Urinary uromodulin, kidney function, and cardiovascular disease in elderly adults

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Urinary uromodulin (uUMOD) is the most common secreted tubular protein in healthy adults. However, the relationship between uUMOD and clinical outcomes is still unclear. Here we measured uUMOD in 192 participants of the Cardiovascular Health Study with over a 30% decline in estimated glomerular filtration rate (eGFR) over 9 years, 54 with incident end-stage renal disease (ESRD), and in a random subcohort of 958 participants. The association of uUMOD with eGFR decline was evaluated using logistic regression and with incident ESRD, cardiovascular disease, heart failure, and mortality using Cox proportional regression. Mean age was 78 years and median uUMOD was 25.8 µg/ml. In a case–control study evaluating eGFR decline (192 cases and 231 controls), each 1-s.d. higher uUMOD was associated with a 23% lower odds of eGFR decline (odds ratio 0.77 (95% CI 0.62–0.96)) and a 10% lower risk of mortality (hazard ratio 0.90 (95% CI 0.83–0.98)) after adjusting for demographics, eGFR, albumin/creatinine ratio, and other risk factors. There was no risk association of uUMOD with ESRD, cardiovascular disease, or heart failure after multivariable adjustment. Thus, low uUMOD levels may identify persons at risk of progressive kidney disease and mortality above and beyond established markers of kidney disease, namely eGFR and the albumin/creatinine ratio. Future studies need to confirm these results and evaluate whether uUMOD is a marker of tubular health and/or whether it plays a causal role in preserving kidney function.

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The prevalence of chronic kidney disease (CKD) in individuals over the age of 65 years is nearly 44%,[1] and older adults with even moderate reductions in kidney function are at an increased risk for cardiovascular disease (CVD).[2] Current assessment of kidney function and the definition of CKD are limited to measures of estimated glomerular filtration rate (eGFR) and urinary albumin/creatinine ratio (ACR). Tubular health is essential for maintenance of acid–base status, mineral metabolism, and hormone production. In addition, tubular secretion is the means by which medications are excreted through the kidneys. There are no biomarkers that have been validated as surrogates of tubular health.[3,4]

Urinary uromodulin (uUMOD), also known as Tamm–Horsfall protein, is a 95-kDa glycoprotein synthesized by the thick ascending limb of the loop of Henle and early distal convoluted tubule. It is the most abundant urinary protein among healthy adults (20–70 mg/day).[5] Mutations in the *UMOD* gene cause congenital hyperuricemic and cystic kidney diseases, lead to kidney failure, and are associated with low uUMOD levels.[6,7] Recently, large genome-wide association studies have identified that the strongest association with CKD was with common variants in the region of *UMOD* gene on chromosome 16.[8,9] Single-nucleotide polymorphisms in this region appear to be more strongly associated with maintenance of kidney function in older adults than in younger individuals.[10] As a result, there has been a renewed interest in the role of uUMOD in the development and progression of CKD.

To date, studies evaluating uUMOD concentrations with CKD prevalence and incidence have not been consistent. Early studies suggested that low uUMOD levels may be associated with reduced kidney function.[11,12] In contrast, a more recent case–control study reported an association between higher uUMOD levels and incident CKD,[13] whereas another showed no statistically significant relationship.[14] These studies, however, were all relatively small and did not

adjust for kidney function measures such as ACR.[8] The aims of our study were to evaluate the correlates and cross-sectional distribution of uUMOD, and to evaluate the associations of uUMOD with kidney function decline, incident end-stage renal disease (ESRD), CVD, and mortality independent of eGFR and ACR in community-dwelling older adults.

RESULTS
Baseline correlates of uUMOD levels
Among the 958 randomly selected participants at baseline (see Figure 1 for participant sampling), median (interquartile range) value of uUMOD was 25.8 µg/ml (17.2–38.8) and the distribution was right skewed (Figure 2). The mean age of participants was 78 ± 5 years, 60% were women, and 15%

Figure 1 | Population sampling from within the Cardiovascular Health Study (CHS). Rectangle: all CHS participants at 1996–1997 visit. Large circle: random subcohort. Black circle: participants included as controls in the case–control study for the chronic kidney disease (CKD) progression outcome. Light gray area: participants included as cases in the case–control study for the CKD progression. Dark gray area: participants included in the case–cohort study for the incident end-stage renal disease (ESRD) outcome. CVD, cardiovascular disease; HF, heart failure.
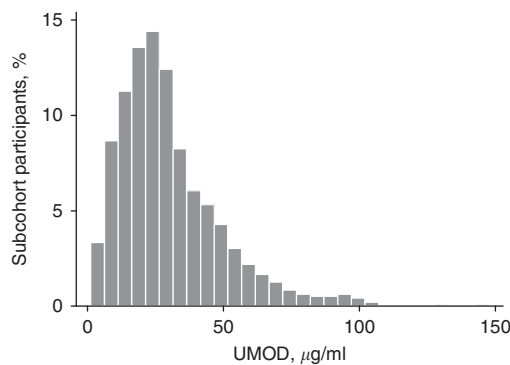
Figure 2 | Distribution of urine uromodulin (UMOD) levels in 958 community-living elderly participants in the Cardiovascular Health Study.

were black. The mean $\pm$ s.d. eGFR was 63 ± 18 ml/min per 1.73 m^2, and median (interquartile range) urine ACR was 8 (5–20) mg/g. Table 1 shows baseline characteristics by quartiles of uUMOD in the random subcohort. Compared with participants with low uUMOD, individuals with higher levels were less likely to have diabetes, history of coronary artery disease, stroke, and heart failure (HF), and had lower systolic blood pressure and lower body mass index. Individuals with higher uUMOD also had higher eGFR, lower urinary ACR, and lower C-reactive protein. At baseline, uUMOD levels were weakly and inversely correlated with ACR (Spearman's $r = -0.12$) and directly correlated with eGFR (Spearman's $r = 0.20$) values.

uUMOD and kidney outcomes
Supplementary Table S1 online shows a comparison of baseline characteristics between individuals who had $\geqslant 30\%$ decline in eGFR and those who did not. There were 193 participants with progressive decline of eGFR during the follow-up period. Table 2 shows the association of uUMOD with 30% decline in eGFR. Each 1-s.d. (19.7 µg/ml) higher uUMOD was associated with a 26% lower risk of progressive eGFR decline in demographic adjusted models and this association was only modestly attenuated after adjusting for baseline eGFR, ACR, CVD, and CKD risk factors (odds ratio (OR) = 0.77, 95% confidence interval (CI) 0.62–0.96). Participants in the highest quartile of uUMOD (> 38.8 µg/ml) had 40% lower risk of progressive GFR decline compared with those in the lowest quartile, but this was not statistically significant in fully adjusted analyses (OR = 0.59, 95% CI 0.32–1.09).

We identified 54 incident ESRD cases during 9.5 years of follow-up (Table 3). Owing to the relatively few ESRD cases in quartiles 2–4, these were collapsed and compared with quartile 1. In demographic adjusted models, participants with uUMOD levels in quartiles 2–4 had 80% lower risk of incidence ESRD. After adjusting for eGFR, ACR, and CVD risk factors, individuals in quartiles 2–4 had 16% lower risk of ESRD, but this association failed to reach statistical significance.

uUMOD and cardiovascular events and mortality
There were 289 incident CVD events during the follow-up period. The association of uUMOD and incident CVD appeared curvilinear (Figure 3). The fourth quartile of uUMOD was associated with a 21% decreased risk of incident CVD events. However, this association was not statistically significant in multivariable analysis (Table 4). There were 260 incident HF events, and no association was noted between uUMOD and incident HF. There were 694 deaths in the subcohort during follow-up (Table 4). Each 1-s.d. increment in uUMOD was associated with a 10% decrease in mortality in adjusted analyses. Compared with the first quartile, the fourth quartile of uUMOD had a 30% lower risk of death (hazard ratio (HR) 0.69, 95% CI 0.55–0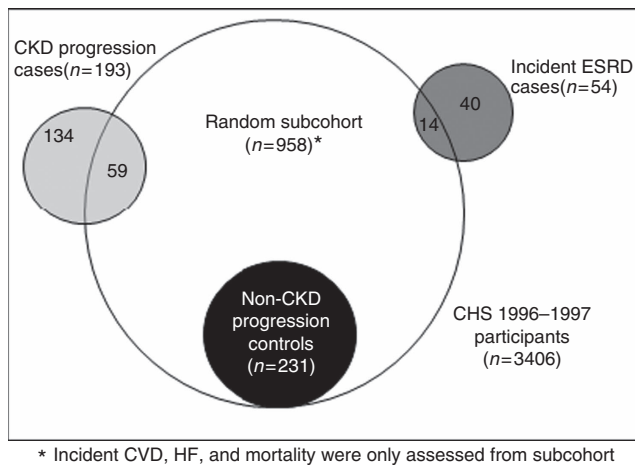.87) in multivariable analysis.