Title

Association of Lower Urinary Tract Symptom Severity with Kidney Function among Community Dwelling Older Men.

Permalink

https://escholarship.org/uc/item/9ds970gr

Journal

Investigative Urology, 204(6)

ISSN

0021-0005

Authors

Bauer, Scott R
Scherzer, Rebecca
Zhao, Shoujun
et al.

Publication Date

2020-12-01

DOI

10.1097/ju.0000000000001310

Peer reviewed

Association of Lower Urinary Tract Symptom Severity with Kidney Function among Community Dwelling Older Men

Scott R. Bauer,*,† Rebecca Scherzer, Shoujun Zhao, Benjamin N. Breyer, Stacey A. Kenfield, Michael Shlipak, and Lynn M. Marshall for the Osteoporotic Fractures in Men (MrOS) Research Group

From the Department of Medicine (SRB) and Department of Urology (SRB, SZ, BNB, SAK), University of California, San Francisco, University of California, Veterans Affairs Medical Center (SRB, RS, MS), San Francisco, California, and Department of Orthopaedics and Rehabilitation (LMM), Oregon Health and Science University, Portland, Oregon

Purpose: Most international practice guidelines recommend screening for chronic kidney disease among older men with lower urinary tract symptoms. However, prior studies supporting these guidelines are insufficient due to incomplete assessments of kidney function and inadequate adjustment for confounding factors.

Materials and Methods: We conducted a cross-sectional study among 5,530 American men older than 65 years in the multicenter Osteoporotic Fractures in Men Study. Chronic kidney disease was defined per international guidelines as estimated glomerular filtration rate less than 60 ml/minute/1.73 m^2 based on serum creatinine or cystatin C, or urinary albumin-to-creatinine ratio 30 mg/gm or greater. Lower urinary tract symptoms were assessed with the American Urological Association Symptom Index. Associations were estimated using multivariable linear and modified Poisson regression models.

Results: Chronic kidney disease prevalence was 16% among 5,530 men with serum creatinine, 24% among 1,504 men with serum cystatin C and 14% among 1,487 men with urinary albumin-to-creatinine measurements. Lower urinary tract symptoms were not associated with lower estimated glomerular filtration rate based on serum creatinine or cystatin C. Although symptom severity was modestly associated with a higher prevalence of chronic kidney disease in age/site adjusted analyses, confidence intervals were wide and associations using all 3 definitions were not statistically significant after adjustment for important confounders, including cardiovascular disease and analgesic use.

Conclusions: Lower urinary tract symptoms are not independently associated with multiple measures of kidney dysfunction or prevalence of chronic kidney disease among older community dwelling men. Our results do not support recommendations for kidney function testing among older men with lower urinary tract symptoms.

Abbreviations and Acronyms

ACR = albumin-to-creatinine ratio

AUASI = American Urological Association Symptom Index

BMI = body mass index

BPH = benign prostatic hyperplasia

CKD = chronic kidney disease

eGFR = estimated glomerular filtration rate

eGFRcr = estimated glomerular filtration rate based on serum creatinine

eGFRcys = estimated glomerular filtration rate based on cystatin C

LUTS = lower urinary tract symptoms

NSAID = nonsteroidal anti-inflammatory drug

RIGHTSLINK()

BLADDER outlet obstruction due to BPH is the most common cause of LUTS in older men and affects approximately half of men by age 70 years.[1,2] CKD also increases with age and confers a threefold higher risk of all cause mortality among men older than age 65 years.[3] Because chronically elevated bladder filling pressures, and particularly acute urinary retention, could theoretically cause CKD in older men, most international practice guidelines recommend testing serum creatinine among men with LUTS and suspected CKD.[4] The evidence for these guidelines rests on a few studies suggesting that men with severe LUTS have a higher prevalence of CKD compared to men without LUTS.[5,6] However, except for end stage kidney disease, CKD is mostly asymptomatic, raising the concern among some urologists that these recommendations may lead to over testing. Accordingly, the American Urological Association has concluded that there is insufficient evidence that men with LUTS have an elevated prevalence of CKD and recommends against screening for CKD among men with LUTS in their practice guidelines[7] and the Choosing Wisely® campaign.[8] Thus, it remains unknown, and controversial, whether or not older men with severe LUTS have a higher prevalence of CKD compared to men with mild or absent LUTS.

Prior cross-sectional studies of the relationship between LUTS severity and CKD have been limited by inconsistent or narrow outcome definitions, insufficient adjustment for confounders and small sample sizes.[5,6,9–14] Because no existing measure is perfectly sensitive or specific, international guidelines for CKD diagnosis recommend using several kidney function measures to assess different aspects of kidney health, including estimated glomerular filtration rate based on serum creatinine and/or cystatin C plus albumin-to-creatinine ratio.[15] Due to the challenge of accurately characterizing kidney health and defining CKD in older men, the association between LUTS severity and CKD has not been thoroughly assessed. To address this gap in knowledge we evaluated the association of LUTS severity, overall and by voiding and storage subscores, with eGFRcr, eGFRcys and ACR in a large cohort of community dwelling older men. We hypothesized that more severe LUTS, and particularly voiding symptoms, would be associated with worse kidney health and higher prevalence of CKD.

MATERIALS AND METHODS

Participants
The Osteoporotic Fractures in Men Study (MrOS) is a large, multicenter cohort study of 5,994 community dwelling men 65 years old or older as previously described.[16,17] Briefly, this cohort was designed to collect comprehensive data to study older men's health, with a particular focus on fracture risk factors. Serum and urine were stored in a biorepository for future studies.[16] Men were recruited from March 2000 to April 2002 from 6 academic medical centers in Birmingham, Alabama, Minneapolis, Minnesota, Palo Alto, California, Pittsburgh, Pennsylvania, Portland, Oregon and San Diego, California. All participants gave written informed consent and institutional review boards at each participating institution approved the study.

LUTS Assessment
Lower urinary tract symptoms were assessed using the 7-item AUASI.[18] AUASI scores range from 0 (lowest severity) to 35 (highest severity). AUASI has clinically relevant categories of 0 to 7 (none/mild), 8 to 19 (moderate) and 20 to 35 (severe). We also evaluated AUASI subscores separately for storage and voiding symptoms using approximate tertiles as well as continuously given the lack of accepted thresholds.[19] Secondary exposures included AUASI urinary bother score, urinary incontinence, self-reported history of BPH surgery and total number of LUTS medications as described in the supplementary Appendix (https://www.jurology.com).

Other Independent Variable Assessment
Age, race, smoking status and alcohol consumption were assessed via self-administered questionnaires.[20] Comprehensive prescription medication use was coded from labels on pill packets and canisters brought in by the participant. Participants reported history of myocardial infarction, angina, congestive heart failure, hypertension, diabetes, stroke, Parkinson's disease or nephrolithiasis. Study staff measured height and weight to calculate BMI.

Kidney Function Assessment and CKD Definition
Creatinine was measured in all MrOS participants who had a sufficient quantity of stored serum. In addition, to provide a study-wide resource, stored biospecimens from a random sample of 1,504 cohort members with creatinine measurements were assayed for serum cystatin C and urinary albumin. To maximize sensitivity CKD was defined as eGFRcr or eGFRcys less than 60 ml/minute/1.73 m^2 or urinary ACR 30 mg/gm or greater per Kidney Disease Improving Global Outcomes (KDIGO) guidelines.[15] We did not analyze ACR as a continuous variable because the majority (54%) had undetectable concentrations. Details regarding assays, eGFR and ACR calculations are included in the supplementary Appendix (https://www.jurology.com).

Statistical Analysis
For this study the primary analyses were conducted among men with complete data for each outcome, including 5,530 with eGFRcr, 1,504 with eGFRcys and 1,487 with ACR (fig. 1). Men who did not complete the AUASI or were ineligible for kidney function measurement were not included in primary analyses.

We first compared distributions of established CKD and LUTS risk factors between men included and not
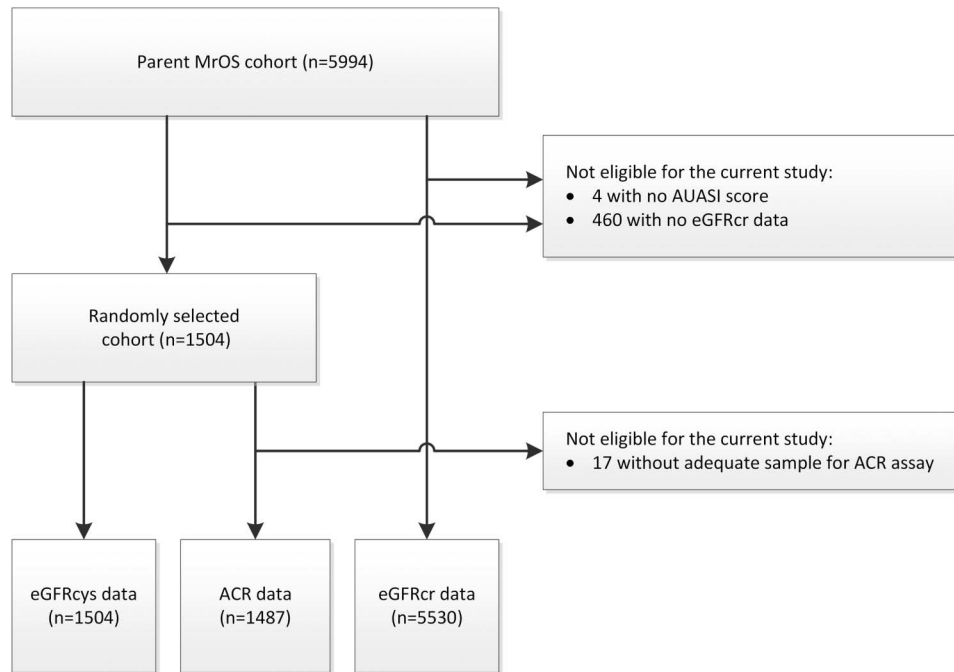
Figure 1. Study flowchart illustrating selection of analytic cohort for primary outcomes of CKD based on eGFRcr, eGFRcys and ACR

included in the analytic sample, and across LUTS categories. We then used multivariable linear regression to estimate regression coefficients and their 95% CI for the association between the predictor variable (categories of AUASI total score and subscores) and the outcomes of eGFRcr and eGFRcys modeled continuously (per 1 ml/minute/1.73 m^2 increment). Associations of LUTS categories with prevalent eGFR less than 60 ml/minute/1.73 m^2 and prevalent ACR 30 mg/gm or greater were estimated using prevalence ratios from a log-binomial regression model with a robust variance estimator.[21] These models were repeated for secondary predictors including urinary bother (low, moderate and high), at least weekly urinary incontinence (yes/no), history of BPH surgery (yes/no) and number of LUTS medications (0, 1, and 2 or greater).

To control for confounding factors we first adjusted for age and study site in minimally adjusted models. In fully adjusted models we included factors known to be strongly associated with eGFR, including race/ethnicity, self-reported history of diabetes, hypertension, coronary artery disease, heart failure, nephrolithiasis, and use of aspirin and nonaspirin NSAIDs. We also adjusted for known risk factors of LUTS, including BMI, smoking status, alcohol intake, Parkinson's disease and stroke. We considered diuretic use but did not include because adding it to the final model did not materially change the results.

Tests of linear association with each outcome variable were obtained by replacing categories of the AUASI total score and each subscore with the continuous variable in the final model. We tested for multiplicative interactions by including a cross-product term between AUASI total score (continuous) and history of prostate cancer (yes/no) or LUTS medication use (yes/no) in multivariable models including the main effect variables. Effect

modification was considered present if the p value for interaction was <0.01. We also conducted sensitivity analyses by restricting the analytic sample to men without a history of prostate cancer, heart failure or diabetes. Other than for interaction tests, p <0.05 was considered statistically significant. All analyses were performed using SAS® version 9.4.

RESULTS

Characteristics of 5,530 men with complete data are reported in supplementary table 1 (https://www.jurology.com). Men with severe LUTS (AUASI 20 or greater) were older and more likely to report CKD risk factors such as aspirin or nonaspirin NSAID use and cardiovascular comorbidities. Men who were excluded due to missing eGFR or ACR data had similar distributions of covariates compared to the analytic study sample (data not shown). Unadjusted prevalence of CKD based on eGFRcr, eGFRcys and ACR was 15%, 22% and 13% among men with none/mild LUTS, 17%, 27% and 15% among men with moderate LUTS, and 19%, 26% and 16% among men with severe LUTS, respectively (fig. 2).

Higher AUASI score category was not associated with lower eGFRcr or eGFRcys when modeled as a continuous variable (see table, supplementary table 2, https://www.jurology.com). After final adjustments mean eGFRcr and eGFRcys (ml/minute/1.73 m^2) were slightly higher among men with moderate and severe LUTS compared to none/mild LUTS, but the differences were not clinically meaningful,
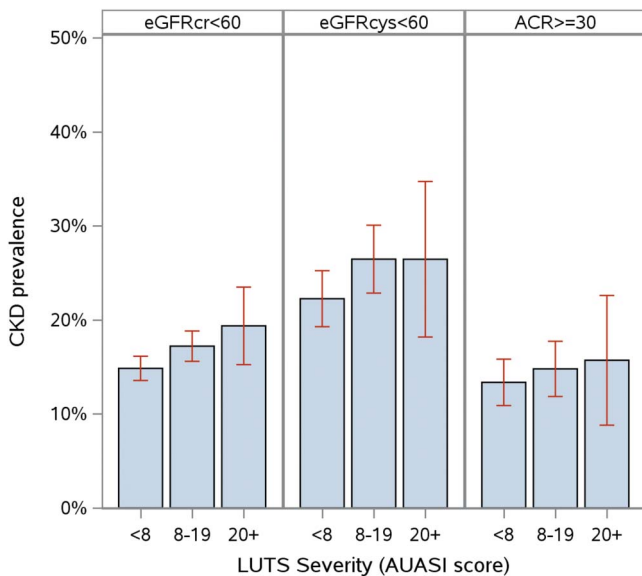
Figure 2. Unadjusted prevalence of CKD defined by eGFRcr, eGFRcys and ACR stratified by LUTS severity.

confidence intervals included 0 and tests of a linear association were not statistically significant. When examined by AUASI subscores, eGFRcr and eGFR-cys were higher on average with higher voiding subscore category but not with higher storage subscore categories. There was statistically significant evidence of a linear association between increasing storage subscore and higher eGFRcr, but not voiding subscore.

Supplementary table 3 (https://www.jurology.com) reports associations between categories of LUTS severity and CKD prevalence based on eGFRcr, eGFRcys and ACR. LUTS severity was not associated with prevalent CKD based on eGFRcr less than 60 ml/minute/1.73 m², eGFRcys less than 60 ml/minute/1.73 m², or ACR 30 mg/gm or greater in age and site adjusted and multivariable adjusted models (linear p >0.6 for all and confidence intervals excluded moderate or large effects sizes; supplementary tables 3 and 4, https://www.jurology.com). Associations did not vary significantly when AUASI subscores were examined separately.

In secondary analyses urinary bother and urinary incontinence were not associated with CKD defined by eGFRcr, eGFRcys or ACR (supplementary table 5, https://www.jurology.com). History of BPH surgery was associated with a 21% higher prevalence of ACR 30 mg/gm or greater (95% CI 0.88, 1.67), although CIs were wide and it was not associated with eGFRcr less than 60 ml/minute/1.73 m² or eGFRcys less than 60 ml/minute/1.73 m². Number of LUTS medications was associated

Association of lower urinary tract symptom severity with estimated glomerular filtration rate based on serum creatinine and cystatin C

	Age/Site Adjusted Model β† (95% CI)	Fully Adjusted Model‡ β† (95% CI)	Linear p Value§
	eGFRcr (5,530 pts)		
AUASI score (points):*			
Less than 8	Reference	Reference	
8—19	0.20 (−0.58, 0.99)	0.58 (−0.19, 1.35)	
20 or Greater	−0.09 (−1.60, 1.42)	0.65 (−0.84, 2.1)	0.08
AUASI voiding subscore:			
0	Reference	Reference	
1—3	0.56 (−1.68, 2.8)	0.83 (−1.36, 3.0)	
4 or Greater	1.09 (−1.11, 3.3)	1.76 (−0.39, 3.9)	0.9
AUASI storage subscore:			
Less than 4	Reference	Reference	
4—6	0.15 (−0.83, 1.14)	0.41 (−0.56, 1.37)	
7 or Greater	−0.50 (−1.62, 0.63)	−0.16 (−1.26, 0.94)	0.01
	eGFRcys (1,504 pts)		
AUASI score (points):*			
Less than 8	Reference	Reference	
8—19	0.91 (−0.82, 2.6)	1.30 (−0.36, 3.0)	
20 or Greater	−1.42 (−4.5, 1.69)	−0.36 (−3.4, 2.7)	0.6
AUASI voiding subscore:			
0	Reference	Reference	
1-3	1.74 (−3.3, 6.8)	2.5 (−2.3, 7.4)	
4 or Greater	2.9 (−2.1, 7.9)	3.8 (−0.95, 8.6)	0.8
AUASI storage subscore:			
Less than 4	Reference	Reference	
4—6	0.98 (−1.14, 3.1)	1.52 (−0.53, 3.6)	
7 or Greater	0.07 (−2.4, 2.5)	0.24 (−2.1, 2.6)	0.5

* AUASI score range is 0 to 35 and equals the sum of 2 validated subscores based on symptom type of storage (urgency, frequency, nocturia) and voiding (intermittency, weak stream, straining, incomplete emptying). Higher score indicates more frequent symptoms.

† Linear regression used to calculate β coefficients within categories of AUASI score or subscore compared to the reference group.

‡ Adjusted for study site, age, BMI, race/ethnicity, smoking status, alcohol intake, history of diabetes, hypertension, myocardial infarction, angina, heart failure, nephrolithiasis, stroke or Parkinson's disease, and aspirin or NSAID use.

§ Linear p value calculated from the fully adjusted model per 1 point increment in AUASI score or subscore.

with higher prevalence of eGFRcys less than 60 ml/minute/1.73 m^2, but not eGFRcr less than 60 ml/minute/1.73 m^2 or ACR 30 mg/gm or greater. There was no evidence of effect modification by history of prostate cancer or LUTS medication use, and results of the sensitivity analyses among men without a history of prostate cancer, heart failure or diabetes were similar to the main results (data not shown).

DISCUSSION

In this large, multicenter study of community dwelling older men, poor kidney function and prevalent CKD were common but we did not observe evidence that greater LUTS severity, overall and by voiding and storage subtype, was independently associated with worse kidney function. Although results from 1 analysis suggested a weak positive association such that kidney function was greater with increasing LUTS severity, the remaining analyses demonstrated no evidence of association between LUTS severity and measures of kidney function by multiple different assays. Likewise, there were no statistically significant differences in prevalence of CKD defined by eGFRcr, eGFRcys or ACR across categories of LUTS severity. Similar to prior studies, the observed prevalence of CKD defined by eGFRcr ranged from 15% among men with none/mild LUTS to 19% among men with severe LUTS, but these differences disappeared after appropriate adjustment for easily measured patient characteristics. The results of this large study provide no evidence that LUTS severity is independently associated with the prevalence of impaired kidney function by multiple different assays or CKD using standard international definitions. Therefore, we question whether the presence or absence of LUTS should impact decisions regarding screening for CKD in older men.

Prior cross-sectional studies have examined associations between LUTS severity, particularly voiding symptoms[6,12] and kidney function,[5,9,14,22] but the results are equivocal. Two small studies with important limitations observed a positive association between LUTS severity and CKD. The first, in the Olmsted County Study, was limited by small sample size (476), outdated CKD definitions based solely on serum creatinine thresholds rather than eGFR or ACR, and lacked adjustment for several important confounders, such as cardiovascular disease, BMI and analgesic use.[5] In our study twice as many men with severe LUTS reported a history of myocardial infarction or NSAID use compared to men with none/mild LUTS (myocardial infarction 20% versus 12%, NSAID use 22% versus 14%) and adjustment for these confounders

attenuated the modest positive association observed in age/site adjusted models between LUTS severity and CKD prevalence. The second, in a cohort of Korean men, observed that LUTS were associated with worse kidney function only among a subset of 784 men older than 55 years with normal prostate volume.[6] However, this study did not assess for CKD and subgroup findings were not further observed among younger men or men with enlarged prostates for whom one would expect a greater degree of obstruction. In contrast, others observed no association between LUTS and renal function or CKD. Specifically, among almost 1,400 male Korean police officers, 40 to 59 years old with moderate-to-severe LUTS (AUASI 8 or greater) identified during a health screening examination, the correlation between AUASI score and eGFRcr was weak and not statistically significant (r=−0.18, p=0.49).[9] Likewise, among 2,741 men evaluated in a Korean academic urology clinic AUASI, post-void residual, prostate volume and prostate specific antigen were not associated with eGFRcr.[12]

Two prospective cohort studies that evaluated the association between LUTS severity and risk of impaired kidney function did not observe any relationship. Among 30,466 men enrolled in the Second Health Study in Nord-Trøndelag (HUNT II) and followed for an average of 10.5 years, moderate-to-severe LUTS (AUASI 8 or greater) were not associated with kidney failure compared to none/mild LUTS (AUASI less than 8), although only 78 events of kidney failure occurred and CIs were wide.[22] Another study conducted among residents of Vienna, Austria included 2,469 men in a cross-sectional analysis and 439 in a prospective analysis, and no association between LUTS severity and eGFRcr was observed.[23] Importantly, both prospective cohort studies and several cross-sectional studies have observed significant associations between higher LUTS severity and impaired kidney function in unadjusted models that were strongly attenuated after adjustment for important confounders. No randomized studies have evaluated the effect of CKD screening among men with elevated LUTS symptom scores. However, kidney function was monitored as an adverse drug event in multiple randomized controlled trials of medication for physician diagnosed BPH and the rates of decreased kidney function were consistently less than 1% per year.[24] Consistent with these studies, we did not find LUTS severity to be independently associated with reduced kidney function or greater CKD prevalence, although these conditions are common among older community dwelling men. Therefore, urologists treating older men with LUTS should be aware that CKD is a common comorbidity, but they should not feel compelled to initiate CKD screening and treatment.

Despite the inconsistent relationship between LUTS severity and CKD, several objective measures of bladder outlet obstruction are associated with impaired kidney function. In cross-sectional studies lower peak flow rate is associated with increased odds of prevalent CKD[5,9,12] and higher post-void residual is inconsistently associated with prevalent CKD.[9,10] Observed differences between associations with LUTS severity based on symptom scores and objective measures of bladder outlet obstruction could be explained by the poor diagnostic accuracy of LUTS symptom scores for bladder outlet obstruction.[25] In our study BPH surgery was associated with higher prevalence of 30 mg/gm or greater ACR and number of LUTS medications was associated with eGFRcys less than 60 ml/minute/1.73 m[2], and both treatments are more common among men with LUTS and confirmed bladder outlet obstruction.[24] However, these associations were not observed across other measures of kidney function. Rigorous prospective studies of urodynamic studies and standard measures of kidney function are still needed.

This study has several strengths, including a large sample of community dwelling older men with a wide range of LUTS severity and renal function, recruitment from geographically diverse sites, comprehensive assessment of age related conditions and risk factors, and properly stored biospecimens for evaluating several aspects of renal function. However, this study also has limitations. We do not have direct measures of bladder outlet obstruction, such as urodynamic studies, and therefore cannot evaluate associations with bladder outlet obstruction. However, AUASI is the surrogate most widely available to clinicians and guidelines do not distinguish how LUTS should be diagnosed prior to screening for CKD. This cross-sectional study design addresses whether LUTS severity is associated with worse kidney function or with prevalent CKD and does not address risk of future declines in kidney function or incident CKD. However, current practice guidelines recommend onetime CKD screening among men with LUTS to identify if co-occurring impaired kidney function is present. Thus, evaluation of this guideline is best informed by cross-sectional data rather than longitudinal data which inform recommendations for ongoing CKD surveillance among high risk groups. Observational studies are susceptible to unmeasured or residual confounding. However, we do not believe that there are unmeasured confounders for which adjustment would reveal a true association in this study. Conversely, there is no evidence of over-adjustment since the unadjusted and adjusted results were consistent. Lastly, the study population is mostly white men and, therefore, study results may not be generalizable to more diverse populations.

CONCLUSIONS

This large multicenter study provides additional evidence that LUTS severity is not independently associated with worse kidney function or prevalent CKD among older men. Future studies are needed to determine the associations between other LUTS measurements and kidney health using standard definitions of CKD based on serum creatinine, cystatin C and urinary albumin. In the meantime, our results do not support recommendations for CKD screening among older men with severe LUTS.

REFERENCES

1. Wei JT, Calhoun E and Jacobsen SJ: Urologic Diseases in America project: benign prostatic hyperplasia. J Urol, suppl., 2008; **179:** S75.

2. Taylor BC, Wilt TJ, Fink HA et al: Prevalence, severity, and health correlates of lower urinary tract symptoms among older men: the MrOS study. Urology 2006; **68:** 804.

3. United States Renal Data System: 2017 USRDS Annual Data Report: Epidemiology of Kidney Disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Maryland 2017.

4. Chua ME, Mendoza J, See M et al: A critical review of recent clinical practice guidelines on the diagnosis and treatment of non-neurogenic male lower urinary tract symptoms. Can Urol Assoc J 2015; **9:** E463.

5. Rule AD, Jacobson DJ, Roberts RO et al: The association between benign prostatic hyperplasia and chronic kidney disease in community-dwelling men. Kidney Int 2005; **67:** 2376.

6. Kwon YM, Cho B, Son KY et al: Lower urinary tract symptoms have negative associations with glomerular filtration rate irrespective of prostate volume in Korean men. Urology 2012; **79:** 182.

7. Abrams P, Chapple C, Khoury S et al: Evaluation and treatment of lower urinary tract symptoms in older men. J Urol, suppl., 2013; **189:** S93.

8. American Urological Association: Fifteen Things Physicians and Patients Should Question. Available at https://www.choosingwisely.org/societies/american-urological-association/. Updated June 6, 2019. Accessed October 12, 2019.

9. Lee JH, Kwon H, Park YW et al: Relationship of estimated glomerular filtration rate with lower urinary tract symptoms/benign prostatic hyperplasia measures in middle-aged men with moderate to severe lower urinary tract symptoms. Urology 2013; **82:** 1381.

10. Yamasaki T, Naganuma T, Iguchi T et al: Association between chronic kidney disease and small residual urine volumes in patients with benign prostatic hyperplasia. Nephrology (Carlton, Vic) 2011; **16:** 335.

11. Plantinga L, Lee K, Inker LA et al: Association of sleep-related problems with CKD in the United States, 2005-2008. Am J Kidney Dis 2011; **58:** 554.

12. Hong SK, Lee ST, Jeong SJ et al: Chronic kidney disease among men with lower urinary tract symptoms due to benign prostatic hyperplasia. BJU Int 2010; **105:** 1424.

13. Krol E, Rutkowski B, Czarniak P et al: Early detection of chronic kidney disease: results

of the PolNef study. Am J Nephrol 2009; **29:** 264.

14. Gerber GS, Goldfischer ER, Karrison TG et al: Serum creatinine measurements in men with lower urinary tract symptoms secondary to benign prostatic hyperplasia. Urology 1997; **49:** 697.

15. Stevens PE and Levin A: Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. Ann Intern Med 2013; **158:** 825.

16. Orwoll E, Blank JB, Barrett-Connor E et al: Design and baseline characteristics of the osteoporotic fractures in men (MrOS) study—a large observational study of the determinants of fracture in older men. Contemp Clin Trials 2005; **26:** 569.

17. Blank JB, Cawthon PM, Carrion-Petersen ML et al: Overview of recruitment for the osteoporotic fractures in men study (MrOS). Contemp Clin Trials 2005; **26:** 557.

18. Barry MJ, Fowler FJ Jr, O'Leary MP et al: The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. J Urol 1992; **148:** 1549.

19. Barry MJ, Williford WO, Fowler FJ Jr et al: Filling and voiding symptoms in the American Urological Association symptom index: the value of their distinction in a Veterans Affairs randomized trial of medical therapy in men with a clinical diagnosis of benign prostatic hyperplasia. J Urol 2000; **164:** 1559.

20. Pahor M, Chrischilles EA, Guralnik JM et al: Drug data coding and analysis in epidemiologic studies. Eur J Epidemiol 1994; **10:** 405.

21. Spiegelman D and Hertzmark E: Easy SAS calculations for risk or prevalence ratios and differences. Am J Epidemiol 2005; **162:** 199.

22. Hallan SI, Kwong D, Vikse BE et al: Use of a prostate symptom score to identify men at risk of future kidney failure: insights from the HUNT II Study. Am J Kidney Dis 2010; **56:** 477.

23. Ponholzer A, Temml C, Obermayr RP et al: The association between lower urinary tract symptoms and renal function in men: a cross-sectional and 5-year longitudinal analysis. J Urol 2006; **175:** 1398.

24. McVary KT, Roehrborn CG, Avins AL et al: Update on AUA guideline on the management of benign prostatic hyperplasia. J Urol 2011; **185:** 1793.

25. D'Silva KA, Dahm P and Wong CL: Does this man with lower urinary tract symptoms have bladder outlet obstruction?: the Rational Clinical Examination: a systematic review. JAMA 2014; **312:** 535.