4.55)	.01
Cr, mg/dL	0.88 (0.24)	0.90 (0.25)	0.88 (0.25)	0.86 (0.22)	<.001
eGFR	92.68 (26.33)	90.87 (25.81)	92.06 (25.20)	94.88 (27.53)	<.001
Na, mmol/L	138.96 (2.20)	139.00 (2.23)	139.07 (2.16)	138.83 (2.22)	.009
K, mmol/L	3.93 (0.34)	3.96 (0.35)	3.92 (0.34)	3.92 (0.34)	.003
Cl, mmol/L	103.83 (2.83)	103.90 (2.85)	103.80 (2.81)	103.77 (2.82)	.38
Albumin, g/L	42.96 (3.26)	42.66 (3.24)	42.98 (3.19)	43.23 (3.32)	<.001
Glucose, mg/dL	101.59 (38.39)	102.30 (39.64)	101.74 (35.40)	100.81 (39.50)	.53
HbA1c, %	5.76 (1.11)	5.77 (1.04)	5.80 (1.14)	5.71 (1.14)	.09
Uric acid, mg/dL	5.44 (1.42)	5.42 (1.41)	5.42 (1.47)	5.48 (1.40)	.44
T CHOL, mg/dL	191.70 (41.48)	191.83 (42.70)	191.51 (41.57)	191.73 (40.24)	.98
HDL, mg/dL	52.28 (14.68)	52.07 (14.55)	52.88 (15.27)	51.99 (14.31)	.20
LDL, mg/dL	113.33 (34.80)	112.70 (34.07)	112.85 (35.62)	114.33 (34.83)	.59
TG, mg/dL	125.27 (89.26)	126.00 (85.26)	125.32 (84.87)	124.52 (96.40)	.95
P <sub>osm</sub> , mmol/Kg	277.62 (4.77)	277.81 (4.82)	277.86 (4.77)	277.25 (4.70)	<.001
U <sub>osm</sub> , mmol/Kg	639.38 (264.37)	669.89 (253.83)	644.77 (258.10)	606.46 (275.21)	<.001
Urine ACR, mg/g	30.08 (153.32)	33.30 (160.27)	30.97 (153.63)	26.35 (146.25)	.005 <sup>#</sup>

Continuous variables were presented as mean (standard deviation) and were tested by Student's *t* tests. Categorical variables were presented as numbers (percent) and were compared by  $\chi^2$  tests. BW = body weight; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; BUN = blood urea nitrogen; Cr = plasma creatinine; eGFR = estimated glomerular filtration rate (in ml/min/1.73 m<sup>2</sup>); Na = plasma sodium; K = plasma potassium; Cl = plasma chloride; HbA1c = hemoglobin A1c; T CHOL = total cholesterol; HDL = High density lipoprotein-cholesterol; LDL = Low density lipoprotein-cholesterol; TG = triglyceride; P<sub>osm</sub> = plasma osmolality; U<sub>osm</sub> = urine osmolality; ACR = albumin-creatinine ratio.

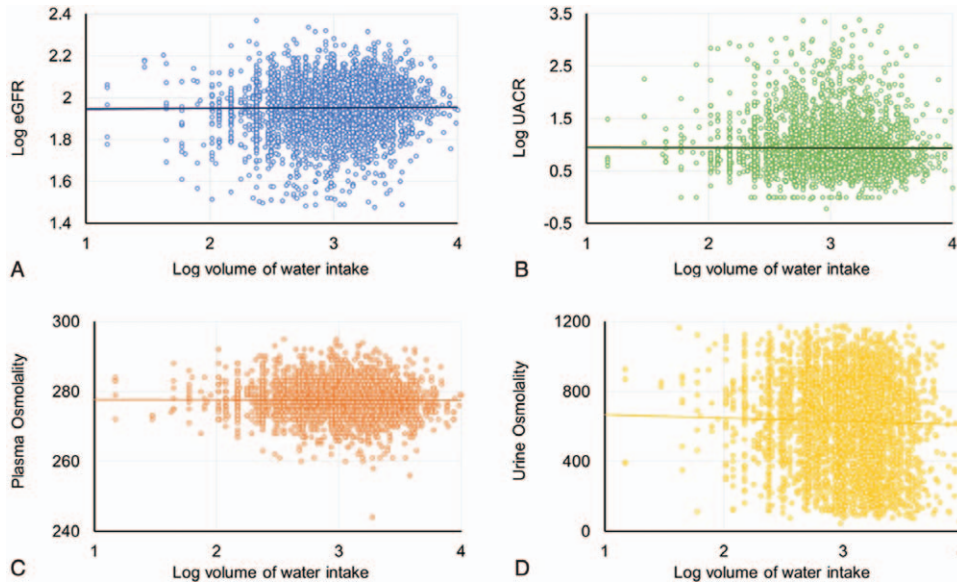
<sup>#</sup> Statistics was tested by Kruskal-Wallis method.

After adjusted for age, sex, race/ethnicity, BMI, and self-reported history of diabetes and hypertension, our results showed that the low water intake group had 35% higher risk of CKD when compared to high water intake group (OR 1.35, 95% CI 1.01–1.82,  $P < .05$ ) (Figure 4A). In addition, the low water intake group was also associated with higher risk of albuminuria when compared to high water intake group (OR 1.42, 95% CI 1.13–1.79,  $P < .01$ ) after adjusted for age, sex, race/ethnicity, BMI, eGFR and self-reported history of diabetes and hypertension (Figure 4B). When stratified by eGFR  $< 60$  and  $\geq 60$  ml/min/1.73 m<sup>2</sup>, our results showed that low (OR 1.40, 95% CI 1.09–1.80,  $P < .01$ ) and moderate (OR 1.31, 95% CI 1.01–1.70,  $P < .05$ ) water intake groups had higher risk of albuminuria when compared to high water intake group among individuals with eGFR  $\geq 60$  ml/min/1.73 m<sup>2</sup> (Figure 5A), while there was no significant difference between the 3 groups among those with eGFR  $< 60$  ml/min/1.73 m<sup>2</sup> (Figure 5B). Additionally, among

individuals with eGFR  $< 60$  ml/min/1.73 m<sup>2</sup>, we showed that higher water intake was not significantly associated with greater eGFR; similar finding was also observed among individuals with eGFR  $\geq 60$  ml/min/1.73 m<sup>2</sup> (Table S1, Supplemental Digital Content: <http://links.lww.com/MD/G128>).

#### 4. Discussion

In this population-based cross-sectional study, we showed that volume of daily water intake positively correlated to eGFR and negatively correlated to urinary ACR, as well as plasma and urine osmolality. In addition, our results showed that high water intake group was associated with lower prevalence of CKD and albuminuria compared with moderate and low water intake groups. By multivariable logistic regression analysis, we demonstrated that risk of CKD was higher in low water intake group compared with high water intake group. Furthermore,



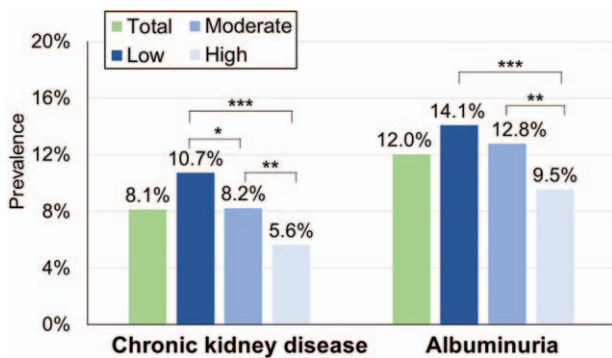
**Figure 2.** Volume of water intake positively correlated to estimated glomerular filtration rate (eGFR), and negatively correlated to urinary albumin to creatinine ratio (UACR), as well as plasma osmolality and urine osmolality, although the correlations were weak. (A) Spearman’s correlation coefficient ( $r_s$ ) between volume of water intake and eGFR was 0.06,  $P < .001$ . (B) Correlation coefficient ( $r_s$ ) between volume of water intake and UACR was -0.04,  $P < .05$ . (C) Correlation coefficient ( $r_s$ ) between volume of water intake and plasma osmolality was -0.06,  $P < .001$ . (D) Correlation coefficient ( $r_s$ ) between volume of water intake and urine osmolality was -0.11,  $P < .001$ .

individuals with low water intake had higher risk of albuminuria as opposed to high water intake group.

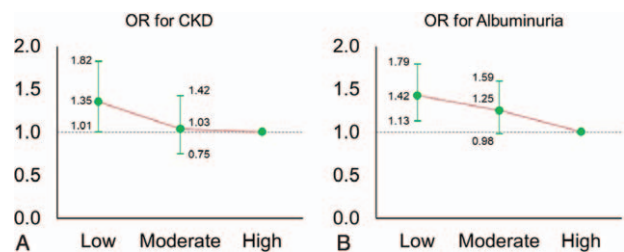
Increased water intake has been shown to not only correlate with lower plasma and urine osmolality, but also lower level of plasma copeptin,<sup>[8,18,19]</sup> a surrogate of vasopressin.<sup>[20,21]</sup> Studies showed that vasopressin may pose negative effect on kidney function through increasing renal blood flow and glomerular hyperfiltration.<sup>[9–11,22–26]</sup> A population-based study had shown the correlation between plasma vasopressin levels and incidence of CKD, as well as rapid kidney function decline.<sup>[27]</sup> Additionally, high vasopressin level was associated with disease progression among patients with autosomal dominant polycystic kidney

disease,<sup>[28,29]</sup> probably through hemodynamic effect in addition to participation in the regulation of cyst growth.<sup>[30]</sup> Furthermore, vasopressin may also play an important role in declining glomerular filtration rate in people with diabetic kidney disease.<sup>[25,31,32]</sup> As vasopressin is pivotal in regulation of water homeostasis and its secretion is aroused mainly by hypertonicity and hypovolemia, the association between lower water intake and higher risk of CKD in our study may be ascribed to the deleterious effect of vasopressin.

The association between water and/or fluid intake and decline in kidney function had been examined in general population, with the results conflicted and inconclusive. Among adult

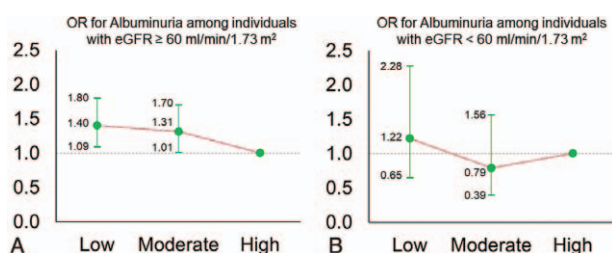


**Figure 3.** Higher volume of water intake is associated with lower prevalence of chronic kidney disease (CKD) and albuminuria. While 377 (8.1%) out of 4633 participants had CKD, the prevalence inversely correlated to volume of water intake – 10.7% (170/1589) in low, 8.2% (112/1359) in moderate, and 5.6% (95/1685) in high intake groups, respectively. The prevalence of albuminuria was also lower in the high intake group (160/1678, 9.5%) compared with moderate (172/1348, 12.8%) and low intake groups (221/1571, 14.1%), respectively. \*:  $P < .05$ ; \*\*:  $P < .01$ ; \*\*\*:  $P < .001$ .



**Figure 4.** Low water intake is associated with higher risk of chronic kidney disease (CKD) and albuminuria. We showed that low water intake group was associated with 35% higher risk of CKD when compared to high intake group after adjusted for age, sex, race/ethnicity, body mass index (BMI), and self-reported history of diabetes and hypertension (Odds ratio 1.35, 95% confidence interval 1.01–1.82,  $P < .05$ ) (panel A). In addition, our results showed that low water intake group was associated with 42% higher risk of albuminuria when compared to high water intake group (Odds ratio 1.42, 95% confidence interval 1.13–1.79,  $P < .01$ ) after adjusted for age, sex, race/ethnicity, BMI, estimated glomerular filtration rate (eGFR) and self-reported history of diabetes and hypertension (panel B).





**Figure 5.** Lower volume of water intake was associated with graded higher risk of albuminuria among individuals without chronic kidney disease (CKD). Among individuals with estimated glomerular filtration rate (eGFR)  $\geq 60$  ml/min/1.73 m<sup>2</sup>, our results showed that low (Odds ratio 1.40, 95% confidence interval 1.09–1.80,  $P < .01$ ) and moderate (Odds ratio 1.31, 95% confidence interval 1.01–1.70,  $P < .05$ ) water intake groups had higher risk of albuminuria when compared to high water intake group after adjusted for age, sex, race/ethnicity, BMI, estimated glomerular filtration rate (eGFR) and self-reported history of diabetes and hypertension (panel A). However, the association between water intake and albuminuria was not significantly different among individuals with CKD (eGFR  $< 60$  ml/min/1.73 m<sup>2</sup>) (panel B).

participants of 2005–2006 NHANES in the U.S., Sontrop et al showed that low intake of plain water, but not with other fluids, was associated with increased risk of CKD.<sup>[33]</sup> Strippoli et al showed that higher fluid intake appears to have lower risk of CKD among Australian adults older than 49 years. In this study, they did not differentiate plain water from other fluid and did not have the plasma or urine osmolality data, and thus the causal relationship was less clear.<sup>[14]</sup> In addition, a cohort study showed that individuals with high urine volume, who were assumed to have high volume of water intake, were associated with slower decline in kidney function.<sup>[13]</sup> While we did not report the data of urine volume, our results showed that individuals with low water intake had higher urine osmolality. As higher urine osmolality had been shown to be a risk factor of dialysis initiation among individuals with CKD,<sup>[34]</sup> provision of supplemental water may benefit kidney function.

On the other hand, Palmer et al failed to demonstrate the long-term effect of fluid intake on change in kidney function among adults aged 49 years or older. However, the fluid content in this study included tea, coffee, milk, juices, sugar-sweetened beverage, and alcohol, but not water.<sup>[35]</sup> Studies showed that alcohol, fructose-containing beverages, or high plasma glucose level may resulted in greater stimulation of the vasopressin<sup>[36,37]</sup>; this may explain why the study of Palmer et al had null findings. In addition, the CKD WIT trial showed that increased water intake, compared with maintaining the same water intake, did not significantly slow the decline in kidney function despite having lower copeptin level<sup>[15]</sup>; this suggested that vasopressin may not be responsible for progression of CKD. However, this study failed to achieve target enrollment of 700 participants and may be underpowered to detect the significance difference.<sup>[15]</sup> Furthermore, as shown in our study, the beneficial effect of water intake was observed particularly among individuals with eGFR  $\geq 60$  ml/min/1.73 m<sup>2</sup> (Figure 5); this may also explain why the CKD WIT trial had null findings, in which their study population were individuals with eGFR  $< 60$  ml/min/1.73 m<sup>2</sup>.<sup>[15]</sup>

Our study showed that low water intake was associated with higher risk of albuminuria, which had not been reported previously. In animal and human studies, vasopressin appeared to induce glomerular hyperfiltration and increased urinary albumin excretion.<sup>[11]</sup> Population-based studies also showed

that increased level of vasopressin correlated with higher urinary ACR and higher prevalence and incidence of albuminuria.<sup>[12,27,38]</sup> We speculated that lower water intake related to higher plasma levels of vasopressin, which lead to albuminuria as demonstrated in our study. Albuminuria is an independent risk factor of CKD progression and incident end-stage renal disease (ESRD).<sup>[39,40]</sup> As low water intake is a modifiable risk factor, future research to elucidate the potential role of increased water intake on preservation of kidney function and albuminuria will be needed.

Our study bares several limitations. First, the diagnosis of albuminuria was based on a single random measurement of urinary albumin and creatinine, which may over-diagnose by misclassifying individuals with physiologic albuminuria. In addition, CKD is defined as glomerular filtration rate (GFR)  $< 60$  ml/min/1.73 m<sup>2</sup> for at least 3 months. Using single measurement of plasma creatinine to define CKD in our study may not be valid. Second, the volume of water intake may not be consistent day by day; stratifying participants by volume of single daily water intake may be biased. Third, as a cross-sectional study, the causal relationship between water intake and albuminuria as well as CKD is unable to deduce. Future research will be needed to elucidate the causation and the underlying mechanism between water intake and kidney function.

## 5. Conclusion

Our findings support that increased water intake is associated with lower risk of albuminuria and CKD, in which vasopressin may play important roles. As water intake could suppress the secretion of vasopressin, encouraging water intake is an economical way to prevent the development of albuminuria and decline in kidney function. Meticulous research will be warranted to investigate the effect of water intake on change in kidney function and albuminuria, as well as the underlying mechanism.

## Author contributions

**Conceptualization:** Ming-Yan Jiang.

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**Formal analysis:** Ming-Yan Jiang.

**Investigation:** Ming-Yan Jiang.

**Methodology:** Ming-Yan Jiang.

**Software:** Ming-Yan Jiang.

**Supervision:** Ming-Yan Jiang.

**Validation:** Ming-Yan Jiang.

**Visualization:** Ming-Yan Jiang.

**Writing – original draft:** Hung-Wei Wang, Ming-Yan Jiang.

**Writing – review & editing:** Hung-Wei Wang, Ming-Yan Jiang.

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