ORiGiNaL ARTiCLE

Lifestyle and health factors associated with progressing and remitting trajectories of untreated lower urinary tract symptoms among elderly men

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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 US men aged ≥65 years, the American Urological Association Symptom Index (AUA-SI) was repeated four times, once at baseline (2000–2002) and then every 2 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 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 with stable trajectories, and with remitting compared with progressing trajectories. Lifestyle, body mass index (BMI) (kg/m²), mobility, mental health (Short-Form 12), medical history and prescription medications were considered for selection. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated for variables in each model.

RESULTS: We identified 10 AUA-SI trajectories: 4 stable (1277 men, 73%), three progressing (345 men, 20%), two remitting (98 men, 6%) and one mixed (20 men, 1%). Men in progressing compared with 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 with 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.

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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.3–6 Multiple etiologies, including BPH and bladder overactivity, manifest as LUTS.7 LUTS severity is assessed with the validated American Urological Association Symptom Index (AUA-SI) or International Prostate Symptom Score.8 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 United States.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 decisions18 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.17,20–26 Apparently spontaneous symptom remission and symptom stability are also consistently documented.20–26 Identification of these patterns requires repeated AUA-SI or International Prostate Symptom Score assessments, because LUTS fluctuate considerably within men over time.20 To date, nearly all previous

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Lower urinary tract symptom trajectories in men
LM Marshall et al

MATERIALS AND METHODS

Setting
We used data collected prospectively in the Osteoporotic Fractures in Men Study, a cohort of community-dwelling men aged ≥65 years. Participants were recruited in 2000–2002 from six US regions. Men completed baseline questionnaires and in-person research visits. Subsequently, data were updated about every 2 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). Urinary bother was categorized as 0–2, 3 and 4–6. Men reported histories of diagnosed BPH, laser surgery or TURP and medication use for prostate symptoms. Current prescription medications were inventoried at each time point and matched to ingredients using a standardized method as described previously. LUTS medications were α-blockers, urinary antispasmodics, anticholinergics and 5-α-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 two or more positive responses to the CAGE questionnaire. Caffeine consumption (mg per day) was obtained from a Block Food Frequency Questionnaire and categorized into quartiles. Physical activity was obtained with the validated Physical Activity Scale for the Elderly, which assesses amount of leisure and household activities. 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. Health-related quality of life was obtained with the Short Form-12 physical component (PCS) and mental component (MCS) scores. A MCS ≤50 is a valid measure of common mental health disorders (depression or anxiety disorders). 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) categories as <25.0 (normal), 25.0–29.9 (overweight), or ≥30.0 (obese). Baseline prescription medications included hypoglycemics (insulin and glucose), diuretics (thiazide, loop and potassium sparing) and other anti-hypertensives (ACE inhibitors, angiotensin II receptor antagonists, ß-blockers and calcium channel blockers), statins (HMG-CoA reductase inhibitors) and central nervous system (CNS) medications (antiepileptics, benzodiazepines, antidepressants, opioids and sedatives). α-Blockers could not be included as anti-hypertensives because the use of these medications was an exclusion criterion (described below). Herbal supplements for LUTS were saw palmetto, South African star grass, stingling nettle, rye grass pollen, pumpkin seed, or African plum from self-report or inventory listing. Men with missing medication information were

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.
categorized as 'normal' and 'overweight/obese' improved model fit. Odds ratios (ORs) and their 95% confidence intervals (CIs) are reported for the final multivariable models. Therefore, final models contained the medical history variables. BMI, body mass index; LUTS, lower urinary tract symptom; MrOS, Osteoporotic Fractures in Men Study; PASE, Physical Activity Scale for the Elderly; SF-12, Short Form 12.

### RESULTS
The 1740 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 (s.d.) 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 1277 (73%) men and were observed in the low and high AUA-SI range. Three trajectories consistent with progression (red) contained 345 men (20%), 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%). Supplementary 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.

### Analytic cohort
The 3594 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%), or experienced abrupt increase late in follow-up. Two trajectories were excluded (Figure 1). The analytic cohort of 1740 had mean (s.d.) 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
Statistical analyses were performed with SAS 9.1 software (SAS Institute, Cary, NC, USA). 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 of the change in the Bayesian Information Criterion (2\( \Delta \)BIC). Values >10 are considered evidence of better fit of the larger trajectory number compared with 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 Supplementary 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 improvement with progressing LUTS were compared. Men with remitting LUTS were compared with 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 (ORs) and their 95% confidence intervals (CIs) are reported for the final multivariable models.

### Table 1. Baseline characteristics among men with no history of LUTS treatment and the analytic sample derived from this initial cohort, the MrOS Study, USA, 2000–2009

| Characteristic | Men with no history of treatment for LUTSa | Analytic sample, N = 1740 |
|---------------|-------------------------------------------|--------------------------|
| Mean (s.d.) | Mean (s.d.) |
| Age (years) | 72.7 (5.6) | 71.4 (4.8) |
| BMI (kg m\(^{-2}\)) | 27.3 (3.8) | 27.3 (3.7) |
| PASE score\(^b\) | 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) |
| 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 per week | 12 | 13 |
| 7–13.9 Drinks per week | 14 | 16 |
| ≤6.9 Drinks per week | 40 | 40 |
| None | 33 | 32 |
| History of problem drinking | 16 | 16 |
| Walk daily for exercise | 50 | 51 |
| Mobility limitation | 11 | 8 |
| BPH | 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 |

Abbreviations: AUA-SI, American Urological Association Symptom Index; BMI, body mass index; LUTS, lower urinary tract symptom; MrOS, Osteoporotic Fractures in Men Study; PASE, Physical Activity Scale for the Elderly; SF-12, Short Form 12.

\( a \)Men untreated at baseline and with no prostate cancer history. \( b \)PASE. Higher scores indicate greater activity. Percentages may not add to 100% due to rounding.

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Prostate Cancer and Prostatic Disease (2014), 265 – 272
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 with stable trajectories more often had 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 with stable LUTS. When Physical Activity Scale for the Elderly score replaced the walking variable, the OR was elevated for the lowest level of physical activity (0–99 points) compared with 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 with stable LUTS were 1.5- to 2.5-fold more likely to have MCS < 50, hypertension and back pain, and were less likely to have diabetes. Men with remitting compared with 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 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 with stable LUTS. When Physical Activity Scale for the Elderly score replaced the walking variable, the OR was elevated for the lowest level of physical activity (0–99 points) compared with 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 with stable LUTS were 1.5- to 2.5-fold more likely to have MCS < 50, hypertension and back pain, and were less likely to have diabetes. Men with remitting compared with 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.
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.a

| Trajectory type | AUA-SI 1–7 points (mild) | AUA-SI 8–19 points (moderate) |
|----------------|-------------------------|-------------------------------|
| Number in group |                        |                               |
|                 | Progressing | Stable | P-value   | Progressing | Stable | P-value   |
| Age group       |            |        |           |            |        |           |
| 65–69 Years     | 42%        | 45%    | 0.73      | 41%        | 32%    | 0.16      |
| ≥75 Years       | 27%        | 24%    |           | 28%        | 34%    |           |
| White race      |            |        |           |            |        |           |
| High school education or less |    |        |           |            |        |           |
| Live alone      | 17%        | 11%    | 0.37      | 9%         | 15%    | 0.06      |
| BMI ≥ 25.0 kg m⁻² | 81%      | 72%    | 0.05      | 76%        | 72%    | 0.34      |
| Cigarette smoking |            |        |           |            |        |           |
| ≥40 Pack-years  | 15%        | 15%    | 0.94      | 19%        | 19%    | 0.91      |
| <20 Pack-years  | 25%        | 27%    |           | 27%        | 24%    |           |
| None            | 42%        | 40%    |           | 36%        | 39%    |           |
| Alcohol consumption |        |        | 0.43      | 0.66      |        |           |
| ≥14 Drinks per week | 12%      | 13%    |           | 13%        | 14%    |           |
| 7–13.9 Drinks per week | 19%   | 15%    |           | 18%        | 13%    |           |
| <7 Drinks per week | 35%     | 42%    |           | 36%        | 39%    |           |
| None            | 35%        | 30%    |           | 33%        | 34%    |           |
| 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 scoreb |          |        | 0.04      | 0.45      |        |           |
| 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 |        |        | 0.002     | 0.88      |        | 0.98      |
| SF-12 physical component score |            |        | 0.29      | 0.38      |        |           |
| SF-12 mental component score |            |        | 0.02      | 0.01      |        |           |
| 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%    |           |
| 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      |

Abbreviations: AUA-SI, American Urological Association Symptom Index; BMI, body mass index; LUTS, lower urinary tract symptom; PASE, Physical Activity Scale for the Elderly.

*aVariables with P ≤ 0.25 were considered for selection in logistic regression.

*bPASE. Higher scores indicate greater activity.
Prostate Cancer and Prostatic Disease (2014), 265 – 272

Table 3. Comparison of baseline demographic, lifestyle, quality of life and medical factors among elderly men in remitting compared to progressing trajectories

| Trajectory type | Remitting | Progressing | P-value |
|-----------------|-----------|-------------|---------|
| Number in group | 82        | 242         |         |

| Age group       |           |             |         |
|-----------------|-----------|-------------|---------|
| 65–69 Years     | 35%       | 41%         | 0.49    |
| 70–74 Years     | 30%       | 31%         |         |
| ≥ 75 Years      | 34%       | 28%         |         |

| White race      |           |             |         |
|-----------------|-----------|-------------|---------|
| 91%             | 93%       | 0.56        |         |

| Cigarette smoking |           |             |         |
|-------------------|-----------|-------------|---------|
| 10%               | 19%       | 0.17        |         |

| Alcohol consumption |           |             |         |
|---------------------|-----------|-------------|---------|
| ≥ 14 Drinks per week | 10%      | 13%         | 0.67    |
| 7–13.9 Drinks per week | 15%     | 18%         |         |
| < 6.9 Drinks per week | 40%     | 36%         |         |
| None                | 41%       | 36%         |         |

| Physical activity score |           |             |         |
|-------------------------|-----------|-------------|---------|
| 0.84                    |           |             |         |

| Medical history |           |             |         |
|-----------------|-----------|-------------|---------|
| 5%              | 9%        | 0.22        |         |

| Medications or supplements |           |             |         |
|----------------------------|-----------|-------------|---------|
| 4%                         | 6%        | 0.39        |         |

Abbreviations: AUA-SI, American Urological Association Symptom Index; BMI, body mass index; LUTS, lower urinary tract symptom; PASE, Physical Activity Scale for the Elderly.

Variables with P < 0.25 were considered for selection in logistic regression. *PASE. Higher scores indicate greater activity.

benzodiazepines, which enhance GABA actions, was more common among men in remitting than in progressing trajectories in our study (data not shown). Although the 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 progression14,15 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 to 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 others14,15,17 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, ~88% of men remained untreated at each AUA-SI assessment period, a proportion similar to that observed in other community-dwelling cohorts,6,28 suggesting that the Osteoporotic Fractures in Men (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 that 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 CIs for OR estimates. Finally, the analytic cohort consisted of men aged 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,20,22,23 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.

CONFLICT OF INTEREST
Dr Parsons and Dr Marshall received funding as co-Principal Investigators for this research from the US National Institutes of Health under grant R21 DK083675. Dr Parsons also reports relationships with AMS and Sophiris outside the submitted work. All other authors declare no conflict of interests.

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Table 4. Factors independently associated with progressing or remitting LUTS trajectory according to baseline AUA-SI score

| Factor | Progressing versus stable Referent level | OR (95% CI) | P-value |
|--------|-----------------------------------------|-------------|---------|
| Baseline AUA-SI score 0–7 points | | | |
| SF-12 mental component score | <50 Points | ≥ 55 Points | 1.9 (1.1–3.4) | 0.03 |
| 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 m⁻²) | Normal/underweight (BMI < 25.0 kg m⁻²) | 1.7 (1.0–2.8) | 0.06 |

Table 4 continued.

| Baseline AUA-SI score 8–19 points | Progressing versus stable Referent level | OR (95% CI) | P-value |
|----------------------------------|-----------------------------------------|-------------|---------|
| SF-12 mental component score | <50 Points | ≥ 55 Points | 2.5 (1.3–4.9) | 0.005 |
| History of diagnosed hypertension | No hypertension | 1.5 (1.0–2.4) | 0.06 |
| Back pain in past 12 months | 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 |

Table 4 continued.

| Remitting versus progressing Referent level | Progressing versus stable Referent level | OR (95% CI) | P-value |
|----------------------------------|-----------------------------------------|-------------|---------|
| 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 |

Abbreviations: AUA-SI, American Urological Association Symptom Index; BMI, body mass index; CI, confidence interval; LUTS, lower urinary tract symptom; OR, odds ratio; SF-12, Short Form 12.

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Supplementary Information accompanies the paper on the Prostate Cancer and Prostatic Diseases website (http://www.nature.com/pcan)