





ORIGINAL RESEARCH ARTICLE

Do men adapt to lower urinary tract symptoms? An 11-year longitudinal study of male urinary urgency and associated bother

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ABSTRACT

Objective: The study objective is to evaluate prognosis and predictors of bother caused by urinary urgency among middle-aged and older men.

Material and methods: A population-based sample of men born in 1974, 1964, 1954, 1944, 1934 and 1924 was followed-up from 2004 to 2015. The course of urgency and associated bother was evaluated with the Danish Prostatic Symptom Score at baseline and follow-up. Logistic regression was utilized to explore risk factors of increased bother at follow-up.

Results: A total of 2,480 men (39%) who had responded at baseline and follow-up were included in the study. Of them, 1,056 men (43%) had persistent mild urgency and 132 men (5%) persistent moderate or severe urgency at follow-up. The proportions of men experiencing at least moderate bother due to persistent urgency at follow-up were 6% (95% confidence interval 4.5–7.3) of those with mild and 79% (71.7–85.9) of the men with moderate or severe urgency. In multivariable-adjusted logistic regression, moderate to severe urgency was strongly associated with bother (odds ratio, OR 55.2, 95% CI 32.1–95.2). Other predictors of bother included cardiac disease (OR 1.8, 95% CI 1.0–31.1), pulmonary disease (OR 1.9, 95% CI 1.1–3.5) and medical treatment (OR 2.7, 95% CI 1.6–4.6).

Conclusions: Most men with urinary urgency have mild symptoms and bother. Only one out of five men with persistent moderate or severe urgency adapt to the symptoms. Men with a history of medical treatment for lower urinary tract symptoms (LUTS) or impaired cardiopulmonary health are more likely to experience bother from urinary urgency.

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KEYWORDS

Lower urinary tract symptoms; urinary bladder, overactive; cohort studies; observational studies

Introduction

The prevalence of various lower urinary tract symptoms (LUTS) increases with age [1]. Progression of male LUTS is often associated with age-related changes in the morphology and function of the lower urinary tract, such as benign prostatic hyperplasia (BPH) [2]. Furthermore, the etiology of LUTS is typically multifactorial and the course of various symptoms is often modified by comorbidities and behavioral factors, such as metabolic syndrome, diabetes [3, 4].

LUTS can result from dysfunction during bladder filling (storage), emptying (voiding) or post-micturition phase, and symptoms often occur in combination [5, 6]. Responses to LUTS treatment vary widely due to a broad spectrum of dysfunction and differences in the perception of bother. In addition, various comorbidities may pose challenges to the tolerability of treatments, especially among frail elderly patients [7, 8]. Furthermore, despite initial treatment response, many symptoms tend to recur [9].

Cross-sectional studies have shown substantial differences in bother from various male LUTS [5, 6, 10]. However, evidence on long-term adaptation and impact of watchful waiting on symptom perception is, to date, very limited [1, 11, 12]. As only bothersome symptoms are considered patient-important, data on long-term coping with various symptoms from longitudinal studies would serve as an important aid for shared decision making about treatments. Therefore, we measured the longitudinal changes in bother caused by one of the most common male LUTS, urinary urgency, in a population-based cohort of middle-aged and older men.

Materials and methods

This report is based on the population-based Tampere Aging Male Urologic Study (TAMUS). Details of the study protocol have been presented previously [13, 14]. The baseline survey for this analysis was conducted in 2004, with the target population

consisting of all male residents in Tampere and 11 surrounding rural communities aged 30, 40, 50, 60, 70 and 80 years. For the follow-up, the same men were approached again in 2015. In the initial survey, men eligible for the study were identified from the comprehensive, nationwide Population Register Centre. For the 2015 repeat survey, updated addresses were acquired from the Population Register Centre. Postal questionnaires were used to collect study information comprising items on severity and bother of LUTS, as well as sociodemographic, anthropometric and behavioral factors and medical conditions. The Tampere University Hospital Committee of Research Ethics approved the study protocol (tracking number #99050).

Symptom assessment

The LUTS were assessed using the Danish Prostatic Symptom Score (DAN-PSS-1) – a validated questionnaire consistent with the International Continence Society definitions [15, 16]. The current study included men with responses available to the assessments of urgency in 2004 and 2015 with no further exclusion criteria. The symptom-specific DAN-PSS question translated back from Finnish to English was as follows: 'Do you experience a sudden need to void?'. The response options were 'never – rarely – often – always'. Respectively, the classification of bother was based on four response options as follows: 'not at all – a little – moderately – very much'. In terms of both symptom severity and bother, each symptom was scored as 'absent (0 points)', 'mild (1 point)', 'moderate (2 points)' and 'severe (3 points)'. The preceding 2-week period was defined as the reference time frame for the questions.

Registry data sources

To explore care seeking trends among men with LUTS, data on alpha blockers, 5-alpha reductase inhibitors, antimuscarinics and mirabegron medications for BPH and LUTS were obtained from the comprehensive nationwide prescription database of the Social Insurance Institution of Finland. 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 (HILMO) maintained by the National Institute for Health and Welfare (Table S1).

Statistical analyses

To examine the association between the changes of urgency and bother over time, questionnaire surveys were conducted in 2004 and 2015 for the cohort of men aged 30–80 years at baseline. In data analyses, prevalence of no or mild (0–1 DAN-PSS point) and moderate to severe bother (≥2 DAN-PSS points) was estimated for increased, decreased and persistent urgency at follow-up for the age groups of 30–40, 50–60 and 70–80 years (at baseline). To further assess possible exposure-response relationship, urgency severity and bother were cross-tabulated to illustrate frequencies of symptom progression (an increase of 1 vs. ≥2 DAN-PSS points from baseline to follow-up), symptom

resolution (a decrease of 1 vs. ≥2 DAN-PSS points at follow-up), and unchanged symptom status (similar DAN-PSS score at baseline and follow-up).

Multivariable logistic regression was utilized to explore the impact of various potential determinants on adaptation to urgency among men with persistent urgency at follow-up. A subgroup analysis was conducted for men with persistent mild urgency to explore potential predictors of bother independently of symptom severity. Selection of co-variables was based on previous literature on potential risk factors of bothersome male LUTS [3, 4, 17, 18] and factors with potential impact on psychosocial coping and general symptom perception [19, 20]. For comparison, separate analyses were conducted to explore the association of an identical set of covariables with urgency independently of bother. Statistical analyses were performed using Stata 12.1 (StataCorp, College Station, TX, USA).

Results

In 2004, the participation proportion was 59% (4,384 of 7,470 men) and in 2015, 48% (3,063 of 6,358 men). A total of 2,480 men (39%) who had responded to the assessments of urgency both at baseline and follow-up were included in the analysis. Urinary urgency was the most common symptom of the 12 assessed LUTS with prevalence of 66% in 2004 and 73% in 2015 (Figure 1).

Although the majority of men remained married or cohabiting at 11-year follow-up, the prevalence of single or widowed men increased in the oldest age group: the proportions of single/widowed men were 24%, 24% and 29% in the age groups of 30-40, 50-60 and 70-80 (in 2004) at the follow-up in 2015. Smoking showed a decreasing trend in all age groups while the majority of the assessed comorbidities increased with age with exceptions of obesity and depression. The prevalence of previous medical treatment of BPH/LUTS in 2004 were 1%, 6% and 29% among men aged 30-40 years, 50-60 years and 70-80 years, respectively. In 2015, the respective proportions were 6%, 28% and 52%. In 2004, none of the men aged 30-40 had a previous history of operative treatment for BPH/LUTS, while among men aged 50-60 and 70-80, the proportions were 0.3% and 5%. In 2015, the proportions of men having received operative treatment were 0.1%, 4% and 11% in the three respective age groups (Table 1).

Association between symptom severity and bother

Frequency of persistent urgency increased with age (Figure 2). Of the 1,056 men (43%) with persistent mild urgency at follow-up, 6% (4.5–7.3) experienced moderate or severe bother with no differences between the age groups. Of the 132 men (5%) with persistent moderate or severe urgency at follow-up, 79% (71.7–85.9) experienced moderate or severe bother with no differences between the age groups (Table 2).

Fluctuation in urgency severity and bother was common, with either increase or decrease occurring in the majority of affected men (Figure 2). Of the 465 men (17%) with mild

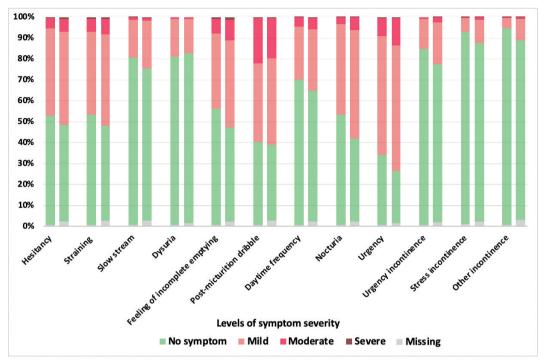


Figure 1. Periodical prevalence of LUTS in 2004 (left) and 2015 (right).

urgency at follow-up but not at baseline, the proportion of men experiencing moderate to severe bother at follow-up was highest in the oldest age group: 17% (8.4–25.8) among men aged 70–80 years (in 2004) compared with approximately 5% in the younger age groups. The proportion of men with moderate to severe bother at follow-up due to increased urgency was lowest in the youngest age group: 31% (15.6–45.9) among men aged 30–40 years, with 63% (53.0–72.0) in those aged 50–60 and 48% (35.0–61.5) at ages 70–80 years (in 2004). Similarly, the proportion of men reporting moderate to severe bother in spite of decreased urgency at follow-up was lowest in the

youngest age group: 6% (0.0–17.3), while it was 19%–33% in the older men (Table 2). Between 2004 and 2014, a total of 607 men (27%) received either medication or surgery. Among the treated men, only 8% (6.2–10.7) experienced symptom resolution from at least moderate urgency to no or mild urgency. Among the 50 men with decreased urgency at follow-up and a history of LUTS treatment, the proportion of those reporting moderate to severe bother at follow-up was non-significantly higher compared to the 40 untreated men reporting bother in spite of decreased urgency: 28% (16.2–42.5) versus 13% (4.2–26.8).

Table 1. Characteristics of the cohort by age group at study baseline in 2004.

	Age at baseline											
			50–60 years (n = 1,193)				70–80 years (n = 392)					
	20	004	20	15	2004		2015		2004		2015	
	n	%	n	%	n	%	n	%	n	%	n	%
Single or widowed	276	30.9	213	24.1	260	21.8	284	23.8	62	15.8	114	29.1
Current smoker	240	26.8	177	19.8	301	25.2	208	17.4	28	7.1	22	5.6
BMI ≥30	106	12.0	170	19.0	232	19.6	266	22.6	61	15.9	49	12.8
Diabetes	13	1.5	36	4.0	71	6.0	201	16.9	50	12.8	98	25.0
Hypertension	97	10.8	149	16.7	414	34.7	534	44.8	212	54.1	222	56.6
Cardiac dis.	12	1.3	32	4.3	99	8.3	234	19.6	133	33.9	207	52.8
Pulmonary dis.	33	3.7	34	3.8	118	9.9	114	9.6	79	20.2	70	17.9
Cerebrovascular dis.	5	0.6	8	0.9	34	2.9	55	4.6	37	9.4	50	12.8
Neurological dis.	23	2.6	28	3.1	45	3.8	53	4.4	18	4.6	25	6.4
Cancer	10	1.1	21	2.4	32	2.7	116	9.7	54	13.8	88	22.5
Depression	77	8.6	98	11.0	109	9.1	92	7.7	21	5.4	27	6.9
LUTS medication ^a	4	0.5	53	5.9	70	5.9	339	28.4	115	29.3	205	52.3
LUTS operation ^b	0	0.0	1	0.1	4	0.3	43	3.6	20	5.1	41	10.5

LUTS: lower urinary tract symptoms.

^aIncludes alpha-blockers, 5-alpha reductase inhibitors and anticholinergics, no initiations of mirabegrone as first-line treatment during the follow-up (not available until 2013); ^bendoscopic and surgical procedures during the follow-up for benign prostatic hyperplasia and overactive bladder listed in Table S1.

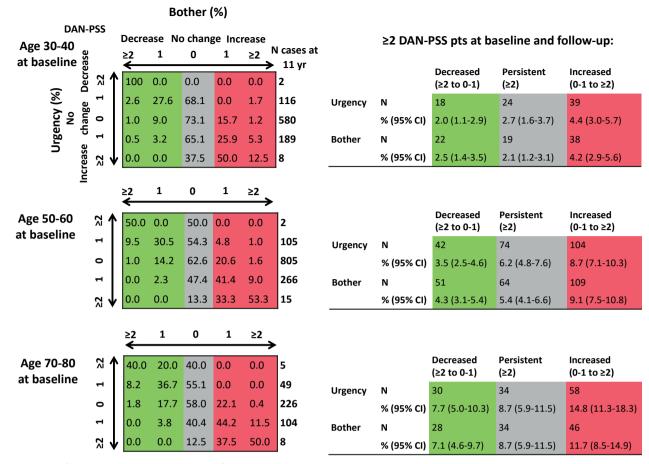


Figure 2. Course of urgency and associated bother at follow-up.

Table 2. Prevalence of bother among men with urgency at follow-up.

						Age	at baseline							
		30-	-40 years		50–60 years				70–80 ye	ars		All		
		N	%	95% CI	N	%	95% CI	Ν	%	95% CI	Ν	%	95% CI	
	Persist	ent urgenc	y of 1 DAN	PSS point a	t baseli	ne and follo	ow-up							
Bother at	All	303			578			175			1056			
follow-up	0-1	287	94.7	92.2-97.3	544	94.1	92.2-96.0	163	93.1	89.4-96.9	994	94.1	92.7-95.5	
(DAN-PSS	≥2	16	5.3	2.7-7.8	34	5.9	4.0-7.8	12	6.9	3.1-10.6	62	5.9	4.5-7.3	
points)	Persistent urgency of ≥2 DAN-PSS pts at baseline and follow-up													
	All	24			74			34			132			
	0-1	6	25.0	6.3-43.7	14	18.9	9.8-28.1	8	23.5	8.5-38.6	28	21.2	14.1-28.3	
	≥2	18	75.0	56.3-93.7	60	81.1	71.9–90.2	26	76.5	61.4-91.5	104	78.8	71.7-85.9	
	Incide	Incident urgency from 0 to 1 DAN-PSS point												
	All	174			215			76			465			
	0-1	167	96.0	93.0-98.9	203	94.4	91.3-97.5	63	82.9	74.2-91.6	433	93.1	90.8-95.4	
	≥2	7	4.0	1.1-7.0	12	5.6	2.5-8.7	13	17.1	8.4-25.8	32	6.9	4.6-9.2	
	Increased urgency from 0 to 1 to ≥2 DAN-PSS pts													
	All	39			104			58			201			
	0-1	27	69.2	54.1-84.4	39	37.5	28.0-47.0	30	51.7	38.5-65.0	96	47.8	40.8-54.7	
	≥2	12	30.8	15.6-45.9	65	62.5	53.0-72.0	28	48.3	35.0-61.5	105	52.2	45.3-59.2	
	Decreased urgency from ≥2 to 0–1 DAN-PSS pts													
	All	18			42			30			90			
	0-1	17	94.4	82.7-100	34	81.0	68.6-93.3	20	66.7	48.8-84.6	71	78.9	70.3-87.5	
	≥2	1	5.6	0.0-17.3	8	19.0	6.7-31.4	10	33.3	15.4-51.2	19	21.1	12.5-29.7	

Table 3. Predictors of bother among men with persistent urgency at follow-up – logistic regression.

	Bother ≥2 [DAN-PSS pts at	Odds ratio							
	follow-up		Una	djusted						
	%	95% CI	OR	95% CI	OR	95% CI	р			
All (n = 1,188)	14.0	12.0–15.9								
Urgency ≥2 DAN-PSS pts	78.8	71.7–85.9	59.5	35.6-100.6	55.2	32.1-95.2	< 0.001			
Age 50–60 ^a	14.4	11.7–17.1	1.1	0.8-1.5	0.8	0.4-1.4				
Age 70–80ª	18.2	12.9-23.5	1.5	1.0-2.2	0.5	0.2-1.2				
Single or widowed	16.6	12.4-20.8	1.3	0.9-1.9	0.9	0.5-1.5				
Obesity ^b	14.9	10.3-19.5	1.1	0.7-1.7	0.6	0.3-1.1				
Smoking ^c	13.8	9.0-18.6	1.0	0.6-1.5	0.9	0.5-1.7				
Diabetes	22.5	16.3-28.7	2.0	1.3-3.1	1.1	0.6-2.0				
Hypertension	17.0	13.9-20.1	1.6	1.1-2.3	1.2	0.7-2.0				
Cardiac dis.	21.5	16.6-26.4	2.1	1.4-3.0	1.8	1.0-3.1	0.042			
Pulmonary dis.	25.0	18.4-31.6	2.4	1.6-3.6	1.9	1.1-3.5	0.026			
Cerebrovasc. dis.	26.6	16.6-36.5	2.4	1.3-4.2	1.1	0.5-2.4				
Neurologic dis.	26.7	16.4-36.9	2.4	1.3-4.2	1.3	0.6-3.2				
Cancer	15.5	9.2-21.8	1.1	0.7-1.9	0.7	0.3-1.4				
Depression	26.3	19.2-33.4	2.6	1.7-3.9	1.6	0.9-3.0				
LUTS medication ^d	26.6	21.9-31.2	3.8	2.7-5.4	2.7	1.6-4.6	< 0.001			
LUTS operation ^e	29.6	17.0-42.2	2.8	1.4-5.2	0.9	0.3-2.5				

LUTS: lower urinary tract symptoms.

Predictors of bother among men with persistent urgency

In logistic regression including 1,188 men with persistent urgency, that is stable mild or at least moderately severe urgency at follow-up, several factors were significantly associated with bothersome urgency including: severity of urgency, age older than 70 years, previously diagnosed diabetes, hypertension, cardiac disease, pulmonary disease, cerebrovascular disease, neurologic disease, depression and previous treatment of LUTS with medication or operation. In multivariable-adjusted logistic regression, severity of urgency remained strongly associated with bother in addition to previously diagnosed cardiac and pulmonary disease and a history of medically treated LUTS: the adjusted odds ratios were 55.2 (32.1–95.2, p < 0.001), 1.8 (1.0–3.1, p = 0.042), 1.9 (1.1–3.5, p = 0.026) and 2.7 (1.6–4.6, p < 0.001), respectively (Table 3). In subgroup analysis including 1,056 men with persistent mild urgency, cardiac disease was borderline significantly associated with increased bother, while pulmonary disease and medically treated LUTS remained significantly associated: the adjusted odds ratios were 1.9 (1.0–3.5, p = 0.053), 2.0 (1.0–4.0, p = 0.036) and 2.7 (1.5– 4.9, p < 0.001), respectively (Table S2). For comparison, in multivariable-adjusted analysis of predictors of urgency independently of bother including all 2,480 men, older age, being single/widowed, previously diagnosed pulmonary disease as well as cerebrovascular disease, neurologic disease, depression and a history of medically treated LUTS were associated with at least moderately severe urgency at follow-up (Table S3).

Discussion

During the 11-year follow-up, approximately 60% of the men had mild, that is occasional urinary urgency and the vast

majority of them – over 90% – experienced no or mild bother. Furthermore, approximately 30% of the men younger than 50 years and up to 60% of men aged over 50 reported no or mild bother in spite of symptom progression. These findings suggest that mildly bothersome urgency can be considered a part of normal aging among men. However, in spite of high trends of care seeking for LUTS among older men - up to 50% of men aged over 70 having received medical treatment – the incidence of bothersome urgency increased with age suggesting treatment resistance due to frailty and comorbidity. The proportion of widowers and single men increases with age, but we found no evidence for an effect of marital status on bother. Among the few men – approximately 5% of the cohort – with urgency occurring frequently and as a long-term symptom, 80% experienced moderate or severe bother. Furthermore, approximately 10% of the men aged under 50 and up to 30% of men aged over 50 reported moderate or severe bother despite alleviated urgency at follow-up. This suggests that factors weakening men's coping with urgency and causing treatment resistance to become more common with age. In addition, men with a history of medical treatment for LUTS or impaired cardiopulmonary health were substantially more likely to experience bother due to urinary urgency even with mild symptoms.

Few longitudinal population-based studies have evaluated the relation between changes of LUTS and symptom-specific bother. The comparison of the findings across studies is challenging due to variation in follow-up times, symptom definitions, as well as their assessment tools. A Scottish study evaluated the changes of various LUTS and symptom-specific bother assessed with the American Urological Association Symptom Index (AUA-SI) from baseline to 5-year follow-up in men aged 40–79 years [1]. They found that increase in bother

 $^{^{\}circ}$ Age at baseline, reference group aged 30–40, $^{\circ}$ BMI \geq 30 at follow-up, $^{\circ}$ current smoker at follow-up, $^{\circ}$ includes alpha-blockers, 5-alpha reductase inhibitors and anticholinergics, no initiations of mirabegrone as first-line treatment during the follow-up (not available until 2013), $^{\circ}$ endoscopic and surgical procedures during the follow-up for benign prostatic hyperplasia and overactive bladder listed in Table S1.

was pronounced for all LUTS, and even a small increase in symptom level could cause a large increase in bother. Furthermore, the results suggested decreasing tolerance for symptoms over time. A US study utilized biennial assessments of symptoms with AUA-SI to evaluate changes of symptoms and associated bother during a 7-year follow-up among men aged 40-79 years [11]. Their results indicated that changes in symptom frequency and bother track closely together. However, some men did not report increased bother despite an increase in symptom frequency, which possibly represents adaption. Furthermore, a Japanese study used the International Prostatic Symptom score in a 15-year follow-up of men also aged 40-79 years [12]. Their study also showed a correlation between changes of LUTS and bother. In the previous studies, no detailed data on progression or resolution for symptom-specific bother in relation to changes of symptom severity was available for urinary urgency.

The strengths of our study include the rigorous symptom definitions based on a validated questionnaire and the comprehensive registry data on LUTS treatments. Instead of composite scores to assess the overall LUTS status, the present study investigated urgency separately, providing a patient-centered perspective for a symptom with major population-level burden, typically accompanied by various other LUTS and often considered when choosing treatments [10]. Furthermore, our study was able to utilize a long follow-up time with a broad age spectrum and, to our knowledge, is the first to explore predictors of urgency-specific bother in a longitudinal setting.

The main limitation of the study is the satisfactory, but suboptimal participation, being nearly 60% in 2004 and 50% in 2015. The proportion of eligible participants was further reduced to 39% due to inclusion criteria restricting the analyses only to men who had responded to the assessments of urgency both at baseline and follow-up, thus increasing the risk of selection bias. With the exception of LUTS treatments, the data on co-variables included in logistic regression were based on self-report and frequently imprecise and uncertain. Especially lower urinary tract malignancies, such as prostate cancer, would warrant inclusion in the analyses for their association with urgencyrelated bother. While detailed cancer data was not available, inclusion of any previously diagnosed cancer in the analyses can be justified by the impact of cancer diagnosis on men's general symptom perception [19]. Some of the included men had a history of treatments, potentially modifying their coping with symptoms. However, our objective was to explore the relation between long-term symptoms and bother, not the occurrence of symptoms (or bother) in itself. We did not consider it likely that BPH treatments would importantly modify the relation between dysfunction and bother and therefore decided not to consider them in the analysis. Further, the numbers of men with specific treatment were too small for a meaningful analysis. Furthermore, taking into account the fluctuating nature of LUTS, the single re-evaluation of symptoms is a limitation. As bother is intrinsically subjective and cannot be evaluated in an objective, the results on symptom adaptation based on self-reported bother should be interpreted cautiously. This highlights the

importance of a validated questionnaire in the assessments. While the long interval between symptom assessments can be regarded as a limitation, it can differentiate short-term fluctuation from long-term changes.

Understanding changes in symptom bother related to functional treatment response can guide clinical decision making. Treatment of urgency can be challenging due to uncertain course of bother, especially among older patients. Therefore, it is important to weigh the risks and benefits of the treatments and to consider the psychological aspects affecting men's tolerance to symptoms especially among frail older men. Although long-term data on the effects of medical and surgical treatments for male LUTS is lacking [21–24], several treatment options – also other than medical or surgical – are available. These include behavioral modification, as well as physical training for pelvic floor dysfunction, and especially among frail older men, functional incidental training, including prompted voiding, for impaired motility and toileting skills [25, 26].

In conclusion, the vast majority of men with urinary urgency present with mild symptoms and bother. However, only one out of five men with persistent moderate or severe urgency adapts to his symptoms. Symptomatic men with a history of cardiac or pulmonary disease or medical treatment for LUTS tend to present with worse coping skills in terms of urinary urgency. This highlights the importance of including the assessment of general health in the management of male LUTS. Future investigations should address the impact of preventative health strategies on bothersome urinary urgency.

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Disclosure of interest

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