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Urinary Uromodulin and Risk of Urinary Tract Infections: The Cardiovascular Health Study

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Abstract

Background—Laboratory studies suggest that urinary uromodulin, the most common protein in the urine of healthy adults, may protect against urinary tract infection (UTI). Epidemiological studies evaluating this relationship in humans are lacking.

Study Design—Prospective longitudinal cohort study.

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Contributions: Research idea and study design: PSG, MJS; data acquisition: MJS, MGS, JHI, PD, MRB; data analysis/interpretation: TMB, PSG, MC, MJS; statistical analysis: TMB; supervision or mentorship: MJS. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. PSG takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Supplementary Material

Table S1: Association of uromodulin–urine creatinine ratio with risk of composite UTI events.

Note: The supplementary material accompanying this article (doi:_____) is available at www.ajkd.org

Supplementary Material Descriptive Text for Online Delivery

Supplementary Table S1 (PDF). Association of uromodulin–urine creatinine ratio with risk of composite UTI events.

Setting & Participants—953 participants enrolled in the Cardiovascular Health Study.

Predictor—Uromodulin assayed using ELISA in spot urine samples.

Outcomes—Composite of outpatient UTI events or UTI-related hospitalizations and each of them individually identified using ICD-9 codes using negative binomial regression with robust standard errors adjustment for age, race, sex, body mass index, diabetes, eGFR, urinary albumin and urinary creatinine.

Results—The median uromodulin level was 25.9 (IQR, 17.3-38.9) μg/ml, the mean age of participants was 78 years, 61% were women, and 15% were Black. There were 331 outpatient UTI events and 87 UTI related hospitalizations among 186 participants over a median 9.9 years of follow up. Persons in the highest quartile (>38.93 μg/ml) of uromodulin concentration had a significantly lower risk of composite outcome (incidence rate ratio [IRR], 0.47; 95% CI, 0.29-0.79) compared to those in the lowest quartile (≤17.26 μg/ml). This association remained significant for outpatient UTI events (highest versus lowest quartile even after excluding those with prior UTI: IRR, 0.42; 95% CI, 0.23-0.77). The direction of association with UTI hospitalization was similar, but not statistically significant (IRR, 0.78; 95% CI, 0.39-1.58).

Limitations—Use of ICD-9 codes to identify outcomes and lack of generalizability to younger populations.

Conclusions—High urinary uromodulin levels are associated with a lower risk of UTI in older community dwelling adults independent of traditional UTI risk factors. This finding supports prior laboratory data indicating a protective role of uromodulin against UTI. Further research is needed to understand if this may lead to new treatments to prevent or treat UTI.

Keywords

uromodulin (UMOD); urinary tract infection (UTI); hospitalization; elderly; Tamm-Horsfall protein; geriatric; bacterial infection

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Urinary tract infections (UTIs), which are commonly caused by bacteria, affect nearly 150 million people worldwide, resulting in significant healthcare costs and morbidity.[1,2] They are especially problematic in persons aged 65 years or older, for whom they account for nearly 15% of hospitalizations and 6% of infectious deaths, second only to pneumonia.[3] Common risk factors for UTI include female sex, prior history of UTI, sexual activity, diabetes, obesity and genetic or anatomic susceptibility.[4] *Escherichia, Klebsiella*, *Proteus,* and *Staphyloccus* species account for the vast majority of cases of UTI.[5]

Urinary uromodulin (also known as Tamm-Horsfall protein) is a 95-kDa glycoprotein produced by the thick ascending limb of the loop of Henle and early distal convoluted tubule.[6] It is the most plentiful urinary protein (20-70 mg excreted daily) in healthy adults. Studies in mice[7-11] and genetic studies[12] suggest that uromodulin may have a role in preventing UTI by blocking the colonization of urothelia by bacteria. Mice in which the uromodulin gene (*UMOD*) has been knocked out exhibit impaired clearance of bacteria from the bladder, and a greater severity of histological pyelonephritis.[9] Whether uromodulin levels are linked with risk of UTI in humans is uncertain.

In a recent study of 74 patients who underwent kidney transplantation, those with recurrent UTIs had lower levels of uromodulin compared with persons without UTI.[13] However, to our knowledge, no large studies have evaluated whether uromodulin levels are associated with risk of UTI. To that end, using data from the Cardiovascular Health Study (CHS)[14] a large study of community-living elderly persons, we aimed to evaluate the association between urinary uromodulin levels and UTI in older adults. We hypothesized that lower urinary uromodulin concentrations would be associated with higher risk of UTI.

METHODS

Participants

The CHS is an observational study of risk factors for cardiovascular disease among 5,888 men and women aged 65 years or older living in 4 communities (Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh, Pa). Initially 5,201 participants were enrolled in 1989-1990, and 687 additional predominantly African American participants were enrolled in 1992-1993. For both enrollment periods, random samples of Medicare eligibility lists were used to recruit participants who were non-institutionalized, were expected to remain in the area for the next 3 years and were not wheelchair-bound, receiving hospice treatment, or receiving radiation therapy or chemotherapy for cancer. All participants gave informed consent at the time of enrollment, and the study was approved by institutional review boards at each site and the coordinating center (IRB #37714, University of Washington, Seattle). A detailed description of the recruitment and examination methods has been published previously.[15]

For this study, we used data from the 1996-1997 visit, as this was the first time urine measurements were obtained and stored in CHS. Of the 3,406 individuals at this visit who provided blood and urine samples, we excluded individuals with missing serum creatinine (n=1) or albumin-creatinine ratio (ACR; n=92), leaving us with 3,313 participants. From these we randomly selected a sub-cohort of 960 individuals who were representative of the CHS population and have been used in prior studies.[14,16] Of the 960, two lacked sufficient urine to measure urinary uromodulin and five lacked data on body mass index (BMI) resulting in a sub-cohort of 953 individuals for this analysis. Follow up began at the 1996-1997 visit and ended on June 30, 2013 or at time of death or last recorded follow up date.

Exposure

Spot urine specimens were obtained at the time of the 1996-97 study visit and stored at −70°C until thawing for uromodulin measurement in 2014 at the University of Cincinnati Children's Hospital Medical Center. We measured uromodulin by a commercially available ELISA kit (MD Bioproducts, St. Paul, MN) according to the manufacturer's instructions. The principle of the assay is based on a colorimetric sandwich immunoassay utilizing a polyclonal antibody against human uromodulin as the capture antibody and a biotinylated polyclonal antibody against human uromodulin as the detection antibody. For this assay, the inter-assay coefficient of variation is 10.5% at a mean concentration of 21.8 ng/mL and 12.2% at a mean concentration 95 ng/mL. The intra-assay coefficient of variation is 9.2% at

a mean concentration of 22.9 ng/mL and 7.0% at 103.4 ng/mL. The minimum detectable level was 0.75 ng/mL.

Outcomes

The primary outcome was a composite of outpatient UTI or hospitalization with a principal discharge diagnosis of UTI both assessed by ICD-9 codes. Recurrent events were counted towards the outcome. Outcomes were obtained both through review of Medicare claims records and through the scheduled visits and phone contact as per the CHS follow up protocol. During follow-up, participants were contacted semi-annually to ascertain clinically relevant events including hospitalizations. Contact was by telephone alternating with annual examination visits through 1999 and subsequently by semi-annual telephone contact. At the semi-annual contacts, participants were asked about major illnesses and hospital admissions. Medical records were obtained for all reported hospitalizations. All hospitalizations and outpatient Medicare claims data during follow-up were examined and included in the analyses if the principal diagnosis was a UTI. When UTI events were identified by both outpatient records and hospital discharge records, we considered them UTI related hospitalizations only. If a UTI was recorded within 14 days of the prior UTI, it was considered to be the same rather than a separate event. Secondary outcomes were outpatient UTI events and UTI related hospitalizations evaluated separately.

The ICD-9 codes for cystitis (595, 595.0, 595.1) and urethritis (597.80, 597.81 and 597.89) were used to capture outpatient UTI episodes when present in the primary diagnosis position only. In addition, the following diagnosis codes when present in the primary position only were used to capture outpatient UTI episodes or hospitalizations for UTI, pyelonephritis or renal/peri-nephric abscess: 599.0, 590, 590.0, 590.00, 590.01, 590.1, 590.10, 590.11, 590.2, and 590.3 from Medicare claims data.

Covariates

Covariates were selected based on prior knowledge about the factors that could confound the associations of uromodulin with UTI and were ascertained at the CHS clinic visit in 1996-1997. These included age, gender, BMI, diabetes (defined by use of hypoglycemic agents, fasting plasma glucose >126 mg/dL or non-fasting glucose ≥ 200 mg/dL), baseline eGFR, urinary albumin, and urinary creatinine. The eGFR was estimated using the 2008 CKD-EPI cystatin C equation (eGFR = 127.7 × [nonstandardized CysC]$^{1.17}$ × age$^{0.13}$ × 0.91 [if female] × 1.06 [if black]).[17] Cystatin C was measured by a Siemens nephelometric assay.[18]

Statistical Analyses

We described baseline participant characteristics of the random subcohort across uromodulin quartiles with mean ± standard deviation for continuous variables and number (percentage) for categorical variables. There were no samples with uromodulin concentrations below the assay's limit of detection. Uromodulin was log transformed to examine a multiplicative association with UTI. In previous studies in CHS, Poisson regression has been selected over other statistical methodologies when the outcome of interest has been rate of hospitalization over time.[19] Due to over-dispersion in our Poisson models, we used negative binomial

regression with robust standard errors to examine whether higher uromodulin levels were associated with the risk of UTI.[20] We report incidence rate ratios (IRRs) and their corresponding 95% confidence intervals (CIs).

We evaluated uromodulin as a continuous exposure variable and as quartiles, using the first quartile as the reference category. We used a series of models to adjust for potential confounders. Model 1 was unadjusted, while model 2 included adjustment for age, sex, race, and clinic site. Model 3 was further adjusted for BMI, diabetes, eGFR and albuminuria and urine creatinine. We adjusted for urine creatinine in model 3 to account for tonicity of urine, as has been previously done. As a secondary analysis, we repeated these models with outpatient UTI events and UTI related hospitalizations evaluated separately.

We conducted two sensitivity analyses to examine whether the association of uromodulin with UTI was influenced by prior UTIs. In the first sensitivity analysis, we excluded persons who had a documented UTI during the study period prior to when uromodulin was assayed (1989-1996). In the second sensitivity analysis, time to the first UTI was examined using a Cox proportional hazards model among those without a documented UTI from 1989-1996. For the latter analysis we report hazard ratios (HRs) and the corresponding 95% CI. Finally, we also repeated the primary analysis using uromodulin–urine creatinine ratio as the exposure variable given that indexed values take urinary concentration into account. All analyses were performed using STATA (version 12.1, STATACorp LP, College Station, TX) and a two-sided p value <0.05 was considered significant for all analyses.

RESULTS

Baseline Characteristics

Among the 953 participants, the median urinary uromodulin was 25.9 (interquartile range [IQR], 17.3-38.9) μg/mL. The mean age of participants was 78 ±4.7 (standard deviation) years, 61% were women, and 15% were Black. The mean eGFR was 71.0 ±19.2 ml/min/ $1.73m^2$, and median ACR was 8.5 (IQR, 4.8–20.2) mg/g. Participants in the lowest quartile of uromodulin were older, and had a greater prevalence of female gender and comorbidities including diabetes, coronary artery disease, and heart failure (**Table 1**). In addition, those in the lowest quartile also had worse kidney health as evidenced by both lower eGFR and higher ACR.

Urinary Uromodulin and Risk of UTI

Over a median of 9.9 years of follow-up, there were 418 UTIs among 186 participants. Of these, 99 participants had 1 UTI, 44 had 2 UTIs, 18 had 3 UTIs and 25 had 4 or more UTIs. Overall there were 331 UTIs in the outpatient setting and 87 UTI related hospitalizations. In unadjusted models, each doubling of uromodulin concentration was associated with a 20% (95% CI, 34%-4%) lower risk of the composite outcome(**Table 2**). After adjusting for demographics, BMI, diabetes, eGFR, urine albumin and urine creatinine, each doubling of uromodulin was associated with 17% lower IRR of primary outcome, but this finding was no longer statistically significant (95% CI, 31% lower to 0.4% higher). Higher quartiles of uromodulin were associated with lower IRR for the composite outcome. That is, the highest

quartile of uromodulin had 53% (95% CI, 71%-21%) lower risk of composite UTI outcome when compared to the lowest quartile in the fully adjusted model.

In secondary analyses, the associations of uromodulin with outpatient UTI events were similar to those with the composite outcome. Although higher uromodulin was not associated with a statistically significant risk of outpatient UTI in continuous models, compared to the first quartile, the fourth quartile was associated with a 58% (95% CI, 77%-23%) lower IRR of outpatient UTI events after adjustment. Levels of uromodulin were not significantly associated with hospitalizations for UTI although all IRRs were below 1.

In the sensitivity analysis restricting to participants without any documented history of UTI since CHS enrollment (n=901), the highest quartile of uromodulin was associated with 44% (95% CI, 67%-5%) lower risk of the composite primary outcome after multivariable adjustment, and 50% (95% CI, 73%-6%) lower risk of outpatient UTI events but not significantly associated with hospitalizations due to UTI (**Table 3**). In the sensitivity analysis examining time to first UTI event using Cox regression (n=901), there were 164 UTI events. In continuous analysis, each doubling of uromodulin levels was associated with a non-significant 13% lower risk (95% CI, 27% lower to 3% higher) of the composite outcome. Similarly, the highest quartile of uromodulin was associated with a 37% (95% CI, 60%-0.5%) lower risk of composite outcome compared to the first quartile in fully adjusted models (**Table 4**). When the ratio of uromodulin to urine creatinine concentrations was the exposure variable, its association with composite UTI events was weaker compared to the primary analysis (IRR per 1-unit higher uromodulin–urine creatinine ratio, 0.96; 95% CI, 0.93-1.00) after multivariable adjustment (**Table S1**, available as online supplementary material). However, the highest quartile (in comparison with the lowest quartile) of uromodulin–urine creatinine ratio was significantly associated with lower risk of composite outcome (IRR, 0.52; 95% CI, 0.30-0.90), and was consistent with the primary analysis.

DISCUSSION

This is the first study to demonstrate that laboratory findings showing that urinary uromodulin prevents the binding of pathogenic bacteria to the uroepithelium may have clinical relevance to humans.[21] We evaluated a large and representative cohort of community dwelling older adults who are at particularly high risk of UTI and associated morbid consequences. Our findings remained statistically significant, and only minimally altered, after adjusting for confounders and in sensitivity analysis excluding those with prior UTI. The association was quite strong, with persons in the highest quartile of uromodulin having approximately 50% lower risk of UTI during long-term follow-up. Moreover, we found that results were similar irrespective of sex, diabetes or kidney function.

The principal mechanism of defense against UTI lies in the innate immune response. These include activation of immunocompetent cells, signaling by Toll-like receptors, cytokines, and adhesion prevention molecules such as uromoduli.[22] By forming a gel on the surface of the thick ascending limb of the loop of Henle, uromodulin prevents water permeability in this segment. Uromodulin's presence in the kidney of all vertebrates has led to the hypothesis that its evolutionary conservation must be indicative of a functional role.[12] One

of its many postulated functions has been protection against bacterial UTI. Studies in mice demonstrated that uromodulin is the main urinary protein that binds to and inhibits the type 1 fimbriae of *Escherichia coli.*[10] These findings have been confirmed in *UMOD* knockout mice, which have a higher predisposition to bladder infections from *E coli.*[7,11,23] Additional studies have demonstrated a greater degree of bacteriuria and more inflammatory bladder changes in comparison with *UMOD* wild-type mice after transurethral inoculation with *Klebsiella pneumonia, Staphylococcus saprophyticus* and *Proteus mirabilis*.[8,9] By preventing bacterial adhesion to the uroepithelium, uromodulin facilitates the urinary wash-out of bacteria, thus reducing overall pathogen burden. Studies in mice also suggest that uromodulin activates dendritic cells via Toll-like receptor 4, triggering an immune response against bacteria which may have translocated across the uroepithelium.[24] These findings all provide insights into the biological methods through which uromodulin may protect against UTI.[23] Despite these insights, the role of uromodulin for prevention of UTIs in humans has remained uncertain.

We found statistically significant associations between the highest quartile of uromodulin and the composite outcome and outpatient UTIs. While the association was in a similar direction for continuous models and for the outcome of UTI hospitalizations, it was not statistically significant. There are at least two potential reasons for the lack of association between uromodulin and UTI hospitalizations. First, we had relatively few UTI related hospitalizations, and may have lacked statistical power. Second, compared to outpatient UTI events, hospitalizations for UTI may involve cases of greater severity such as pyelonephritis, abscesses, or urosepsis, possibly due to structural or functional abnormalities of the urinary tract, infection by resistant organisms and an overall poorer health status. These factors may overwhelm any potential benefit provided by higher levels of uromodulin.

A recent genomic study demonstrated that the global frequency of the UMOD ancestral allele, leading to high levels of uromodulin, correlated positively and significantly not only with the prevalence of antibiotic-resistant UTIs worldwide but also with greater markers of UTI (urinary leukocytes and nitrites).[12] Taken together, this result in conjunction with the data from animal models and our novel results in humans support the biological plausibility that the uromodulin gene may have evolved, at least in part, to protect against UTIs in humans. Future studies are need to evaluate if uromodulin levels can be used to identify persons at high risk of UTIs, especially those in whom prophylactic antibiotics are being considered.[25] Furthermore, understanding mechanisms that increase uromodulin concentrations or prevent degradation of uromodulin may guide the development of new treatments for UTIs. For example, a new class of small molecular weight compounds known as mannosides are being developed for the treatment and prevention of UTI.[27,28] These agents inhibit the type 1 fimbriae of *E coli* and prevent bacterial colonization in the uroepithelium, similar to uromodulin.

Our study has a number of important limitations. First, the CHS participants were 65 years of age or older at study entry. Whether our results generalize to younger persons is presently unknown. However, UTI is most common in the 65+ age group and is associated with significant morbidity and mortality.[4] Second, we only examined principal discharge diagnoses for hospitalization, so our study may underestimate the true burden of UTI in this

population. Data support the approach of using principal discharge diagnoses to improve the identification of UTI among hospitalized patients using ICD-9 codes,[29] and we extended this approach to outpatient events by only including events when the diagnosis of UTI was in the primary position. Although the diagnosis of UTI based on ICD-9 codes in the absence of bacterial culture may have occurred, we believe that this should be non-differential with regard to uromodulin levels. Third, our use of ICD-9 codes to identify UTI events rather than laboratory results does not allow for identification of the causative bacteria. However, given that prior studies demonstrate the protective role of uromodulin against *E coli, K pneumonia, S saprophyticus* and *P mirabilis*, which together account for over 90% of cases, our results can likely be generalized to most causes of bacterial UTI. Fourth, we performed our measurements of uromodulin in urine specimens that were collected and stored for approximately 16 years beforehand. Although storage for more than 8 months may slightly decrease the values of uromodulin (even at −80°C),[30] decreases in uromodulin levels due to freezing and storage should be similar in persons with and without UTI events. However, we are unable to comment on how asymptomatic bacteriuria present at the time of collection of the urine samples may affect uromodulin levels. Fifth, our not including the full cohort limits this study. We used a random sub-sample, which is representative of the entire cohort without bias. However, this resulted in evaluation of a smaller cohort and a lower number of events, which may have decreased statistical power particularly for hospitalized UTI events. Sixth, we do not have data on certain comorbidities such as prostatic hyperplasia, genitourinary surgery or prior bladder catheterization that may be associated risk of UTI. Finally, a number of studies have shown that uromodulin levels are affected by *UMOD* polymorphisms.[31,32] While the focus of this study was not on uromodulin genotype, further studies need to evaluate if uromodulin genotype is associated with clinical UTI in humans.

Our study also has several strengths. First, while prior studies used bacterial load and histology as surrogate outcomes when evaluating the protective role of uromodulin,[7,9] our findings represent the first attempt to study the association with clinically relevant UTI events in humans. Second, the CHS has robust ascertainment of baseline co-morbidity data with a relatively large number of outcomes. Third, the use of ICD-9 codes in our study captures the important association between uromodulin and possible clinical UTI infections requiring medical attention and possibly treatment. Last, we used a commercially available ELISA, which has been evaluated in prior studies of clinical outcomes, to assay uromodulin in our study.[14,33-35]

In conclusion, the highest levels of urinary uromodulin, the most abundant urinary protein in healthy adults, are associated with lower risk of clinical UTIs in community-living older adults. This finding supports prior laboratory data indicating a protective role of uromodulin against UTI. Further research is needed to evaluate if the underling mechanism leading to a lower UTI risk with higher urinary uromodulin can be used to develop new methods to prevent or treat UTI.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline participant characteristics by quartiles of urine uromodulin

Characteristic	Q1: ≤17.26 μg/mL	Q2: >17.26-25.94 μg/mL	Q3: >25.94-38.93 μg/mL	Q4: >38.93 μg/mL
No. of participants	239	238	238	238
Age, y	78.5±5.2	78.03±4.5	78.4±4.8	77.3±4.2
Male Sex	39.3	36.1	41.6	40.8
African American	15.1	18.9	11.8	15.1
Diabetes	28.5	16.4	13.4	14.7
CHD	27.6	24.8	20.6	21.4
Heart Failure	13.0	7.6	9.7	5.5
Smoking status				
Never	41.8	42.9	46.2	42.4
Former	49.4	51.7	44.5	50.8
Current	8.8	5.5	9.2	6.7
BMI, (kg/m^2)	26.9±5.1	27.0±4.6	26.7±4.6	26.8±4.3
eGFR (ml/min/1.73m2)	64.6±20.7	72.0±18.6	71.0±17.5	76.3±17.7
Albuminuria, (mg/dl)	9.31±31.35	4.40±18.31	2.53±11.87	5.53±31.55
Urine creatinine, (mg/dl)	85.81±64.07	103.03±70.38	107.52±61.95	118.41±56.27
Urine ACR, (mg/g)	95.2±276.8	43.7±168.1	21.7±66.3	47.7±282.0
Serum CRP, (mg/L)	5.3±8.7	5.0±10.0	4.0±6.9	4.4±7.0
Serum IL-6, (pg/mL)	4.1±2.7	3.7±2.6	3.4±2.3	3.5±2.4

Note: Unless otherwise indicated, values for categorical variables are given as percentage; for continuous variables, as mean ± standard deviation. Conversion factor for serum creatinine in mg/dL to μmol/L, ×88.4.

Abbreviations: CHD-coronary heart disease, BMI- body mass index, eGFR-estimated glomerular filtration rate, ACR- albumin-creatinine ratio CRP- C reactive protein, IL-6-interleukin 6.Q, quartile

Table 2

Association of urine uromodulin with risk of UTI

	Q2: >17.26-25.94 μg/mL	Q3: >25.94-38.93 μg/mL	Q4: >38.93 μg/mL	per doubling of uromodulin
Composite Outcome*				
No. of events	106	87	84	
Model 1	0.68 (0.41,1.14); p=0.1	0.60 (0.32,1.13); p=0.1	0.45 (0.26,0.77); p=0.003	0.80 (0.66,0.96); p=0.02
Model 2	0.66 (0.41,1.06); p=0.09	0.65 (0.35,1.21); p=0.2	0.48 (0.29,0.79); p=0.004	0.83 (0.69,0.99); p=0.05
Model 3	0.66 (0.41,1.08); p=0.1	0.63 (0.34,1.17); p=0.1	0.47 (0.29,0.79); p=0.004	0.83 (0.69,1.00); p=0.06
Outpatient UTI Only				
No. of events	82	71	62	
Model 1	0.64 (0.35,1.15); p=0.1	0.62 (0.30,1.28); p=0.2	0.42 (0.23,0.76); p=0.004	0.80 (0.65,0.99); p=0.04
Model 2	0.58 (0.34,1.01); p=0.05	0.66 (0.32,1.34); p=0.2	0.43 (0.24,0.77); p=0.004	0.82 (0.66,1.02); p=0.07
Model 3	0.57 (0.32,1.00); p=0.05	0.64 (0.31,1.32); p=0.2	0.42 (0.23,0.77); p=0.005	0.82 (0.66,1.03); p=0.09
UTI Hospitalization Only				
No. of events	24	16	22	
Model 1	0.84 (0.41,1.71); p=0.6	0.56 (0.26,1.20); =0.1	0.64 (0.30,1.36); p=0.2	0.82 (0.64,1.06); p=0.1
Model 2	0.88 (0.45,1.73); p=0.7	0.59 (0.29,1.23); =0.2	0.71 (0.35,1.43); p=0.3	0.86 (0.67,1.11); p=0.2
Model 3	0.97 (0.51,1.86); p=0.9	0.63 (0.30,1.29); =0.2	0.78 (0.39,1.58); p=0.5	0.89 (0.69,1.15); p=0.4

Note: Unless otherwise indicated, values are given as incidence rate ratio (95% confidence interval); P. Model 1: Unadjusted. Model 2: Adjusted for age, race, sex. Model 3: Adjusted for age, race, sex, body mass index, diabetes, estimated glomerular filtration rate, urine albumin and urine creatinine. Q1 (≤17.26 μg/mL) is referent category for composite outcome, outpatient UTI only, and UTI hospitalization only (numbers of events of 141, 116, and 25, respectively).

Q, quartile; UTI, urinary tract infection

*Outpatient + hospitalization.

Table 3

Association of urine uromodulin with UTI excluding those with UTI 1989- 1996

	Q2: >17.26-25.94 μg/mL	Q3: >25.94-38.93 μg/mL	Q4: >38.93 μg/mL	per doubling of uromodulin
Composite outcome*				
No. of events	95	83	78	
Model 1	0.81 (0.47,1.37); p=0.4	0.72 (0.38,1.38); p=0.3	0.54 (0.31,0.93); p=0.03	0.84 (0.69,1.01); p=0.07
Model 2	0.76 (0.46,1.26); p=0.3	0.77 (0.40,1.47); p=0.4	0.56 (0.33,0.95); p=0.03	0.86 (0.71,1.05); p=0.1
Model 3	0.77 (0.46,1.29); p=0.3	0.75 (0.40,1.42); p=0.4	0.56 (0.33,0.95); p=0.03	0.87 (0.71,1.05); p=0.2
Outpatient UTI only				
No. of events	73	68	58	
Model 1	0.74 (0.40,1.37); p=0.3	0.75 (0.36,1.56); p=0.4	0.50 (0.27,0.92); p=0.03	0.84 (0.68,1.05); p=0.1
Model 2	0.66 (0.37,1.20); p=0.2	0.78 (0.37,1.64); p=0.5	0.50 (0.27,0.93); p=0.03	0.85 (0.68,1.08); p=0.2
Model 3	0.66 (0.36,1.20); p=0.2	0.76 (0.36,1.61); p=0.5	0.50 (0.27,0.94); p=0.03	0.87 (0.69,1.09); p=0.2
UTI hospitalization only				
No. of events	22	15	20	
Model 1	1.06 (0.51,2.21); p=0.9	0.70 (0.32,1.53); p=0.4	0.79 (0.37,1.71); p=0.6	0.84 (0.64,1.09); p=0.2
Model 2	1.08 (0.53,2.20); p=0.8	0.71 (0.33,1.53); p=0.4	0.85 (0.40,1.78); p=0.7	0.87 (0.67,1.14); p=0.3
Model 3	1.18 (0.58,2.39); p=0.6	0.74 (0.34,1.60); p=0.4	0.93 (0.44,1.98); p=0.9	0.89 (0.68,1.17); p=0.4

Note: Unless otherwise indicated, values are given as incidence rate ratio (95% confidence interval); P. Model 1: Unadjusted; Model 2: Adjusted for age, race, sex; Model 3: adjusted for age, race, sex, body mass index, diabetes, estimated glomerular filtration rate, urine albumin and urine creatinine. Q1 (≤17.26 μg/mL) is referent category for composite outcome, outpatient UTI only, and UTI hospitalization only (numbers of events of 102, 84, and 18, respectively).

Q, quartile; UTI, urinary tract infection

*Outpatient + hospitalization

Table 4

Association of urine uromodulin with time to first UTI excluding those with UTI 1989-1996

Composite outcome*	Q2: >17.26-25.94 μg/mL	Q3: >25.94-38.93 μg/mL	Q4: >38.93 μg/mL	per doubling of uromodulin
No. of events	47	37	37	
Model 1	0.88 (0.58,1.33); p=0.5	0.68 (0.44,1.05); p=0.08	0.56 (0.36,0.87); p=0.01	0.82 (0.70,0.96); p=0.01
Model 2	0.88 (0.58,1.34); p=0.6	0.68 (0.44,1.05); p=0.08	0.60 (0.39,0.94); p=0.03	0.85 (0.72,0.99); p=0.05
Model 3	0.93 (0.60,1.43); p=0.7	0.69 (0.44,1.09); p=0.2	0.63 (0.40,0.99); p=0.05	0.87 (0.73,1.03); p=0.1

Note: Unless otherwise indicated, values are given as incidence rate ratio (95% confidence interval); P. Model 1: Unadjusted; Model 2: Adjusted for age, race, sex; Model 3: adjusted for age, race, sex, body mass index, diabetes, estimated glomerular filtration rate, urine albumin and urine creatinine. Q1 (≤17.26 μg/mL) is referent category (number of events, 43).

Q, quartile; UTI, urinary tract infection

*Outpatient + hospitalization.

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