THE JOURNAL of UROLOGY®
www.auajournals.org/journal/juro

JU Insight

Lower Urinary Tract Symptoms and Mortality among Finnish Men: The Roles of Symptom Severity and Bother

Jonne Åkerla, Jori S. Pesonen, Antti Pöyhönen et al.

Correspondence: Jonne Åkerla (email: jonne.akerla@gmail.com).

Full-length article available at auajournals.org/10.1097/JU.0000000000002450.

Study Need and Importance: Due to very uncertain cause-and-effect relationships and the confounding effects of aging and comorbidity, the relevance of male lower urinary tract symptoms (LUTS) as mortality risk factors remains unclear. While traditionally only more severe and bothersome LUTS have been considered to require treatment, evaluating the potentially modifying effect of symptom severity and bother on LUTS-associated mortality is warranted.

What We Found: A questionnaire including the Danish Prostatic Symptom Score was mailed to a population-based cohort of 3,143 men aged 50, 60 and 70 years in 1994, with repeat surveys in 1999, 2004, 2009 and 2015. In time-dependent Cox regression adjusted by age and comorbidity, we found a 1.2-fold increased risk of death among men with moderate or severe voiding LUTS and a 1.4-fold risk among men with storage LUTS (see table). When including also mild symptoms, the mortality risk was reduced to 0.8-fold among men with any voiding LUTS and to 0.9-fold among men with storage LUTS. However, our findings showed a 1.3-fold increased risk of death among men with daytime frequency and a 1.5-fold risk among men with nocturia independently of symptom severity. Furthermore, we found a substantially increased 2.2-fold risk of death among men with frequent urgency incontinence. Mortality did not significantly differ between men with bothersome and nonbothersome LUTS.

Limitations: In spite of satisfactory response rates varying from 66% to 76% between survey rounds, the proportion of eligible participants was reduced to 37% (1,167 men) due to eligibility criteria restricting the analyses to men participating in every survey round.

Interpretation for Patient Care: Moderate and severe male LUTS are potential risk factors for mortality, independently of their bother.

Table. *Association of voiding and storage LUTS with mortality by symptom severity and bother*

	Voiding				Storage			
	Any*		Moderate/Severe†		Any‡		Moderate/Severe§	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Bother:‖								
No/mild	0.81	0.65—0.99	1.22	1.01—1.48	0.80	0.60—1.06	1.20	0.92—1.56
No/any	0.82	0.67—1.00	1.19	1.00—1.40	0.85	0.65—1.13	1.35	1.13—1.62
Moderate/severe	0.88	0.67—1.16	1.12	0.88—1.43	1.10	0.80—1.50	1.46	1.18—1.81

* Any voiding or post-voiding symptom of at least mild severity.
† Any voiding or post-voiding symptom of at least moderate severity.
‡ Any storage symptom of at least mild severity.
§ Any storage symptom of at least moderate severity.
‖ Cox regression for mortality in presence vs absence of symptoms by symptom-specific bother, adjusted by age, body mass index, marital status, smoking, diabetes, hypertension, cardiac disease, pulmonary disease, cerebrovascular disease, neurological disease and cancer.

https://doi.org/10.1097/JU.0000000000002450
Vol. 207, 1285-1294, June 2022
Printed in U.S.A.

THE JOURNAL of UROLOGY®
www.auajournals.org/journal/juro

Lower Urinary Tract Symptoms and Mortality among Finnish Men: The Roles of Symptom Severity and Bother

Jonne Åkerla,[1,2]* Jori S. Pesonen,[3] Antti Pöyhönen,[4] Juha Koskimäki,[1] Jukka Häkkinen,[5] Heini Huhtala,[6] Anssi Auvinen[6] and Teuvo L. J. Tammela[1,2]

[1]Department of Urology, Tampere University Hospital, Tampere, Finland
[2]Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland
[3]Department of Urology, Päijät-Häme Central Hospital, Lahti, Finland
[4]Centre for Military Medicine, Finnish Defence Forces, Riihimäki, Finland
[5]Hospital Mehiläinen, Oulu, Finland
[6]Faculty of Social Sciences, Tampere University, Tampere, Finland

Abbreviations and Acronyms

BMI = body mass index
BPH = benign prostatic hyperplasia
DAN-PSS-1 = Danish Prostatic Symptom Score
LUTS = lower urinary tract symptoms

Accepted for publication January 19, 2022.

Funding/support and role of the sponsor: The TAMUS study was financially supported by the Päivikki and Sakari Sohlberg Foundation and the Competitive State Research Financing of the Expert Responsibility area of Tampere University Hospital. State Research Funding (Finland) was used for collection of the data. The work of Jonne Åkerla was funded by the Finnish Urological Association. The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

Conflict of Interest: J.S. Pesonen: lecture honorarium from Astellas, lecture honorarium from Boston Scientific, lecture honorarium from Ferring, reimbursement for attending a scientific meeting from Orion; J. Häkkinen: Suomen Urologiyhdistys.

Ethics Statement: Study received Institutional Review Board approval (IRB No. 99050).

* Correspondence: Department of Urology, Tampere University Hospital, Teiskontie 35, 33521 Tampere, Finland (telephone: +358 3311611; FAX: +358 331164256; email: jonne.akerla@gmail.com).

Editor's Note: This article is the fourth of 5 published in this issue for which category 1 CME credits can be earned. Instructions for obtaining credits are given with the questions on pages 1357 and 1358.

Purpose: The utility of male lower urinary tract symptoms (LUTS) as mortality risk factors remains unclear. We explored LUTS-associated mortality among Finnish men, evaluating the association of symptom severity and bother with risk of death.

Materials and Methods: A questionnaire including the Danish Prostatic Symptom Score was mailed to a population-based cohort of 3,143 men aged 50, 60 and 70 years in 1994, with repeat surveys in 1999, 2004, 2009 and 2015. The men were followed until the end of 2018. Mortality associated with LUTS was analyzed using time-dependent Cox regression adjusted for age and comorbidity, updating symptom data every 5 years, including interaction terms between symptoms and associated bother.

Results: Of the 1,167 men in the analysis, 591 (50.6%) died during the 24-year followup. In analyses of moderate and severe symptoms disregarding bother, overall voiding and storage LUTS, daytime frequency and urgency incontinence were associated with increased mortality: the multivariable-adjusted hazard ratios were 1.19 (95% CI 1.00–1.40), 1.35 (1.13–1.62), 1.31 (1.09–1.58) and 2.19 (1.42–3.37), respectively. In analyses disregarding symptom severity and bother, voiding LUTS were associated with decreased mortality, while daytime frequency and nocturia were associated with increased mortality: the HRs were 0.82 (95% CI 0.67–1.00), 1.31 (95% CI 1.09–1.58) and 1.52 (95% CI 1.21–1.91), respectively. Excess mortality associated with bothersome daytime frequency and nocturia tended to be slightly higher: the HRs were 1.86 (95% CI 1.41–2.47) and 1.88 (95% CI 1.38–2.58), respectively. No significant interactions were found between symptoms and associated bother, however.

Conclusions: Moderate and severe LUTS are potential risk factors for mortality, independently of their bother.

Key Words: lower urinary tract symptoms, mortality, cohort studies

Lower urinary tract symptoms (LUTS) are common, particularly after age 50 years. Typical etiology for male LUTS involves benign prostatic hyperplasia (BPH), but also many comorbidities such as cardiovascular diseases, metabolic syndrome and neurological disorders can provoke LUTS.[1–3] LUTS can result from dysfunction during bladder filling (storage), emptying (voiding) or post-micturition phase, and symptoms often occur in combination.[4,5] In clinical practice, LUTS are generally weighted according to their impact on

https://doi.org/10.1097/JU.0000000000002450
Vol. 207, 1285-1294, June 2022
Printed in U.S.A.

bother and, accordingly, only bothersome symptoms are considered to require treatment.[6,7] As the current view suggests that only a minority of men seek care for their symptoms, probably the majority of men cope with their LUTS.[4,8,9]

Through various associated health problems, male LUTS could potentially serve as prognostic factors for premature death.[10–12] However, due to very uncertain cause-and-effect relationships and the confounding effect of aging and comorbidity, the relevance of male LUTS as mortality risk factors remains unclear. Furthermore, the previous estimates of LUTS-associated morbidity and mortality have focused mainly on nocturia (waking up at night to void) and typically only on dysfunction while ignoring the contribution of symptom-specific bother.[10–12] While an overall poor perceived health status is linked to both illnesses and bothersome LUTS[13,14] and traditionally only more severe and bothersome LUTS have been considered to require treatment,[4,7] evaluating the potentially modifying effect of symptom severity and bother on LUTS-associated mortality is warranted. We explored mortality among middle-aged and elderly Finnish men with LUTS of varying etiologies testing the relevance of symptom severity and bother for the estimates over a 24-year period.

MATERIALS AND METHODS

Tampere Aging Male Urological Study

A population-based cohort study was launched in 1994 with a postal questionnaire sent to 3,143 men identified from the Finnish Population Register, comprising all men born in 1924, 1934 and 1944 living in Pirkanmaa County. The assessments were repeated in 1999, 2004, 2009 and 2015. At each round, a reminder questionnaire was mailed for nonrespondents 3 months after the first mailing. The questionnaire comprised items on severity and bother of LUTS as well as sociodemographic, anthropometric and behavioral factors and medical conditions. The study protocol was reviewed by the ethics committee of the Pirkanmaa Hospital District (tracking number 99050). Further study details have been published previously.[15–17]

Symptom Assessment

LUTS were assessed using the Danish Prostatic Symptom Score (DAN-PSS-1),[18] a validated questionnaire consistent with the International Continence Society definitions.[19] Both combined and individual symptoms were analyzed. The group of voiding LUTS included hesitancy, weak stream, straining, dysuria and also the available post-voiding LUTS—incomplete emptying and post-micturition dribble. The group of storage LUTS included daytime frequency, nocturia, urgency and 3 incontinence symptoms (urgency, stress and mixed incontinence). The assessed individual symptoms included the previously addressed mortality risk factors—daytime frequency, nocturia, urinary urgency and urgency incontinence.[12,17,20]

As traditionally only more severe and bothersome LUTS have been considered patient-important,[21] symptoms of at least moderate severity causing at least moderate bother were compared to mild or absent symptoms (of any bother) after recoding each symptom into a 4-value categorical variable (any/nonbothersome/bothersome symptomatic vs asymptomatic) based on the DAN-PSS-1 assessments of symptom severity and bother. To test the effect of symptom case definition on the estimates, parallel analyses were conducted for symptoms of at least mild severity compared to absent symptoms after similar recoding of each symptom into a 4-value categorical variable. Accordingly, with stratification by symptom-specific bother, the 2 higher measures of each symptom-specific question of DAN-PSS-1 were compared to the respective 2 lower measures for the analyses of moderate/severe vs no/mild symptoms (Appendix 1).

For the analyzed groups of voiding and storage LUTS, men with at least one of the eligible symptoms for each group were included in analyses. For the analyses of moderate/severe vs absent/mild symptoms, daytime frequency was categorized as daytime voiding intervals of $\leq$2 vs >2 hours and nocturia as $\geq$3 vs 0–2 voids per night. Urgency and urge incontinence were categorized as "often or always" vs "rarely or never." For the analyses of at least mild vs absent symptoms, daytime frequency was categorized as daytime voiding intervals of $\leq$3 vs >3 hours and nocturia as $\geq$1 vs 0 voids per night. Urgency and urgency incontinence were categorized as "rarely, often or always" vs "never."

Registry Data Sources

The data on medications for BPH and LUTS were obtained from the prescription database of the Social Insurance Institution of Finland and covered alpha blockers, 5-alpha reductase inhibitors, antimuscarinics and mirabegron. The data on surgical procedures for BPH/LUTS according to the Nordic Classification of Surgical Procedures were obtained from the Care Register for Social Welfare and Health Care maintained by the National Institute for Health and Welfare (Appendix 2). The data on medications and surgery for BPH/LUTS were available for years 1994–2014. The men with prostate cancer were excluded from the study based on the data available from the Finnish Cancer Registry for years 1987–2015. The data of all-cause mortality were obtained from the Statistics Finland up to the end of 2018.

Statistical Analyses

For analyses of mortality, men providing answers to questions of LUTS at every survey from 1994 up to 2015 (or death) and for comorbidities at least in the baseline survey were considered eligible. For men with and without each symptom, mortality rates were calculated as events per 1,000 person-years stratified by year of birth and followup period. To adjust for confounders, Cox regression analyses were performed for each symptom. Various well-established risk factors for mortality were included as co-variables in multivariable models. These variables, of which many are also known to be associated

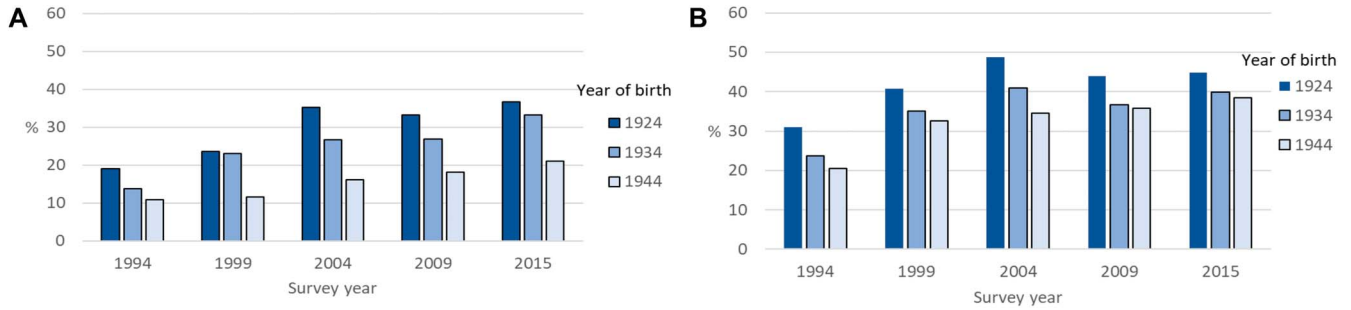

Figure. Periodic prevalence of moderate and severe voiding (*A*) and storage (*B*) LUTS by the year of birth in men.

with LUTS, included age and questionnaire-based assessments of marital status (married or cohabiting versus single or widowed), body mass index (BMI; ≤25 vs >25 kg/m^2), current smoking (yes/no), self-reported previous diagnosis of diabetes, hypertension, cardiac disease, pulmonary disease, cerebrovascular disease, neurological disorders and malignancies (other than prostate cancer). Each characteristic (except age) was treated as a time-dependent categorical variable. "Last observation carried forward" method[22] was used for comorbidities with missing values in the following rounds. Analyses were conducted for each urinary symptom to provide time-varying hazard ratios using variable values updated every 5 years (time-dependent analysis). Interaction terms for symptom-specific bother were evaluated in the regression models for each symptom. For all statistical analyses, SPSS® version 27 was used.

RESULTS

A total of 2,067 men (66% of those eligible) responded to the questionnaire in 1994, 2,133 (75%) in 1999, 1,905 (76%) in 2004, 1,424 (66%) in 2009 and 1,146 (66%) in 2015. For symptom-specific analyses, 935 men (30%) provided eligible data on daytime frequency, 941 (30%) on nocturia, 893 (77%) on urgency and 643 (55%) on urgency incontinence. At baseline, the prevalence of voiding and storage LUTS of at least moderate severity were 24% and 14%, respectively. At followup, ie in 2015 or at the last assessment before death, 39% of men had at least 1 voiding symptom and 28% at least 1 storage symptom of at least moderate severity (see figure, table 1 and supplementary table, https://www.jurology.com,). The majority of men had at least 1 mild voiding or storage symptom at followup: the prevalence was 74% and 75%, respectively.

At followup, 447 men (38%) had received medical treatment and 112 men (9.6%) surgical treatment for BPH/LUTS (supplementary table, https://www.jurology.com). Both in terms of dysfunction and bother, men with more severe LUTS were generally older than those with less severe LUTS. The majority of the assessed comorbidities were more frequent among men with more severe and bothersome LUTS (table 1 and supplementary table, https://www.jurology.com).

During the 24-year followup, 591 men (50.6%) died. Mortality was generally higher among symptomatic compared to asymptomatic men (tables 2 and 3). In age-adjusted analyses of moderate and severe LUTS disregarding bother, both voiding and storage LUTS were associated with increased mortality: the hazard ratios were 1.28 (95% CI 1.09−1.51) for voiding and 1.62 (95% CI 1.36−1.93) for storage LUTS (table 3). In multivariable-adjusted analyses of moderate and severe LUTS disregarding bother, both voiding and storage LUTS remained associated with increased mortality: the multivariable-adjusted HRs were 1.19 (95% CI 1.00−1.40) and 1.35 (95% CI 1.13−1.62), respectively (table 3). In multivariable-adjusted analyses disregarding symptom severity and bother, voiding LUTS were associated with decreased mortality while storage LUTS showed no significant association: the multivariable-adjusted HRs were 0.82 (95% CI 0.67−1.00) and 0.85 (95% CI 0.65−1.13), respectively (table 3). When comparing men with bothersome voiding and storage LUTS to those with nonbothersome LUTS, the mortality risk did not differ significantly between the 2 groups: the multivariable-adjusted HRs for nonbothersome vs bothersome symptoms of at least mild severity were 0.81 (95% CI 0.65−0.99) vs 0.88 (95% CI 0.67−1.16) for voiding and 0.80 (95% CI 0.60−1.06) vs 1.10 (95% CI 0.80−1.50) for storage LUTS (p for interaction between symptom severity and bother 0.773 for voiding and 0.953 for storage LUTS; table 3).

Moderate and severe daytime frequency and nocturia were significantly associated with increased mortality in the age-adjusted analyses disregarding bother: the age-adjusted HRs were 2.01 (1.57−2.59) for daytime frequency and 1.51 (1.15−1.97) for nocturia (tables 2 and 4). In multivariable-adjusted analyses disregarding bother, daytime frequency remained significantly associated with increased mortality (HR 1.75, 95% CI 1.36−2.26), while nocturia showed only a suggestive association: (HR 1.28, 95% CI 0.98−1.68; table 4). However, in multivariable-adjusted analyses

Table 1. *Characteristics of men with moderate and severe LUTS by level of bother at baseline (1994)*

	No. Men (%)		No. Voiding Symptoms (%)*				No. Storage Symptoms (%)†			
			Nonbothersome‡		Bothersome§		Nonbothersome‡		Bothersome§	
Total	1,167	100	204	17.5	77	6.6	88	7.5	73	6.3
Yr of birth:										
1924	278	23.8	60	29.4	26	33.8	27	30.7	26	35.6
1934	392	33.6	66	32.4	27	35.1	27	30.7	27	37.0
1944	497	42.6	78	38.2	24	31.2	34	38.6	20	27.4
Marital status:										
Married/cohabiting	945	81.0	161	78.9	57	74.0	55	62.5	53	72.6
Single/divorced	179	15.3	26	12.7	16	20.8	19	21.6	16	21.9
Widowed	40	3.4	17	8.3	4	5.2	13	14.8	3	4.1
BMI (kg/m^2):										
≤25	401	34.4	74	36.3	27	35.1	26	29.5	25	34.2
25–30	554	47.5	95	46.6	43	55.8	40	45.5	35	47.9
>30	199	17.1	35	17.2	7	9.1	22	25.0	13	17.8
Current smoking	245	21.0	23	11.3	17	22.1	25	28.4	18	24.7
Medical conditions:										
Diabetes	88	7.5	53	26.0	15	19.5	23	26.1	21	28.8
Hypertension	344	29.5	98	48.0	37	48.1	50	56.8	33	45.2
Cardiac disease	216	18.5	90	44.1	36	46.8	43	48.9	43	58.9
Pulmonary disease	124	10.6	37	18.1	29	37.7	20	22.7	25	34.2
Cerebrovascular disease	63	5.4	27	13.2	13	16.9	12	13.6	10	13.7
Neurological disease	29	2.5	21	10.3	14	18.2	6	6.8	13	17.8
Ca	32	2.7	19	9.3	8	10.4	6	6.8	8	11.0
Medical treatment for BPH/LUTS	447	38.3	98	48.0	45	58.4	44	50.0	38	52.1
Surgery for BPH/LUTS	112	9.6	29	14.2	18	23.4	14	50.0	21	28.8

* Any voiding or post-voiding symptom of at least moderate severity.
† Any storage symptom of at least moderate severity.
‡ No or mild bother.
§ Moderate or severe bother.

disregarding symptom severity and bother, both daytime frequency and nocturia were associated with increased mortality: the multivariable-adjusted HRs were 1.31 (95% CI 1.09–1.58) and 1.52 (95% CI 1.21–1.91), respectively (table 4). Excess mortality associated with bothersome daytime frequency and nocturia tended to be slightly higher: the multivariable-adjusted HRs for nonbothersome vs bothersome symptoms of at least mild severity were 1.18 (95% CI 0.97–1.44) vs 1.86 (95% CI 1.41–2.47) for daytime frequency and 1.46 (95% CI 1.16–1.85) vs 1.88 (95% CI 1.38–2.58) for nocturia, respectively. However, the mortality risk did not differ significantly between the 2 groups (p for interaction between symptom severity and bother 0.165 for daytime frequency and 0.515 for nocturia; table 4).

In age-adjusted analyses of moderate and severe urgency and urgency incontinence disregarding bother, urgency alone showed only a suggestive association with increased mortality (HR 1.27, 95% CI 0.99–1.64), while urgency incontinence showed a particularly strong association (HR 2.15, 95% CI 1.41–3.26; table 5). In multivariable-adjusted analyses, association of urgency incontinence with increased mortality remained undiminished (HR 2.19, 95% CI 1.42–3.37; table 5). In multivariable-adjusted analyses disregarding symptom severity and bother, neither urgency nor urgency incontinence was associated with mortality (table 5).

DISCUSSION

During a followup spanning 2 decades, the study found a 1.2-fold increased risk of death among men with moderate or severe voiding LUTS and a 1.4-fold risk among men with storage LUTS. When including also mild symptoms, the mortality risk was reduced to 0.8-fold among men with any voiding LUTS and to 0.9-fold, among men with storage LUTS. However, our findings showed a 1.3-fold increased risk of death among men with daytime frequency and a 1.5-fold risk among men with nocturia independently of symptom severity. This suggests considering daytime voiding interval of 3 hours or less and any nighttime voiding as patient-important especially when appearing as persistent symptoms. Furthermore, the analyses showed a substantially increased 2.2-fold risk of death among men with frequent urgency incontinence.

For clinicians, the analyses show that moderate and severe male LUTS in general are good indicators of poor health whereas mild LUTS can be considered as a normal part of healthy aging with an exception in cases of persistent daytime frequency and nocturia. While the association between LUTS and mortality is largely explained by the comorbidities in men with LUTS, the fact that the association remained even after adjustment for age and comorbidity shows that other, currently unidentified factors increasing the risk of death are

Table 2. *Mortality rates among men with and without daytime frequency and nocturia by age and followup period*

	Daytime Frequency						Nocturia					
	No/Mild*			Moderate/Severe†			No/Mild‡			Moderate/Severe§		
Yr of Birth	No. at Risk	No. Deaths	IR (95% CI)‖	No. at Risk	No. Deaths	IR (95% CI)‖	No. at Risk	No. Deaths	IR (95% CI)‖	No. at Risk	No. Deaths	IR (95% CI)‖
Followup 1994–1998												
1924	186	67	85.6 (67.4–108.7)	29	12	98.6 (56.0–173.6)	200	70	39.9 (31.6–50.4)	23	11	83.6 (46.3–150.9)
1934	279	19	14.1 (9.0–22.0)	26	6	48.5 (21.8–108.0)	293	23	11.8 (7.8–17.7)	16	4	25.6 (9.6–68.3)
1944	376	29	16.0 (11.1–23.0)	39	2	10.7 (2.7–42.6)	403	30	22.1 (15.4–31.5)	6	1	31.8 (4.5–225.6)
Followup 1999–2003												
1924	119	45	88.5 (66.1–118.6)	17	11	173.1 (95.8–312.5)	126	49	90.9 (68.7–120.2)	16	10	167.5 (90.1–311.3)
1934	264	32	25.7 (18.2–36.4)	16	4	55.9 (21.0–149.0)	260	35	28.7 (20.6–40.0)	22	4	39.6 (14.9–105.4)
1944	363	11	6.1 (3.4–11.1)	21	2	19.7 (4.9–78.7)	370	12	6.6 (3.7–11.6)	8	0	
Followup 2004–2008												
1924	69	24	82.8 (55.5–123.5)	11	9	268.8 (139.9–516.6)	67	26	95.6 (65.1–140.4)	16	5	70.7 (29.4–169.8)
1934	187	34	32.4 (23.2–45.4)	21	8	78.3 (39.1–156.5)	188	34	32.4 (23.1–45.3)	21	6	54.8 (24.6–122.1)
1944	352	18	10.4 (6.6–16.5)	19	3	34.4 (11.1–106.7)	355	21	12.1 (7.9–18.5)	11	0	
Followup 2009–2014												
1924	44	19	86.7 (55.3–136.0)	3	1	57.6 (8.1–408.6)	44	22	106.7 (70.3–162.1)	8	4	101.7 (38.2–271.0)
1934	187	34	32.4 (23.2–45.4)	21	8	78.3 (39.1–156.5)	188	34	32.4 (23.1–45.3)	21	6	54.8 (24.6–122.1)
1944	333	31	16.3 (11.4–23.1)	17	1	10.4 (1.5–73.5)	331	32	16.9 (11.9–23.9)	14	3	41.4 (13.4–128.5)
Followup 2015–2018												
1924	17	9	103.5 (53.8–198.9)	2	0		20	10	158.3 (85.2–294.3)	6	3	141.3 (45.6–438.0)
1934	153	18	30.7 (19.3–48.7)	13	6	152.3 (68.4–339.1)	145	17	30.6 (19.1–49.3)	24	6	72.3 (32.5–160.9)
1944	304	15	12.7 (7.6–21.0)	14	3	57.9 (18.7–179.5)	281	11	10.0 (5.5–18.1)	29	2	17.7 (4.4–70.8)

* Daytime voiding interval >2 hours.
† Daytime voiding interval ≤2 hours.
‡ 0–2 voids per night.
§ ≥3 voids per night.
‖ Incidence rate of deaths per 1,000 person-years (95% CI).

Table 3. *Association of voiding and storage LUTS with mortality by symptom severity and bother*

	Voiding Symptoms				Storage Symptoms			
	Any*		Moderate/Severe†		Any‡		Moderate/Severe§	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Unadjusted:‖								
Bother:								
No/mild	0.80	0.65—0.99	1.36	1.13—1.65	1.11	0.84—1.48	1.80	1.39—2.33
No/any	0.85	0.69—1.04	1.40	1.19—1.65	1.25	0.95—1.65	2.01	1.69—2.39
Moderate/severe	1.07	0.82—1.41	1.46	1.15—1.85	1.93	1.42—2.63	2.15	1.75—2.65
Adjusted by age:								
Bother:								
No/mild	0.81	0.66—1.00	1.26	1.04—1.52	0.84	0.63—1.11	1.43	1.10—1.85
No/any	0.84	0.69—1.03	1.28	1.09—1.51	0.92	0.70—1.21	1.62	1.36—1.93
Moderate/severe	1.01	0.77—1.32	1.33	1.05—1.68	1.30	0.96—1.78	1.76	1.43—2.16
Adjusted by age and comorbidity:¶								
Bother:								
No/mild	0.81	0.65—0.99	1.22	1.01—1.48	0.80	0.60—1.06	1.20	0.92—1.56
No/any	0.82	0.67—1.00	1.19	1.00—1.40	0.85	0.65—1.13	1.35	1.13—1.62
Moderate/severe	0.88	0.67—1.16	1.12	0.88—1.43	1.10	0.80—1.50	1.46	1.18—1.81

* Any voiding or post-voiding symptom of at least mild severity.
† Any voiding or post-voiding symptom of at least moderate severity.
‡ Any storage symptom of at least mild severity.
§ Storage symptom of at least moderate severity.
‖ Cox regression for mortality in presence vs absence of symptoms by symptom-specific bother.
¶ BMI, marital status, smoking, diabetes, hypertension, cardiac disease, pulmonary disease, cerebrovascular disease, neurological disease and cancer.

also involved. Furthermore, although increased bother and impaired coping skills may be associated with issues in symptomatic men's general health, mortality did not significantly differ between men with bothersome and nonbothersome LUTS.

Strengths and Limitations

The strengths of the study include analysis of LUTS-associated mortality through repeated assessments to distinguish the long-term patient-important LUTS from short-term fluctuating symptoms, the rigorous symptom definitions based on a validated questionnaire and the reliable registry data on mortality. Rather than relying on composite scores to assess the overall LUTS status, the present study investigated individual LUTS as markers of ill health. To our knowledge, the duration of the followup is the longest to date among the LUTS-association studies. Furthermore, as previous estimates on LUTS-associated mortality are available predominantly for nocturia only,[12]

Table 4. *Association of daytime frequency and nocturia with mortality by symptom severity and bother*

	Daytime Frequency Symptoms				Nocturia Symptoms			
	Any*		Moderate/Severe†		Any‡		Moderate/Severe§	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Unadjusted:‖								
Bother:								
No/mild	1.49	1.23—1.82	2.18	1.55—3.06	2.16	1.72—2.72	2.27	1.52—3.41
Any	1.70	1.42—2.03	2.42	1.88—3.10	2.35	1.88—2.93	2.35	1.80—3.06
Moderate/severe	2.61	1.99—3.44	2.70	1.93—3.79	3.63	2.69—4.90	2.40	1.73—3.34
Adjusted by age:§								
Bother:								
No/mild	1.25	1.02—1.52	1.85	1.32—2.60	1.49	1.18—1.88	1.30	0.87—1.96
Any	1.41	1.18—1.69	2.01	1.57—2.59	1.58	1.26—1.98	1.51	1.15—1.97
Moderate/severe	2.15	1.63—2.83	2.20	1.57—3.09	2.19	1.61—2.98	1.67	1.20—2.34
Adjusted by age and comorbidity:¶								
Bother:								
No/mild	1.18	0.97—1.44	1.63	1.15—2.30	1.46	1.16—1.85	1.10	0.73—1.65
Any	1.31	1.09—1.58	1.75	1.36—2.26	1.52	1.21—1.91	1.28	0.98—1.68
Moderate/severe	1.86	1.41—2.47	1.90	1.34—2.68	1.88	1.38—2.58	1.43	1.02—2.01

* Daytime voiding interval $\leq$3 hours.
† Daytime voiding interval $\leq$2 hours.
‡ $\geq$1 void per night.
§ $\geq$3 voids per night.
‖ Cox regression for mortality in presence vs absence of symptoms by symptom-specific bother.
¶ BMI, marital status, smoking, diabetes, hypertension, cardiac disease, pulmonary disease, cerebrovascular disease, neurological disease and cancer.

Table 5. *Association of urgency and urgency incontinence with mortality by symptom severity and bother*

	Urgency Symptoms				Urgency Incontinence Symptoms			
	Any*		Moderate/Severe†		Any‡		Moderate/Severe§	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Unadjusted:‖								
Bother:								
No/mild	1.04	0.83–1.30	1.42	0.91–2.21	1.16	0.92–1.47	1.28	0.32–5.14
Any	1.15	0.93–1.43	1.63	1.27–2.10	1.28	1.04–1.58	2.33	1.53–3.55
Moderate/severe	1.69	1.27–2.24	1.73	1.30–2.30	1.59	1.19–2.14	2.52	1.62–3.91
Adjusted by age:								
Bother:								
No/mild	0.95	0.76–1.18	0.95	0.61–1.48	1.12	0.88–1.41	1.33	0.33–5.36
Any	1.04	0.84–1.28	1.27	0.99–1.64	1.21	0.98–1.48	2.15	1.41–3.26
Moderate/severe	1.39	1.05–1.84	1.45	1.09–1.93	1.42	1.06–1.90	2.28	1.47–3.52
Adjusted by age and comorbidity:¶								
Bother:								
No/mild	0.93	0.74–1.16	0.92	0.58–1.43	1.07	0.84–1.36	1.65	0.41–6.69
Any	0.98	0.79–1.21	1.08	0.84–1.41	1.10	0.89–1.36	2.19	1.42–3.37
Moderate/severe	1.19	0.89–1.59	1.17	0.87–1.57	1.17	0.86–1.59	2.26	1.44–3.53

* Urgency present rarely, often or always.
† Urgency present often or always.
‡ Urgency incontinence present rarely, often or always.
§ Urgency incontinence present often or always.
‖ Cox regression for mortality in presence vs absence of symptoms by symptom-specific bother.
¶ BMI, marital status, smoking, diabetes, hypertension, cardiac disease, pulmonary disease, cerebrovascular disease, neurological disease and cancer.

TAMUS is the first to provide estimates also for several concomitant daytime LUTS.[17]

The limitations of the study include the reduction of eligible participants due to eligibility criteria, restricting the analyses to only men participating in every survey round, thus increasing the risk of selection bias. Due to unavailability of bladder diaries, our study was unable to further characterize the association between urinary frequency and mortality, ie if daytime frequency and nocturia were due to global/nocturnal polyuria, reduced bladder capacity or mixed etiology.[23] Finally, in spite of extensively adjusted analyses, the estimates are inevitably at risk of some residual confounding.

Implications of Findings

The evidence available suggests the treatment of male LUTS improves quality of life, albeit limited to studies with short followup.[24,25] To date, no randomized trials have examined the impact of treatment of LUTS on morbidity or mortality. Clinicians traditionally consider mainly prostatic obstruction and the associated risk of urinary retention potentially leading to renal failure as high-risk LUTS. However, male LUTS are generally benign and only rarely progress to hazardous urinary obstruction.[7,26,27] Although male LUTS have been proposed as risk factors for morbid events,[10,28,29] the associations between LUTS and mortality should be generally considered as proxies of ill health.[11,12] This indicates the importance of assessing the general health, risk factors and major comorbidities among men with LUTS. The roles of daytime frequency and nocturia as mortality risk factors independently of symptom severity indicates them as particularly useful markers of male ill health. This highlights the importance of including these particular symptoms in the assessment of male LUTS and to take into account the various etiologic factors affecting functional bladder capacity and diuresis such as vascular insufficiency of the pelvic floor due to atherosclerosis, systemic inflammation in metabolic syndrome and fluid shifts caused by cardiac failure as well as various factors impairing sleep.[10–12] Furthermore, the particularly strong association between frequent urgency incontinence and mortality suggests the significance of urinary urgency in late life morbidity and frailty including factors such as white matter hyperintensity load and microvascular disease.[30]

While traditionally only bothersome LUTS have been considered patient-important and to require treatment, as a novel finding, the present study addressed a link between LUTS and mortality independently of associated bother. The lack of association between symptom bother and mortality possibly reinforces the very subjective nature of bother as a construct compared to more objectively measured symptom severity.

CONCLUSIONS

Moderate and severe male LUTS are potential markers of ill health and risk factors for mortality among middle-aged and elderly men. The bother caused by male LUTS is not a relevant predictor of mortality.

Appendix 1. *Assessments and definitions of LUTS*

The question assessing daytime frequency was "What is the longest interval between each voiding, from when you wake up until you go to bed?" with response options of "more than 3 hours," "2–3 hours," "1–2 hours," "less than 1 hour." The question assessing nocturia was "How many times do you have to urinate per night?" with response alternatives of "none," "1 or 2 times," "3 or 4 times," "5 times or more." The question assessing urgency in 1994 was "Is your need to urinate so urgent that it is difficult to hold it back until you reach the toilet?" and was since modified for the subsequent rounds as "Do you experience an imperative (strong) urge to urinate?" with response alternatives of "never—rarely—often—always." The question assessing urgency incontinence was "Is the urge to urinate so strong that urine starts to flow before you reach the toilet?" with response alternatives of "never—rarely—often—always."

Appendix 2. *Surgical procedures included in the study*

Surgical Procedure	Nordic Classification of Surgical Procedures
Transvesical prostatectomy	KED00
Retropubic prostatectomy	KED10
Transurethral resection of prostate	KED22
Transurethral incision of prostate	KED33
Visual laser resection of prostate	KED52
Transurethral needle ablation of prostate	KED62
Transurethral microwave therapy of prostate	KED72
Transurethral electrovaporization of the prostate	KED76
Percutaneous cryotherapy of prostate	KED80
Other partial excision of prostate	KED96
Other transurethral partial excision of prostate	KED98

REFERENCES

1. Bosch JL, Bangma CH, Groeneveld FP et al: The long-term relationship between a real change in prostate volume and a significant change in lower urinary tract symptom severity in population-based men: the Krimpen study. Eur Urol 2008; **53:** 819.
2. Coyne KS, Kaplan SA, Chapple CR et al: Risk factors and comorbid conditions associated with lower urinary tract symptoms: EpiLUTS. BJU Int, suppl., 2009; **103:** 24.
3. Gacci M, Vignozzi L, Sebastianelli A et al: Metabolic syndrome and lower urinary tract symptoms: the role of inflammation. Prostate Cancer Prostatic Dis 2013; **16:** 101.
4. Sexton CC, Coyne KS, Kopp ZS et al: The overlap of storage, voiding and postmicturition symptoms and implications for treatment seeking in the USA, UK and Sweden: EpiLUTS. BJU Int, suppl., 2009; **103:** 12.
5. Irwin DE, Milsom I, Kopp Z et al: Prevalence, severity, and symptom bother of lower urinary tract symptoms among men in the EPIC study: impact of overactive bladder. Eur Urol 2009; **56:** 14.
6. Agarwal A, Eryuzlu LN, Cartwright R et al: What is the most bothersome lower urinary tract symptom? Individual- and population-level perspectives for both men and women. Eur Urol 2014; **65:** 1211.
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. Platz EA, Joshu CE, Mondul AM et al: Incidence and progression of lower urinary tract symptoms in a large prospective cohort of United States men. J Urol 2012; **188:** 496.
9. Kok ET, Groeneveld FPMJ, Busschbach JJV et al: Influence of coping styles on quality of life in men with new and increasing lower urinary tract symptoms. The Krimpen Study in community-dwelling men. Urol Int 2007; **79:** 226.
10. Gacci M, Corona G, Sebastianelli A et al: Male lower urinary tract symptoms and cardiovascular events: a systematic review and meta-analysis. Eur Urol 2016; **70:** 788.
11. Suskind AM: Frailty and lower urinary tract symptoms. Curr Urol Rep 2017; **18:** 67.
12. Pesonen JS, Cartwright R, Vernooij RWM et al: The impact of nocturia on mortality: a systematic review and meta-analysis. J Urol 2020; **203:** 486.
13. Coyne KS, Wein AJ, Tubaro A et al: The burden of lower urinary tract symptoms: evaluating the effect of LUTS on health-related quality of life, anxiety and depression: EpiLUTS. J Urol Int 2009; **10:** 4.
14. Rozanski A, Bavishi C and Kubzansky LD: Association of optimism with cardiovascular events and all-cause mortality: a systematic review and meta-analysis. JAMA Netw Open 2019; **2:** e1912200.
15. Koskimaki J, Hakama M, Huhtala H et al: Prevalence of lower urinary tract symptoms in Finnish men: a population-based study. Br J Urol 1998; **81:** 364.
16. Häkkinen JT, Hakama M, Shiri R et al: Incidence of nocturia in 50 to 80-year-old Finnish men. J Urol 2006; **176:** 2541.
17. Åkerla J, Pesonen JS, Pöyhönen A et al: Impact of lower urinary tract symptoms on mortality: a 21-year follow-up among middle-aged and elderly Finnish men. Prostate Cancer Prostatic Dis 2019; **22:** 317.
18. Hansen BJ, Flyger H, Brasso K et al: Validation of the self-administered Danish Prostatic Symptom Score (DAN-PSS-1) system for use in benign prostatic hyperplasia. Br J Urol 1995; **76:** 451.
19. D'Ancona C, Haylen B, Oelke M et al: The International Continence Society (ICS) report on the terminology for adult male lower urinary tract and pelvic floor symptoms and dysfunction. Neurourol Urodyn 2019; **38:** 433.
20. John G, Bardini C, Combescure C et al: Urinary incontinence as a predictor of death: a systematic review and meta-analysis. PLoS One 2016; **11:** e0158992.
21. O'Leary MP: Validity of the "bother score" in the evaluation and treatment of symptomatic benign prostatic hyperplasia. Rev Urol 2005; **7:** 1.
22. Little RJ and Rubin DB: Statistical Analysis with Missing Data, 2nd ed. New York: Wiley 2002.
23. Hashim H, Blanker MH, Drake MJ et al: International Continence Society (ICS) report on the terminology for nocturia and nocturnal lower urinary tract function. Neurourol Urodyn 2019; **38:** 499.
24. Cornu JN, Ahyai S, Bachmann A et al: A systematic review and meta-analysis of functional outcomes and complications following transurethral procedures for lower urinary tract symptoms resulting from benign prostatic obstruction: an update. Eur Urol 2015; **67:** 1066.
25. Fusco F, Creta M, De Nunzio C et al: Alpha-1 adrenergic antagonists, 5-alpha reductase inhibitors, phosphodiesterase type 5 inhibitors, and phytotherapic compounds in men with lower urinary tract symptoms suggestive of benign prostatic obstruction: a systematic review and meta-analysis of urodynamic studies. Neurourol Urodyn 2018; **37:** 1865.

26. Thomas AW, Cannon A, Bartlett E et al: The natural history of lower urinary tract dysfunction in men: minimum 10-year urodynamic follow-up of untreated bladder outlet obstruction. BJU Int 2005; **96:** 1301.

27. Bates TS, Sugiono M, James ED et al: Is the conservative management of chronic retention ever justified? BJU Int 2003; **92:** 581.

28. Noguchi N, Chan L, Cumming RG et al: A systematic review of the association between lower urinary tract symptoms and falls, injuries, and fractures in community-dwelling older men. Aging Male 2016; **19:** 168.

29. Pesonen JS, Vernooij RW, Cartwright R et al: The impact of nocturia on falls and fractures: a systematic review and meta-analysis. J Urol 2020; **203:** 674.

30. Gibson W, Johnson T, Kirschner-Hermanns R et al: Incontinence in frail elderly persons: report of the 6th International Consultation on Incontinence. Neurourol Urodyn 2021; **40:** 38.