Lifestyle and Health Factors Associated with Progressing and Remitting Trajectories of Untreated Lower Urinary Tract Symptoms among Elderly Men

Lynn M. Marshall, ScD[1,2,3,*], **Kathleen F. Holton, PhD**[4,*], **J. Kellogg Parsons, MD**[6,7,8,*], **Jodi A. Lapidus, PhD**[2,5,*], **Katrina Ramsey, MPH**[2,5], and **Elizabeth Barrett-Connor, MD**[9] **for the Osteoporotic Fractures in Men (MrOS) Study Group**

[1]Department of Orthopaedics and Rehabilitation, Oregon Health and Science University, Portland OR

[2]Department of Public Health and Preventive Medicine, Oregon Health and Science, Portland OR

[3]Department of Medicine, Bone and Mineral Unit, Oregon Health and Science University, Portland OR

[4]Department of Behavioral Neuroscience, Oregon Health and Science University, Portland OR

[5]Biostatistics Design Program, Oregon Clinical and Translational Research Institute, Oregon Health and Science University, Portland Oregon

[6]Division of Urology, University of California San Diego, La Jolla, CA

[7]University of California San Diego Moores Cancer Center, La Jolla, CA

[8]Department of Surgery, San Diego Veterans Affairs Medical Center, La Jolla, CA

[9]Department of Family and Preventive Medicine, University of California San Diego, La Jolla, CA

Abstract

Background—Knowledge of factors associated with the course of lower urinary tract symptoms (LUTS) before treatment is needed to inform preventive interventions. In a prospective study of elderly men untreated for LUTS, we identified factors associated with symptom progression and remission.

Methods—In community dwelling U.S. men age   65 years, the American Urological Association Symptom Index (AUA-SI) was repeated four times, once at baseline (2000–2002) and

Corresponding Author: Lynn M. Marshall, ScD, Department of Orthopaedics and Rehabilitation, Oregon Health and Science University, 3181 SW Sam Jackson Park Road, Mailcode: OP31, Portland OR 97239-3098, 503-494-3990 (office), 503-494-5050 (fax), marshaly@ohsu.edu.
*Lynn M. Marshall, Kathleen F. Holton, J. Kellogg Parsons and Jodi A. Lapidus contributed equally to this work.

then every two years thereafter. Analyses included 1740 men with all four AUA-SI assessments, who remained free from diagnosed prostate cancer, and who reported no treatment for LUTS or benign prostatic hyperplasia (BPH) during follow-up that averaged 6.9 (±0.4) years. LUTS change was determined with group-based trajectory modeling of the repeated AUA-SI measures. Multivariable logistic regression was then used to determine the baseline factors associated with progressing compared to stable trajectories, and with remitting compared to progressing trajectories. Lifestyle, body mass index (BMI) (kg/m^2), mobility, mental health (Short-Form 12), medical history, and prescription medications were considered for selection. Odds ratios (OR) and 95% confidence intervals (CI) were estimated for variables in each model.

Results—We identified 10 AUA-SI trajectories: four stable (1 277 men, 73%), three progressing (345 men, 20%), two remitting (98 men, 6%), and one mixed (20 men, 1%). Men in progressing compared to stable trajectories were more likely to have mobility limitations (OR=2.0, 95% CI: 1.0–3.8), poor mental health (OR=1.9, 95% CI: 1.1–3.4), BMI   25.0 kg/m^2 (OR=1.7, 95% CI: 1.0–2.8), hypertension (OR=1.5, 95% CI: 1.0–2.4), and back pain (OR=1.5, 95% CI: 1.0–2.4). Men in remitting compared to progressing trajectories more often used central nervous system medications (OR=2.3, 95% CI: 1.1–4.9) and less often had a history of problem drinking (OR=0.4. 95% CI: 0.2–0.9).

Conclusions—Several non-urological lifestyle and health factors were independently associated with risk of LUTS progression in older men.

Keywords

cohort studies; elderly; lower urinary tract symptoms; male; risk factor; trajectory

---

Introduction

Male lower urinary tract symptoms (LUTS) represent a cluster of chronic urinary disorders that are highly prevalent worldwide,[1,2] especially among elderly men.[3,4] Multiple etiologies including benign prostatic hyperplasia (BPH) and bladder overactivity manifest as LUTS.[5] LUTS severity is assessed with the validated American Urologic Association Symptom Index (AUA-SI) or International Prostate Symptom Score (IPSS).[6] Moderate and severe LUTS exert a substantial negative effect on public health through diminished quality of life,[7,8] increased risk of falls and mortality,[9,10] and annual treatment costs totaling upwards of $3.9 billion in the US.[11,12] Given that the average life expectancy among US men who reach age 65 years has increased in the past decade,[13] the health burden of male LUTS is unlikely to abate without preventive interventions.

Prevention of LUTS progression requires knowledge of the natural symptom course before treatment is initiated. To date, prospective studies of risk factors for LUTS included a mixture of men with and without treatment.[14–17] However, factors other than symptom severity influence treatment decisions[18] and men with mild symptoms often report treatment.[8,19] Therefore, to distinguish risk factors for natural LUTS progression, additional studies among untreated men are needed.

Symptom progression is just one aspect of LUTS natural history in men.[20–26] Apparently spontaneous symptom remission and symptom stability are also consistently documented.[20–26] Identification of these patterns requires repeated AUA-SI or IPSS assessments, because LUTS fluctuate considerably within men over time.[20] To date, nearly all previous studies of LUTS risk factors assessed symptom change between only two time points. Additionally, a single study has reported factors associated with LUTS remission.[17] Identifying risk factors separately for LUTS progression and for LUTS remission may reveal novel pathways of LUTS etiology, which could enhance the translational potential for prevention and control of this condition.

This study had two objectives. First, to characterize the natural course of untreated LUTS beyond two time points, we applied group based trajectory models[27,28] to four repeated assessments of the AUA-SI in a large cohort of elderly men. Trajectory analysis is a statistical technique designed to identify mutually exclusive groups of subjects who follow a similar longitudinal pattern while accounting for individual heterogeneity in repeated measurements of an outcome variable. This method is gaining recognition in medical research,[29] but it has yet to be applied to LUTS. Second, to elucidate potential targets for LUTS prevention, we determined the independent associations of progressing and remitting LUTS trajectories with a comprehensive set of baseline lifestyle and health factors.

Subjects and Methods

Setting

We used data collected prospectively in the Osteoporotic Fractures in Men (MrOS) Study, a cohort of community-dwelling men aged 65 years. Participants were recruited in 2000–2002 from six US regions.[30,31] Men completed baseline questionnaires and in-person research visits. Subsequently, data were updated about every two years (Figure 1). Institutional Review Boards at each institution approved the study. All men gave written informed consent.

Urinary measures

The AUA-SI, prostate disease history, and medication use were obtained at all four time points. Categories of LUTS severity defined from the AUA-SI were mild (0–7 points), moderate (8–19 points) or severe (20–35 points).[6] Urinary bother was categorized as 0–2, 3, and 4–6.[6] Men reported histories of diagnosed BPH, laser surgery or transurethral resection of the prostate, and medication use for prostate symptoms. Current prescription medications were inventoried at each time point and matched to ingredients using a standardized method[32] as described previously.[16,25] LUTS medications were alpha-blockers, urinary antispasmodics, anticholinergics, and 5-alpha-reductase inhibitors.

Baseline factors

Cigarette smoking was coded into lifetime pack-years and current alcohol consumption into average drinks per week. History of problem drinking was defined as 2–4 positive responses to the CAGE questionnaire.[33,34] Caffeine consumption (mg/day) was obtained from a Block Food Frequency Questionnaire[35] and categorized into quartiles. Physical activity was

obtained with the validated Physical Activity Scale for the Elderly (PASE), which assesses amount of leisure and household activities.[36] Self-reported daily walking for exercise was also assessed. Mobility limitation was defined as difficulty walking two to three blocks or difficulty climbing one flight of stairs.[37] Health related quality of life was obtained with the Short Form-12 (SF-12) Physical Component (PCS) and Mental Component (MCS) scores.[38] MCS ≤ 50 is a valid measure of common mental health disorders (depression or anxiety disorders).[39] Medical conditions included reports of physician-diagnosed diabetes, hypertension, angina, myocardial infarction, stroke, prostatitis, and cancers of the prostate, colon/rectum, lung and skin, as well as dizziness, history of falls and back pain in the past year.

Height and weight were classified into standard body mass index (BMI) (kg/m^2) categories as <25.0 (normal), 25.0–29.9 (overweight), or ≥ 30.0 (obese). [40] Baseline prescription medications included hypoglycemics (insulin, glucose), diuretics (thiazide, loop, and potassium sparing) and other anti-hypertensive (ACE inhibitors, angiotensin II receptor antagonists, beta blockers, calcium channel blockers), statins (HMG-CoA reductase inhibitors), and central nervous system (CNS) medications (antiepileptics, benzodiazapenes, antidepressants, opioids, sedatives). Alpha-blockers could not be included as anti-hypertensives because use of these medications was an exclusion criterion (described below). Herbal supplements for LUTS were saw palmetto, South African star grass, stinging nettle, rye grass pollen, pumpkin seed, or African plum from self-report or inventory listing. Men with missing medication information were coded as non-users, because results with this coding were similar to results excluding the missing observations.

Analytic cohort

The 3 594 men with no baseline history of prostate cancer, BPH surgery, or medication use for LUTS or BPH were followed through the fourth AUA-SI assessment. Men who died or withdrew (n=456, 12%), had incident prostate cancer (n=213, 6%), missing AUA-SI (n=120, 3%), reported BPH treatment or used prescription LUTS medications (n=946, 26%), were excluded (Figure 1). The analytic cohort of 1 740 had mean (sd) follow-up of 6.9 (0.4) years. Treatment onset, which may occur in men with mild LUTS,[19] was not used as a marker of LUTS progression.

Statistical analyses were performed with SAS 9.1 software (SAS Institute, Cary NC). Two-sided p-values were estimated.

LUTS trajectory analysis

Group-based trajectory modeling was applied to the repeated AUA-SI scores as the continuous dependent variable. Trajectory modeling applies a semi-parametric mixture model to longitudinal data using the maximum likelihood method.[27] This method assumes that the population contains an unspecified number of underlying groups, each with different probability distribution for the longitudinal sequence of the dependent variable. Modeling started with three trajectories. As the trajectory number was successively increased by one, model fit was assessed with the product two times the change in the Bayesian Information Criterion (2 ΔBIC). Values >10 are considered evidence of better fit of the larger trajectory

number compared to the next smallest.[27,28] Mean posterior probabilities in each trajectory were computed and values >0.70 indicate high internal reliability.[27] We specified that the sample size in any trajectory must be at least 1% of the analytic cohort. Ultimately, the 10 trajectory model optimized fit, internal reliability, and sample size. Plots of individual AUA-SI scores in each trajectory confirmed that trajectory analysis successfully grouped men with similar longitudinal patterns (see examples in the online supplemental Figure).

Risk factor analyses

We performed risk factor analyses within strata of mild or moderate baseline LUTS. Too few men had severe untreated baseline LUTS for further study. In each stratum, men with stable trajectories formed the referent group to whom men with progressing LUT were compared. Men with remitting LUTS were compared men with progressing LUTS, because factors associated with symptom improvement could also inform LUTS prevention. Baseline variables that differed between the outcome and referent groups with p-values   0.25 were candidates for selection in forward, stepwise logistic regression modeling.

In separate models for each comparison defined above, candidate variables associated with the outcome at p   0.15 were retained. We used this larger alpha-level so as not to ignore potentially important associations for variables with low baseline prevalence. When a medical history variable was replaced with an appropriate medication variable, model fit worsened. Therefore, final models contained the medical history variables. BMI categorized as 'normal' and 'overweight/obese' improved model fit. Odds ratios (OR) and their 95% confidence intervals (CI) are reported for the final multivariable models.

Results

The 1 740 men in the analytic cohort reflected the baseline untreated cohort on nearly all characteristics including mean age, but had slightly lower mean AUA-SI scores (Table 1). In the analytic cohort, mean (sd) change in the AUA-SI score from baseline to the fourth assessment was 1.0 (4.6).

Trajectory results

We identified 10 trajectories of AUA-SI scores (Figure 2), illustrated with mean scores at each time point. Four trajectories consistent with LUTS stability (blue) contained 1 277 (73%) men and were observed in the low and high AUA-SI range. Three trajectories consistent with progression (red) contained 345 men (20%), were primarily in the moderate range, and had distinct profiles including abrupt increase late in follow-up. Two trajectories consistent with remission (green) contained 98 (6%) men and were in the moderate-high range. One trajectory had mixed progression and remission (yellow) and contained 20 men (1%).

Supplemental tables S1–S3 provide mean posterior probabilities and distributions of urinary measures in each trajectory. Patterns of urinary bother, which increased in progressing groups and decreased in remitting groups, further support the internal consistency of the trajectory results.

Percentages of men in stable, progressing or remitting trajectories differed by baseline LUTS severity (Figure 3). In men with mild baseline LUTS, 90% were in stable trajectories. Of men with moderate baseline LUTS, 49% were classified into progressing and 17% into remitting trajectories. Of the 28 men had severe baseline LUTS, most were classified into remitting or stable trajectories.

Risk factors

In univariable analyses, men in progressing compared to stable trajectories more often had MCS <50, history of hypertension, and back pain, regardless of baseline LUTS category (Table 2). Within strata, several additional factors differed between men in progressing compared to stable trajectories. Among men with moderate baseline LUTS, those in remitting compared to progressing trajectories (Table 3) less often had high BMI, 40 pack-years of smoking, problem drinking, high caffeine intake, diabetes, hypertension, angina, or anti-hypertensive medication use (especially diuretics), but more often used CNS medications.

In multivariable analyses among men with mild baseline LUTS (Table 4), men with MCS <50, history of non-prostate cancer, mobility limitations, overweight, dizziness, and no daily walking for exercise were 1.5- to 2-fold more likely to have progressing compared to stable LUTS. When PASE score replaced the walking variable, the OR was elevated for the lowest level of physical activity (0–99 points) compared to the highest (200 points) (1.6, 95% CI: 0.9–2.9) but were null for 100–149 (0.8, 95% CI: 0.5–1.5) and 150–199 points (0.9, 95% CI: 0.5–1.5).

Among men with moderate baseline LUTS, those with progressing compared to stable LUTS were 1.5–2.5-fold more likely to have MCS <50, hypertension, and back pain, and were less likely to have diabetes. Men with remitting compared to progressing LUTS were 2.3-fold more likely to use CNS medications at baseline, but were less likely to have histories of problem drinking, hypertension, or angina.

Discussion

Several distinct AUA-SI trajectories were identified among 1740 elderly men untreated for LUTS and trajectory types differed by baseline LUTS severity. Most men with mild baseline LUTS followed stable trajectories, whereas half of men with moderate baseline LUTS experienced progression and a fifth experienced remission. These data may allow clinicians to advise older men that prospects for worsening (or improving) symptoms are based on their current symptom level. Similarly, the baseline lifestyle and health factors associated with LUTS progression differed somewhat for progression from mild or from moderate baseline symptoms. Clinical or public health interventions that target these factors within different levels of LUTS severity may promote the prevention of symptom progression in older men.

In our study, poor mental health was a strong risk factor for LUTS progression. LUTS remission relative to progression also was associated with factors that could influence mental well-being, such as use of CNS medications and problem drinking.[41] In other

studies, depressive symptoms were associated with LUTS progression,[17] but anti-depressant use was associated with higher likelihood of transition from mild to moderate LUTS.[15] Pharmacological modulation of CNS neurotransmitters, such as serotonin and GABA, may inhibit bladder overactivity and/or improve bladder capacity.[42] It is therefore notable that use of benzodiazepines, which enhance GABA actions, was more common among men in remitting than in progressing trajectories in our study. Although use of certain CNS medications could worsen LUTS,[15] their therapeutic potential warrants a more complete understanding of neurological contributions to lower urinary tract function.

The current results agree with our earlier report that LUTS progression is positively associated with overweight and inversely associated with physical activity.[16] However, others showed no associations of BMI with LUTS progression[14,15] or of physical activity with either LUTS progression or remission.[17] In older men, overweight and low physical activity may contribute to lower urinary tract dysfunction through pathways involving microvascular disease,[43,44] metabolic derangements,[45] or autonomic nervous system overactivity.[46] Consistent with these mechanisms, our results also show associations of hypertension and dizziness (a marker of orthostatic control) with LUTS progression. Our results also document that mobility and back pain may contribute to LUTS progression. Men with mobility limitations or back pain may perceive their symptoms as becoming more severe over time, if difficulty with ambulation alone, or because of pain, interferes with their ability get to or use a toilet. Alternatively, degenerative spinal conditions such as disc herniation or lumbar stenosis could contribute to both back pain and urologic dysfunction by impinging on the spinal cord or nerve roots.[47–49]

Risk factors for LUTS progression and remission identified in this study differ from those reported previously for three key reasons. First, we used trajectory modeling to account for LUTS fluctuation within men. Most earlier studies focused on change of a certain magnitude from a single previous time point, such as transition from mild (AUA-SI 0–7 points) to moderate LUTS (AUA-SI 8 points)[15,16] or 2–3 point difference in AUA-SI voiding or storage subscores.[17] These definitions may introduce misclassification if men who progress are combined with men whose symptoms are randomly fluctuating, or if men with stable and remitting symptoms are combined in the referent group. Misclassification would tend to bias associations with risk factors toward the null, which may explain why we but not others[14,15,17] observed associations with BMI and physical activity. Second, we studied men with untreated LUTS. Studies that included a mix of men with and without treatment for LUTS may have identified factors associated with treatment decisions or treatment effects.[14–17] Third, we studied older men whose risk factors for LUTS progression or remission may differ from those in younger men.

There are limitations to this research. First, we could not assess the reasons that men did not undergo treatment for LUTS. However, about 88% of men remained untreated at each AUA-SI assessment period, a proportion similar to that observed in other community-dwelling cohorts,[8,26] suggesting that the MrOS cohort is not unusual with regard to LUTS treatment initiation. Second, we did not have specific urological metrics. However, such measures would not have necessarily informed this analysis because our aim was to study long-term changes in urinary symptoms which are well-represented by the AUA-SI. Third,

some of the factors studied such as CNS medication use had low baseline prevalence, which resulted in wide confidence intervals for OR estimates. Finally, the analytic cohort consisted of men ages 65 or older who survived an average of 6.9 years and results may not apply to all men at risk for LUTS progression.

This study has multiple strengths. First, MrOS was specifically designed to study LUTS prospectively in elderly men.[30] Second, the large sample size and excellent follow-up allowed us to evaluate multiple trajectory solutions and optimally characterize long-term LUTS changes. The small overall mean change in the AUA-SI during follow-up observed by us and others, [20,22–25] belies the dynamic nature of untreated LUTS among elderly men. Trajectory analysis revealed rare patterns that have not been described previously including persistently severe symptoms and mixed progression and remission. Finally, the comprehensive data available in MrOS allowed a comprehensive investigation of risk factors for LUTS change.

Conclusion

Several lifestyle and factors were associated with progressing and remitting LUTS trajectories. Back pain and CNS medication use may represent novel etiologies of LUTS that could be explored in future research. Intervening on lifestyle and health factors, especially mental health, has the potential to reduce the burden of LUTS in older men.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

References

1. Boyle P, Robertson C, Mazzetta C, Keech M, Hobbs FD, Fourcade R, et al. The prevalence of lower urinary tract symptoms in men and women in four centres. The UrEpik study. BJU Int. 2003; 92:409–14. [PubMed: 12930430]

2. Irwin DE, Kopp ZS, Agatep B, Milsom I, Abrams P. Worldwide prevalence estimates of lower urinary tract symptoms, overactive bladder, urinary incontinence and bladder outlet obstruction. BJU Int. 2011; 108:1132–1138. [PubMed: 21231991]

3. Parsons JK, Bergstrom J, Silberstein J, Barrett-Connor E. Prevalence and characteristics of lower urinary tract symptoms in men aged > or = 80 years. Urology. 2008; 72:318–321. [PubMed: 18554695]

4. Haidinger G, Waldhor T, Madersbacher S, Schatzl G, Vutuc C. Prevalence of lower urinary tract symptoms in Austrian males: update 2009. Urol Int. 2011; 87:385–391. [PubMed: 22041923]

5. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. The standardisation of terminology in lower urinary tract function: report from the standarization sub-committee of the International Continence Society. Urology. 2003; 61:37–49. [PubMed: 12559262]

6. Barry MJ, Fowler FJ Jr, O'Leary MP, Bruskewitz RC, Holtgrewe HL, Mebust WK, et al. The Measurement Committee of the American Urological Association. The American Urological Association symptom index for benign prostatic hyperplasia. J Urol. 1992; 148:1549–1557. [PubMed: 1279218]

7. Taylor BC, Wilt TJ, Fink HA, Lambert LC, Marshall LM, Hoffman AR, et al. Prevalence, severity, and health correlates of lower urinary tract symptoms among older men: the MrOS study. Urology. 2006; 68:804–809. [PubMed: 17070357]

8. Kupelian V, Wei JT, O'Leary MP, Kusek JW, Litman HJ, Link CL, et al. Prevalence of lower urinary tract symptoms and effect on quality of life in a racially and ethnically diverse random sample: the Boston Area Community Health (BACH) Survey. Arch Inter Med. 2006; 166:2381–2387.

9. Parsons JK, Mougey J, Lambert L, Wilt TJ, Fink HA, Garzotto M, et al. Lower urinary tract symptoms increase the risk of falls in older men. BJU Int. 2009; 104:63–68. [PubMed: 19154508]

10. Kupelian V, Fitzgerald MP, Kaplan SA, Norgaard JP, Chiu GR, Rosen RC. Association of nocturia and mortality: results from the Third National Health and Nutrition Examination Survey. J Urol. 2011; 185:571–577. [PubMed: 21168875]

11. Wei JT, Calhoun E, Jacobsen SJ. Urologic diseases in America project: benign prostatic hyperplasia. J Urol. 2005; 173:1256–61. [PubMed: 15758764]

12. Hu TW, Wagner TH, Bentkover JD, LeBlanc K, Piancentini A, Stewart WF, et al. Estimated economic costs of overactive bladder in the United States. Urology. 2003; 61:1123–1128. [PubMed: 12809878]

13. National Center for Health Statistics. Health United States, 2013: With Special Feature on Emergency Care. Hyattsville, MD: 2013. Available at http://www.cdc.gov/nchs/data/hus/hus12.pdf [last accessed July 19, 2013]

14. Burke JP, Rhodes T, Jacobson DJ, McGree ME, Roberts RO, Girman CJ, et al. Association of anthropmetric measures with the presence and progression of benign prostatic hyperplasia. Am J Epidemiol. 2006; 164:41–46. [PubMed: 16611664]

15. Kok ET, Schouten BW, Bohnen AM, Groeneveld FP, Thomas S, Bosch JL. Risk factors for lower urinary tract symptoms suggestive of benign prostatic hyperplasia in a community based population of healthy aging men: the Krimpen study. J Urol. 2009; 181:710–16. [PubMed: 19091352]

16. Parsons JK, Messer K, White M, Barrett-Connor E, Bauer DC, Marshall LM. Obesity increases and physical activity decreases lower urinary tract symptom risk in older men: the Osteoporotic Fractures in Men (MrOS) Study. Eur Urol. 2011; 60:1173–80. [PubMed: 21802828]

17. Martin S, Lange K, Haren MT, Taylor AW, Wittert G. Risk factors for progression and improvement of lower urinary tract symptoms (LUTS) in a prospective cohort of men. J Urol. 2014; 191:130–137. [PubMed: 23770136]

18. Wolters R, Wensing M, van Weel C, van der Wilt GJ, Grol RP. Lower urinary tract symptoms: social influence is more important than symptoms in seeking medical care. BJU Int. 2002; 90:655–661. [PubMed: 12410742]

19. Krambeck AE, Jacobson DJ, McGree ME, Lightner DJ, Lieber MM, Jacobsen SJ, et al. Effectiveness of medical and surgical therapies for lower urinary tract symptoms in the community setting. BJU Int. 2012; 110:1332–1337. [PubMed: 22471348]

20. Jacobsen SJ, Girman CJ, Guess HA, Rhodes T, Oesterling JE, Lieber MM. Natural history of prostatism: longitudinal changes in voiding symptoms in community dwelling men. J Urol. 1996; 155:595–600. [PubMed: 8558668]

21. Lee AJ, Garraway WM, Simpson RJ, Fisher W, King D. The natural history of untreated lower urinary tract symptoms in middle-aged and elderly men over a period of five years. Eur Urol. 1998; 34:325–332. [PubMed: 9748680]

22. Masumori N, Tsukamoto T, Rhodes T, Girman CJ. Natural history of lower urinary tract symptoms in men--result of a longitudinal community-based study in Japan. Urology. 2003; 61:956–960. [PubMed: 12736015]

23. Temml C, Brossner C, Schatzl G, Ponholzer A, Knoepp L, Madersbacher S. The natural history of lower urinary tract symptoms over five years. Eur Urol. 2003; 43:374–380. [PubMed: 12667718]

24. Sarma AV, McLaughlin JC, Jacobsen SJ, Logie J, Dolin P, Dunn RL, et al. Longitudinal change in lower urinary tract symptoms among a chort of black American men: the Flint Men's Health Study. Urology. 2003; 61:595–600.

25. Parsons JK, Wilt TJ, Wang PY, Barrett-Connor E, Bauer DC, Marshall LM. Progression of lower urinary tract symptoms in older men: a community based study. J Urol. 2010; 183:1915–1920. [PubMed: 20303101]

26. Maserejian NN, Chen S, Chiu GR, Araujo AB, Kupelian V, Hall SA, et al. Treatment status and progression or regression of lower urinary tract symptoms in a general adult population sample. J Urol. 2014; 191:107–113. [PubMed: 23851181]

27. Jones BL, Nagin DS, Roeder K. A SAS Procedure Based on Mixture Models for Estimating Developmental Trajectories. Sociol Method Res. 2001; 29:374–393.

28. Nagin DS, Odgers CL. Group-based trajectory modeling in clinical research. Annu Rev Clin Psychol. 2010; 6:109–38. [PubMed: 20192788]

29. Gill TM, Gahbauer EA, Han L, Allore HG. Trajectories of disability in the last year of life. N Engl J Med. 2010; 362:1173–1180. [PubMed: 20357280]

30. Orwoll E, Blank JB, Barrett-Connor E, Cauley J, Cummings S, Ensrud K, 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; 26:569–585. [PubMed: 16084776]

31. Blank JB, Cawthon PM, Carrion-Petersen ML, Harper L, Johnson JP, Mitson E, et al. Overview of the recruitment for the Osteoporotic Fractures in Men Study (MrOS). Contemp Clin Trials. 2005; 26:557–568. [PubMed: 16085466]

32. Pahor M, Chrischilles EA, Guralnik JM, Brown SL, Wallace RB, Carbonin P. Drug data coding and analysis in epidemiologic studies. Eur J Epidemiol. 1994; 10:405–411. [PubMed: 7843344]

33. Ewing JA. Detecting alcoholism. The CAGE questionnaire. JAMA. 1984; 25:1905–1907. [PubMed: 6471323]

34. Buchsbaum DG, Buchanan RG, Welsh J, Centor RM, Schnoll SH. Screening for drinking disorders in the elderly using the CAGE questionnaire. J Am Geriatr Soc. 1992; 40:662–665. [PubMed: 1607581]

35. Block G, Hartman AM, Naughton D. A reduced dietary questionnaire: development and validation. Epidemiol. 1990; 1:58–64.

36. Washburn RA, Smith KW, Jette AM, Janney CA. The Physical Activity Scale for the Elderly (PASE): development and evaluation. J Clin Epidemiol. 1993; 46:153–162. [PubMed: 8437031]

37. Guralnik JM, Ferrucci L, Simonsick EM, Salive ME, Wallace RB. Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability. N Engl J Med. 1995; 332:556–561. [PubMed: 7838189]

38. Ware J Jr, Kosinski M, Keller SD. A 12-item short-form health survey: construction of scales and preliminary tests of reliability and validity. Med Care. 1996; 34:220–233. [PubMed: 8628042]

39. Gill SC, Butterworth P, Rodgers B, Mackinnon A. Validity of the mental health component scale of the 12-item Short-Form Health Survey (MCS-12) as measure of common mental disorders in the general population. Psychiatry Res. 2007; 152:63–71. [PubMed: 17395272]

40. Mokdad AH, Serdula MK, Dietz WH, Bowman BA, Marks JS, Koplan JP. The spread of the obesity epidemic in the United States, 1991–1998. JAMA. 1999; 282:1519–1522. [PubMed: 10546690]

41. Perreira KM, Sloan FA. Excess alcohol consumption and health outcomes: a 6-year follow-up of men over age 50 from the health and retirement study. Addiction. 2002; 97:301–10. [PubMed: 11964106]

42. Andersson KE, Wein AJ. Pharmacology of the lower urinary tract: basis for current and future treatments of urinary incontinence. Pharmacol Rev. 2004; 56:581–631. [PubMed: 15602011]

43. Parsons JK, Sarma AV, McVary K, Wei JT. Obesity and benign prostatic hyperplasia: clinical connections, emerging etiological paradigms and future directions. J Urol. 2012; 189:S102–S106. [PubMed: 23234610]

44. Parsons JK, Kashefi C. Physical activity, benign prostatic hyperplasia, and lower urinary tract symptoms. Eur Urol. 2008; 53:1228–35. [PubMed: 18358592]

45. De Nunzio C, Aronson W, Freedland SJ, Giovannucci E, Parsons JK. The correlation between metabolic syndrome and prostatic diseases. Eur Urol. 2013; 61:560–570. [PubMed: 22119157]

46. McVary KT, Rademaker A, Lloyd GL, Gann P. Autonomic nervous system overactivity in men with lower urinary tract symptoms secondary to benign prostatic hyperplasia. J Urol. 2005; 174:1327–1338. [PubMed: 16145413]

47. Yamanishi T, Yasuda K, Sakakibara R, Murayama N, Hattori T, Ito H. Detrusor overactivity and penile erection in patients with lower lumbar spine lesions. Eur Urol. 1998; 34:360–4. [PubMed: 9748686]

48. Bartolin Z, Savic I, Persec Z. Relationship between clinical data and urodynamic findings in patients with lumbar intervertebral disk protrusion. Urol Res. 2002; 30:219–222. [PubMed: 12202938]

49. Inui Y, Doita M, Ouchi K, Tsukuda M, Fujita N, Kurosaka M. Clinical and radiologic features of lumbar spinal stenosis and disc herniation with neuropathic bladder. Spine. 2004; 29:869–873. [PubMed: 15082986]
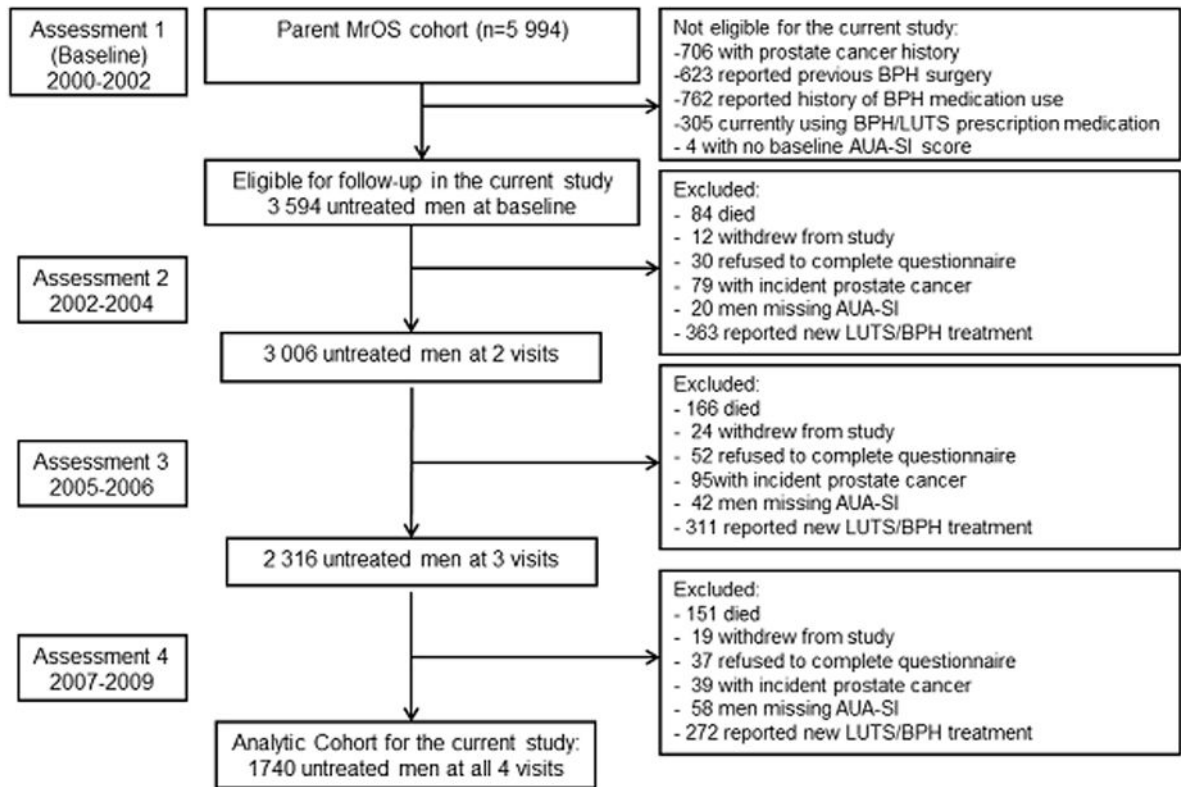
Figure 1.
Study flow diagram illustrating the selection of the analytic cohort of 1740 men from the Osteoporotic Fractures in Men (MrOS) Study, USA, 2000–2009.
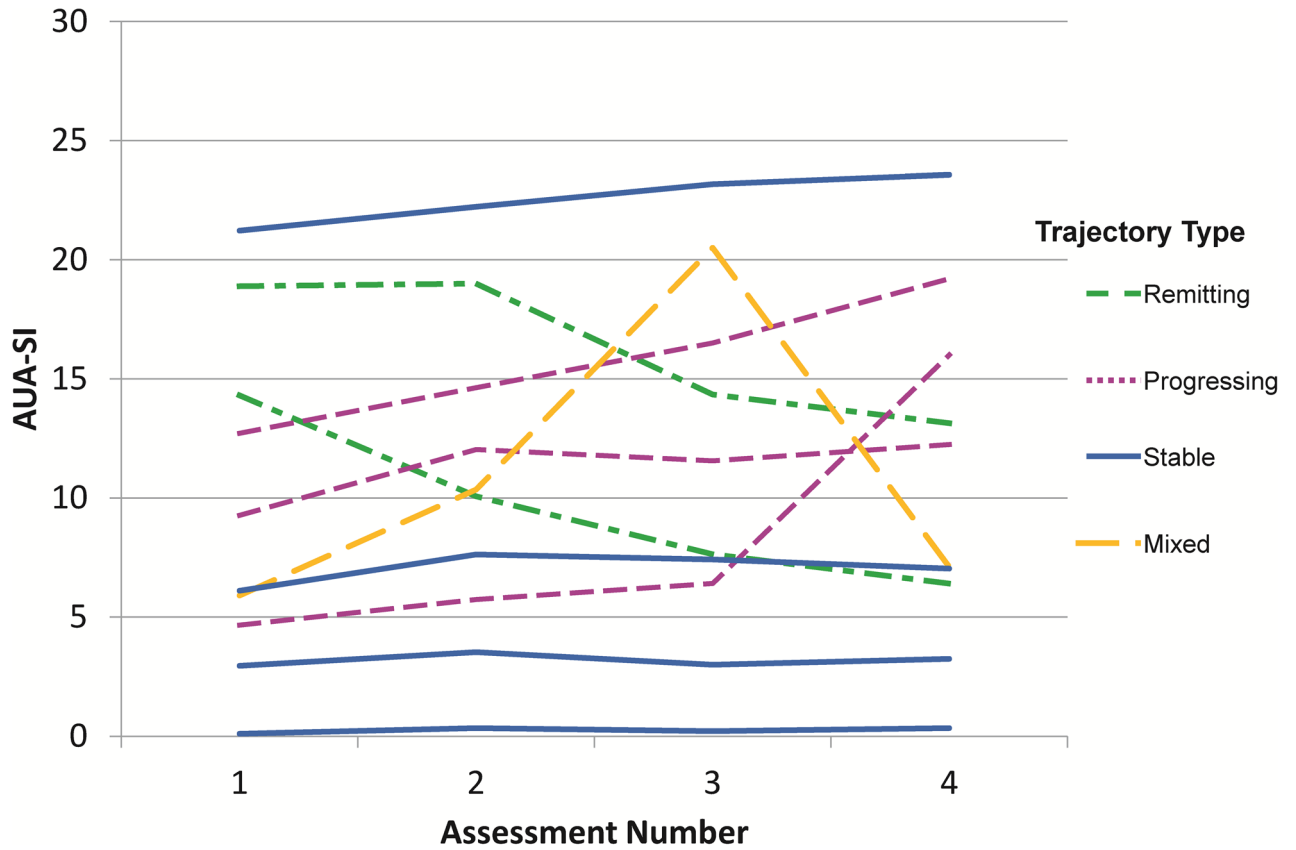
Figure 2.
Trajectory shape as illustrated with plots of mean American Urologic Association-Symptom Index (AUA-SI) scores over time among elderly men never treated for lower urinary tract symptoms (LUTS), the Osteoporotic Fractures in Men (MrOS) Study, USA, 2000–2009.
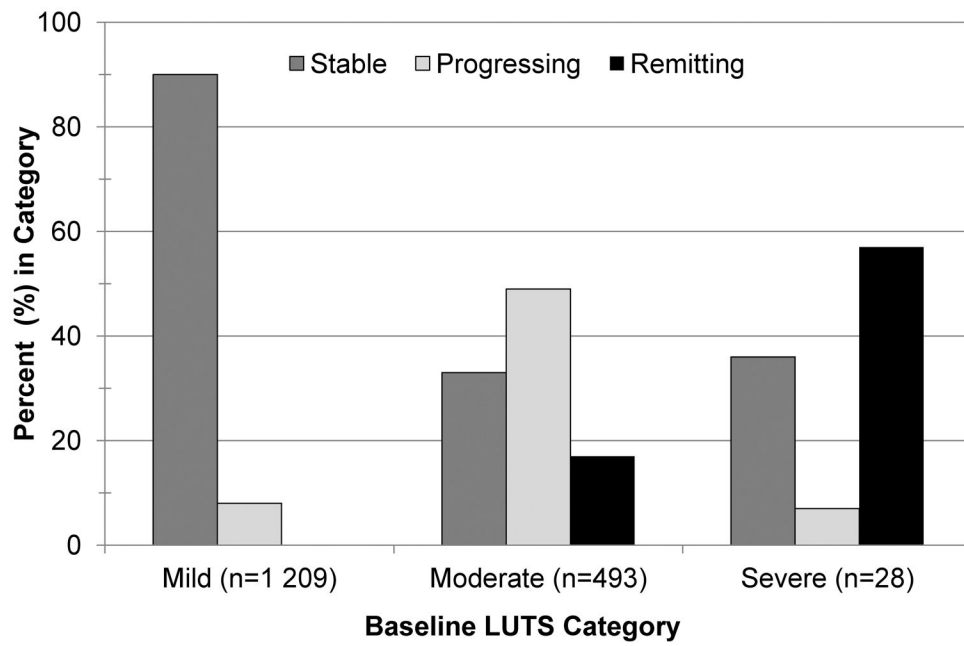
Figure 3.
Percentages of men in stable, progressing or remitting trajectories according to baseline LUTS severity, the Osteoporotic Fractures in Men (MrOS) Study, USA, 2000–2009.

Table 1

Baseline Characteristics among Men with no History of LUTS Treatment and the Analytic Sample Derived from this Initial Cohort, the Osteoporotic Fractures in Men (MrOS) Study, USA, 2000–2009.

Characteristic	Men with no History of Treatment for LUTS [1] N=3 594	Analytic Sample N=1 740
	Mean (SD)	**Mean (SD)**
Age (years)	72.7 (5.6)	71.4 (4.8)
BMI (kg/m^2)	27.3 (3.8)	27.3 (3.7)
PASE Score [2]	152 (69)	158 (66)
SF-12 Physical Component Score	50 .0 (9.6)	51.4 (8.1)
SF-12 Mental Component Score	55.7 (6.8)	56.3 (6.0)
AUA-SI	7.3 (5.7)	6.0 (4.8)
	Percent (%)	**Percent (%)**
Race/Ethnicity		
Caucasian	89%	90%
African American	4%	3%
Asian	3%	3%
Hispanic/Other	3%	3%
High school education or less	24%	23%
Live alone	13%	11%
Cigarette Smoking		
40 pack years	17%	15%
20–39.9 pack years	17%	19%
<20 pack years	27%	27%
None	38%	39%
Alcohol Consumption		
14 drinks/week	12%	13%
7–13.9 drinks/week	14%	16%
6.9 drinks/week	40%	40%
None	33%	32%
History of Problem Drinking	16%	16%
Walk Daily for Exercise	50%	51%
Mobility Limitation	11%	8%
Benign Prostatic Hyperplasia	29%	25%
Diabetes	11%	9%
Hypertension	38%	36%
Anti-hypertensive use		
Diuretic	17%	13%
Non-diuretic	27%	25%
Statins	25%	24%
Central nervous system medication use	10%	8%
Herbal supplements for LUTS/BPH	12%	10%

[1] Men untreated at baseline and with no prostate cancer history.

[2] Physical Activity Scale for the Elderly (PASE).[36] Higher scores indicate greater activity. Percentages may not add to 100% due to rounding.

Table 2

Comparison of baseline demographic, lifestyle, quality of life and medical factors among elderly men in stable and progressing trajectories stratified by mild or moderate LUTS.[1]

	AUA-SI 1–7 points (mild)			AUA-SI 8–19 points (moderate)		
Trajectory type	Progressing	Stable	P	Progressing	Stable	P
Number in group	101	1 103		242	156	
Age Group			0.73			0.16
65–69 years	42%	45%		41%	32%	
70–74 years	32%	31%		31%	34%	
75 years	27%	24%		28%	34%	
White race	87%	90%	0.37	93%	89%	0.13
High school education or less	19%	22%	0.41	22%	24%	0.60
Live alone	17%	11%	0.11	9%	15%	0.06
BMI 25.0 kg/m^2	81%	72%	0.05	76%	72%	0.34
Cigarette Smoking			0.94			0.91
40 pack years	15%	15%		19%	19%	
20–39.9 pack years	18%	19%		18%	18%	
<20 pack years	25%	27%		27%	24%	
None	42%	40%		36%	39%	
Alcohol Consumption			0.43			0.66
14 drinks/week	12%	13%		13%	14%	
7–13.9 drinks/week	19%	15%		18%	13%	
6.9 drinks/week	35%	42%		36%	39%	
None	35%	30%		33%	34%	
History of Problem Drinking	19%	14%	0.15	23%	22%	0.87
Caffeine Intake			0.56			0.82
Quartile 1	27%	24%		20%	23%	
Quartile 2	25%	24%		25%	24%	
Quartile 3	24%	24%		25%	23%	
Quartile 4	25%	27%		30%	30%	
Physical Activity Score[2]			0.04			0.45

Trajectory type	AUA-SI 1–7 points (mild)			AUA-SI 8–19 points (moderate)		
	Progressing	Stable	P	Progressing	Stable	P
Number in group	101	1 103		242	156	
0–99 points	27%	16%		20%	22%	
100–149 points	25%	31%		31%	33%	
150–199 points	24%	28%		30%	23%	
200 points	24%	26%		19%	22%	
Walk Daily for Exercise	42%	53%	0.03	48%	51%	0.51
Mobility Limitation	14%	6%	0.002	8%	8%	0.98
SF-12 Physical Component Score			0.29			0.38
<50 points	28%	24%		33%	34%	
50–54 points	27%	22%		26%	20%	
55 points	46%	54%		41%	46%	
SF-12 Mental Component Score			0.02			0.01
<50 points	18%	10%		19%	9%	
50–54 points	13%	10%		14%	12%	
55 points	69%	80%		67%	79%	
Medical History						
Diabetes	11%	8%	0.26	9%	13%	0.17
Hypertension	44%	34%	0.06	43%	33%	0.05
Angina	8%	11%	0.33	16%	12%	0.33
Myocardial infarction	10%	9%	0.88	12%	16%	0.31
Stroke	5%	3%	0.19	5%	3%	0.51
Cancer (other than prostate)	23%	23%	0.04	21%	20%	0.97
Trouble with dizziness	25%	16%	0.02	27%	23%	0.40
Back pain in past year	68%	59%	0.08	74%	64%	0.04
Prostatitis	9%	5%	0.11	12%	10%	0.54
Medications or Supplements						
Hypoglycemic	11%	6%	0.05	6%	10%	0.15
Anti-hypertensive			0.71			0.25
Diuretic	15%	12%		18%	12%	
Non-diuretic	27%	26%		26%	29%	

Trajectory type	AUA-SI 1–7 points (mild)	Stable		AUA-SI 8–19 points (moderate)	Stable	
	Progressing		P	Progressing		P
Number in group	101	1 103		242	156	
Statin	19%	24%	0.25	29%	25%	0.38
Antidepressant	8%	3%	0.02	4%	3%	0.63
Central nervous system	9%	6%	0.35	10%	8%	0.37
Herbal use for LUTS/BPH	7%	7%	0.98	20%	15%	0.26

[1] Variables with p 0.25 were considered for selection in logistic regression.

[2] Physical Activity Scale for the Elderly (PASE).[36] Higher scores indicate greater activity.

Table 3

Comparison of baseline demographic, lifestyle, quality of life and medical factors among elderly men in remitting compared to progressing trajectories.[1]

| Trajectory type | AUA-SI 8–19 points (moderate) | | |
| | Remitting | Progressing | |
Number in group	82	242	*P*
Age Group			0.49
65–69 years	35%	41%	
70–74 years	30%	31%	
75 years	34%	28%	
White race	91%	93%	0.56
High school education or less	29%	21%	0.15
Live alone	7%	9%	0.62
BMI 25.0 kg/m^2	68%	76%	0.15
Cigarette Smoking			0.17
40 pack years	10%	19%	
20–39.9 pack years	15%	18%	
<20 pack years	34%	27%	
None	41%	36%	
Alcohol Consumption			0.67
14 drinks/week	10%	13%	
7–13.9 drinks/week	15%	18%	
6.9 drinks/week	40%	36%	
None	35%	33%	
History of Problem Drinking	12%	23%	0.03
Caffeine Intake			0.25
Quartile 1	26%	20%	
Quartile 2	26%	25%	
Quartile 3	29%	25%	
Quartile 4	20%	30%	
Physical Activity Score[2]			0.84
0–99 points	24%	20%	
100–149 points	30%	31%	
150–199 points	27%	30%	
200 points	18%	19%	
Walk Daily for Exercise	56%	45%	0.28
Mobility Limitation	11%	8%	0.46
SF-12 Physical Component Score			0.31
<50 points	43%	33%	
50–54 points	21%	26%	
55 points	37%	41%	
SF-12 Mental Component Score			0.43

Trajectory type	AUA-SI 8–19 points (moderate)		
	Remitting	Progressing	
Number in group	82	242	P
<50 points	13%	19%	
50–54 points	12%	14%	
55 points	74%	67%	
Medical History			
Diabetes	5%	9%	0.22
Hypertension	30%	43%	0.05
Angina	7%	16%	0.06
Myocardial infarction	12%	12%	0.96
Stroke	4%	5%	1.00
Cancer (other than prostate)	20%	21%	0.82
Trouble with dizziness	26%	27%	0.82
Back pain in past year	72%	74%	0.72
Prostatitis	15%	12%	0.47
Medications or Supplements			
Hypoglycemic	4%	6%	0.39
Anti-hypertensive			0.06
Diuretic	9%	17%	
Non-diuretic	21%	26%	
Statin	24%	29%	0.47
Antidepressant	7%	4%	0.25
Central nervous system	17%	10%	0.10
Herbal use for LUTS/BPH	15%	20%	0.29

[1] Variables with p 0.25 were considered for selection in logistic regression.

[2] Physical Activity Scale for the Elderly (PASE).[36] Higher scores indicate greater activity.

Table 4

Factors independently associated with progressing or remitting LUTS trajectory according to baseline AUA-SI score.[1]

Baseline AUA-SI Score 0–7 points :	Progressing vs. Stable		
Factor	Referent level	OR (95% CI)	p
SF-12 Mental Component Score			
<50 points[2]	55 points	1.9 (1.1 – 3.4)	0.03
50–54 points	55 points	1.5 (0.8 – 2.8)	0.21
History of cancer (not prostate)	No cancer	1.7 (1.0 – 2.9)	0.03
Mobility limitation	No mobility limitation	2.0 (1.0 – 3.8)	0.04
Overweight or obese (BMI ≥ 25.0 kg/m²)	Normal/Underweight (BMI<25.0 kg/m²)	1.7 (1.0–2.8)	0.06
Trouble with dizziness	No dizziness	1.6 (0.9 – 2.6)	0.08
No daily walking for exercise	Daily walking for exercise	1.4 (0.9 – 2.2)	0.10

Baseline AUA-SI Score 8–19 points:	Progressing vs. Stable		
Factor	Referent level	OR (95% CI)	p
SF-12 Mental Component Score			
<50 points	55 points	2.5 (1.3 – 4.9)	0.005
50–54 points	55 points	1.5 (0.8 – 2.8)	0.22
History of diagnosed hypertension	No hypertension	1.5 (1.0 – 2.4)	0.06
Back pain in past 12 mo	No back pain	1.5 (1.0 – 2.4)	0.07
Live with spouse, family, or roommate	Live alone	1.8 (1.0 – 3.4)	0.07
White (Caucasian)	Non-white	1.9 (0.9 – 3.9)	0.10
History of diabetes	No diabetes	0.6 (0.3 – 1.2)	0.12

Baseline AUA-SI Score 8–19 points:	Remitting vs. Progressing		
Factor	Referent level	OR (95% CI)	p
Central nervous system medication	No use	2.3 (1.1 – 4.9)	0.03
History of problem drinking	No such history	0.4 (0.2 – 0.9)	0.03
History of diagnosed hypertension	No hypertension history	0.6 (0.3 – 1.0)	0.04
History of diagnosed angina	No angina history	0.4 (0.2 – 1.1)	0.07
High school education or less	Some college or more	1.7 (0.9 – 3.1)	0.08

[1] Factors evaluated during model building were those from univariable analyses with p ≤ 0.25 and retained in the stepwise selection procedure at p ≤ 0.15 as described in Methods.