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Incidence and Progression of Lower Urinary Tract Symptoms in a Large Prospective Cohort of US Men

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Abstract

Purpose—To support trials testing lifestyle interventions for lower urinary tract symptoms (LUTS), often a consequence of benign prostatic hyperplasia (BPH), we estimated LUTS incidence and progression rates in US men unselected for BPH.

Methods—We studied men in the Health Professionals Follow-up Study who we asked to report periodically by mailed survey whether they had had surgery or used medications for LUTS and to complete the International Prostate Symptom Score (IPSS) survey. For incidence, we included 25,879 men with an IPSS of 0–7 and no surgery history, who were followed 1992–2008. Incident “moderate or worse” LUTS (N=6,058) was defined as IPSS of ≥15, surgery, or medication use. “Modest or worse” LUTS was similarly defined but with IPSS ≥8 (N=11,352). For progression, we included 9,628 men with an IPSS of 8–14 and no surgery, who were followed from when they first reported an IPSS of 8–14 to 2008. Progression to “severe” LUTS (N=2,557) was defined as IPSS of ≥20, surgery, or medication use. We estimated age-specific and age-standardized rates.

Results—Incidence and progression rates increased with age (P-trend<0.0001); progression rates were higher than incidence rates. The age-standardized rates were: incidence of moderate to worse LUTS 18.5; incidence of modest to worse LUTS 40.5; and progression to severe LUTS 44.9 per 1,000 man-years.

Conclusions—LUTS incidence and progression rates are high and rise steeply as men age. These rates may be used for planning adequately powered trials to test lifestyle interventions for LUTS well before surgical or pharmacologic treatment is indicated.

Keywords

Lower urinary tract symptoms; incidence; progression; men

Research on lower urinary tract symptoms (LUTS) in men, often a consequence of benign prostatic hyperplasia (BPH), traditionally has focused on the development and testing of treatments for progressive disease.¹ The high prevalence of BPH and reliance on long-term medication use and surgery to treat symptoms has resulted in large healthcare costs.^{2, 3} One strategy for containing costs while optimizing care is risk stratification for treatment

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decision-making in the primary care setting.⁴ However, in the era of healthcare reform, a complementary strategy is to target lifestyle factors to intervene on LUTS well before treatment is indicated. Indeed, the 2008 National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Prostate Strategic Plan indicated “The search for and study of primary prevention for benign prostate disease, such as male LUTS, is an important priority for the future.” and lists as a research priority “Develop specific clinical trial concepts, including...behavioral and lifestyle interventions...”¹

To plan adequately powered trials to test lifestyle interventions, LUTS incidence and progression rates in men are needed. Most studies on LUTS occurrence have reported prevalence,² that is, the proportion of men who are symptomatic at one point in time. Prevalence estimates are less useful for calculating needed trial sample sizes because they do not indicate the number of men who may become symptomatic over time. LUTS progression rates have been reported in trials and cohort studies, but these rates were for more extreme outcomes.^{5–7} Few studies have estimated LUTS rates in population-based,^{8–11} rather than clinic-based cohorts of men. Thus, we estimated LUTS incidence and progression rates in a cohort of US men unselected for BPH and prospectively followed over 16 years.

METHODS

Study Design and Population

We conducted a prospective study using data from the Health Professionals Follow-up Study (HPFS). The HPFS includes 51,529 US men ages 40–75 years who in 1986 reported their birth date, race, medical, lifestyle, and diet information on a mailed survey. Exposure and outcome information has been updated every two years and diet every four years. We learn of a participant’s death from family members or the postal system or by searches of the National Death Index. By 2008, 94% of eligible men responded to the biennial survey. This study was approved by the Institutional Review Boards at the Harvard School of Public Health and the Johns Hopkins Bloomberg School of Public Health.

Assessment of LUTS Incidence and Progression

Surgery for LUTS, including transurethral resection of the prostate, was assessed biennially since 1988. We asked the men whether in the past two years they had any of the following professionally diagnosed conditions and “Prostatic enlargement, surgically treated (e.g., TURP)” was a choice listed. Use of medications to treat LUTS was assessed biennially since 1996. We asked the men whether they currently used any of the listed medications and included a line item for “finasteride” and a line item for “alpha-blocker for BPH”. We also provided example generic and brand drug names for both line items; the specific examples changed as new drugs were approved. The American Urological Association Symptom Index,¹² now called the International Prostate Symptom Score (IPSS), was assessed in 1992, 1994, 1998, 2000, and 2008 as described previously;¹³ the possible range of points was 0 to 35.

We defined two analytic cohorts, one for incidence and one for progression. Men who ever had a prostate cancer diagnosis were excluded. The incidence analytic cohort consisted of 25,879 men who returned the long form of the 1992 survey, did not have a cancer diagnosis in 1992 or earlier, returned a valid food frequency questionnaire in 1986 (to enhance the reliability of subsequent response and be able to use the analytic cohorts for diet and lifestyle studies), had not had surgery to treat LUTS in 1992 or earlier, and had an IPSS of 0 to 7 in 1992. We used four definitions of incident LUTS: a) subsequent surgery (“surgery”, N=2,948 cases); b) subsequent medication use (“medications”; N=2,203 cases); c)

subsequent IPSS of 8 or surgery or medication use (“modest or worse LUTS”; N=11,352 cases); and d) subsequent IPSS of 15 or surgery or medication use (“moderate or worse LUTS”; N=6,058 cases).

For progression, men entered the analytic cohort when they first experienced an IPSS of 8 to 14, but did not have a cancer diagnosis then or earlier, returned a valid food frequency questionnaire in 1986, had not had surgery or used medications to treat LUTS. The progression analytic cohort consisted of 9,628 men. We used four definition of LUTS progression: a) subsequent surgery (“surgery”; N=1,416 cases); b) subsequent medication use (“medications”; N=928 cases); c) subsequent IPSS of 15 or surgery or medication use (“moderate or worse LUTS”, N=3,426 cases); and d) subsequent IPSS of 20 or surgery or medication use (“severe LUTS”, N=2,557 cases).

Statistical Analysis

We estimated age-specific rates of LUTS incidence and progression for men 40–54, 55–59, 60–64, 65–69, 70–74, and 75 years old. Men first began contributing person-time at risk when they entered the analytic cohort – for incidence, the date they returned the 1992 survey or for progression, the date they returned the survey on which they reported an IPSS of 8–14. We censored men if they did not answer the IPSS questions twice consecutively. As the men aged during follow-up, we apportioned their person-time at risk to the appropriate age group. For transition to surgery, person-time was accumulated until surgery, death, or the end of follow-up (return date of the 2008 survey), whichever occurred first, irrespective of medication use or IPSS. For transition to medication use, person-time was accumulated until medication use, surgery, death, or the end of follow-up, whichever occurred first. For transition to the combined LUTS endpoints, person-time was accumulated until the IPSS cutpoint was reached, medication use, surgery, death, or the end of follow-up.

We calculated directly age-standardized rates, which allows for comparison of rates between the groups in the analysis that had different age distributions. For incidence (Table 2), we used the distribution of person-time at risk across age for men in the analysis of the incidence of moderate to worse LUTS as the age standard. To reflect the older age of men at risk for progression, we used the distribution of person-time at risk across age for men in the analysis of the progression to moderate or worse LUTS as the age standard (Table 3). Statistical analyses were performed using SAS 9.2 (SAS Institute, Cary, NC). Tests were 2-sided with $p < 0.05$ considered to be statistically significant.

RESULTS

LUTS Incidence

At baseline, the men were, on average, 57.3 years old and had an IPSS of 2.4 (Table 1). Mean follow-up time was 12.7 years. The incidence rate increased across age for surgery, medication use, modest or worse LUTS, and moderate to worse LUTS (Table 2). For the transition from an IPSS of <8 to 15 or surgery or medications (“moderate or worse LUTS”), the rate increased from 6.3/1,000 man-years in men 40–54 years old to 39.3/1,000 man-years in men 75 years old. These rates were only slightly lower when excluding men with diabetes or who used a diuretic (data not shown). Using a less stringent definition, an IPSS 8 or surgery or medications (“modest or worse LUTS”), the rate was higher, ranging from 24.6/1,000 man-years in the youngest age group to 62.4/1,000 man-years in the oldest age group. The rates of transition to moderate or worse LUTS (ages 75–79: 37.5 80–84: 42.3, 85: 42.6 per 1,000 man-years; Figure 1) and modest or worse LUTS (ages 75–79: 62.1, 80–84: 64.7, 85: 56.7 per 1,000 man-years) tended to increase less steeply at the oldest ages. The age-standardized incidence rates (per 1,000 man-years) were 9.0, 6.7, 40.5,

and 18.5 for surgery, medication use, modest or worse LUTS, and moderate to worse LUTS, respectively (Table 2).

LUTS Progression

At baseline, the men were, on average, 63.3 years old and had an IPSS of 9.9 (Table 1). Mean follow-up time was 5.9 years. The progression rate increased across age for surgery, medication use, moderate or worse LUTS, and severe LUTS (Table 3) and these age-specific progression rates were higher than for incidence. For the transition from an IPSS of 8–14 to 20 or surgery or medications (“severe LUTS”), the rate increased from 21.4/1,000 man-years in men 40–54 years old to 62.9/1,000 man-years in men 75 years old. Using a less stringent definition, an IPSS 15 or surgery or medications (“moderate or worse LUTS”), the rate was higher, ranging from 45.0/1,000 man-years in the youngest age group to 76.2/1,000 man-years in the oldest age group. The rates of transition to severe LUTS (ages 75–79: 64.3, 80–84: 59.8, 85: 63.5 per 1,000 man-years; Figure 2) and moderate or worse LUTS (ages 75–79: 76.7, 80–84: 73.5, 85: 81.6 per 1,000 man-years) tended to increase less steeply at the oldest ages. The age-standardized progression rates (per 1,000 man-years) were 24.9, 16.2, 63.0, and 44.9 for surgery, medication use, moderate or worse LUTS, and severe LUTS, respectively (Table 3).

DISCUSSION

LUTS incidence and progression rates were high and rose steeply with age until the oldest ages. The progression rate was higher than the incidence rate at each age. These rates may be used for planning adequately powered trials, including on modifiable risk factors as called for by the NIDDK,¹ with the goal of intervening on LUTS well before they require surgical or pharmacologic treatment.

Previous studies have reported the prevalence of LUTS, but few reported the incidence rate of LUTS.² Because there is no consensus about the definition of LUTS, many different measures have been used to capture its occurrence, including IPSS or subsets of these symptoms, surgery, medication use, change in urological parameters such as urine flow rate, prostate volume, PSA concentration over time^{11, 14–20}, including in large primary care database studies.^{9, 10} In our study, we used several case definitions. Surgery and use of medications to treat LUTS reflect both the symptom severity and propensity to seek medical care. The report of the frequency of urinary symptoms is subjective, but symptoms are the clinical endpoint experienced by men. Using the combined definition of symptoms, surgery, and medication use may best capture the full range of symptomatic cases.

We estimated age-standardized incidence rates of 18.5 to 40.5 per 1,000 man-years for the combination of symptoms, surgery, and medication use in middle-aged and older men with an IPSS <8 and no surgery history at the start of follow-up; the incidence rates for surgery and medication use were 9.0 and 6.7/1,000 man-years. Despite differences in study population characteristics and case definitions, the incidence rates in the HPFS were generally of the same order of magnitude as those in other large studies in the US and in Europe. For example, in the Olmsted County Study, which was designed specifically to assess LUTS and BPH in a population-based setting, the incidence of an increase of at least 4 IPSS points was 97.1/1,000 man-years, and the incidence of surgery was 6.6/1,000 man-years;⁸ the analytic cohort included men 50–79 years old with a mean baseline IPSS of 6.6. In the UK General Practice Research Database, which included 11,153 LUTS surgery cases, reported an incidence of surgery of 4/1,000 man-years in men 50 years old and 15/1,000 man-years in men 80 years old.⁹ In the Netherlands Integrated Primary Care Information database, LUTS incidence was 15/1,000 man-years, ranging from 3 to 38 per 1,000 man-years in men 45–49 to 75–79 years old;¹⁰ the analytic cohort consisted of 80,774 men

without prior BPH/LUTS and cases (N=2,181) were defined as a physician diagnosis of BPH, medication use, two or more symptoms suggestive of BPH without any other explanation, or surgery. In 5,667 men in the placebo arm of the Prostate Cancer Prevention Trial who reported on IPSS, surgery, and medication use annually, the incidence rates of total (surgery, medication use, or IPSS ≥ 15 on two occasions; N=1,041) and severe BPH (same definition except IPSS ≥ 20 ; N=693) were 34.4 and 22.3 per 1,000 man-years in men with a baseline IPSS of 0–14; the rates were 16.3 and 13.6 in men with IPSS 0–4.9 at baseline.¹¹ In each of these studies, incidence increased with age. Two of the studies, the Netherlands Study¹⁰ and our study, separately estimated rates in men 80–84 and ≥ 85 years old, and both found that the rate dropped or increased less steeply in these oldest men; explanations are likely complex.

We estimated age-standardized progression rates of 44.9 to 63.0 per 1,000 man-years for the combination of symptoms, surgery, and medication use in middle-aged and older men with an IPSS 8–14 and no history of surgery to treat LUTS at the start of follow-up; the incidence rates for surgery and medication use were 24.9 and 16.2 per 1,000 man-years, respectively. Rates increased less steeply in the oldest men. Although based on different entry criteria and case definitions, the progression rates in HPFS are not notably different than in the placebo arm of the Medical Therapy of Prostate Symptoms (MTOPS).⁵ In MTOPS, the rate of clinical progression, defined as an increase in IPSS of ≥ 4 points, acute urinary retention, urinary incontinence, renal insufficiency, or recurrent urinary tract infection was 45/1,000 man-years, and the rate of invasive BPH therapy including surgery was 13/1,000 man-years;⁵ the trial included men with a mean IPSS of 16.9.

Our study had several strengths, including determining rates in a population in the age range at risk for LUTS and BPH, but who were unselected for these conditions, the large sample size, and long-term prospective follow-up. We had repeated measurements of the IPSS, and surgery and medication use to treat LUTS. We were able to estimate both incidence rates and progression rates in this cohort. Limitations include that we did not perform urological assessments (e.g., uroflowmetry) and the outcomes we captured may reflect prostatic pathologies as well as bladder abnormalities and other conditions. We directly assessed the influence of other conditions by excluding men with two common conditions with urinary sequelae – diabetes and/or diuretic use; LUTS incidence rates were only slightly reduced. Nevertheless, symptoms are what men experience and are a relevant endpoint for LUTS intervention trials. We did not confirm the men's reports of surgery and medication use; however, these men are health professionals and we previously found their reports of surgery to treat LUTS to be valid in a subset.²¹ The men in the HPFS are primarily white, reflecting the demographics of male health professionals during the era in which they trained; the sample size was not adequate to estimate precise age-specific LUTS incidence and progression rates for African-American and Asian men in the cohort.

CONCLUSIONS

In this prospective cohort study of US men unselected for BPH, LUTS incidence and progression rates were high and rose steeply with age until the oldest ages. These rates may be used for planning trials to intervene on LUTS well before they require surgical or pharmacologic treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations and Acronyms

LUTS	lower urinary tract symptoms
BPH	benign prostatic hyperplasia
IPSS	International Prostate Symptom Score
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
HPFS	Health Professionals Follow-up Study
RR	hazard ratio
CI	confidence interval
PCPT	Prostate Cancer Prevention Trial
MTOPS	Medical Therapy of Prostate Symptoms

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Figure 1.
Incidence Rate of Moderate or Worse Lower Urinary Tract Symptoms*, Health Professionals Follow-up Study, 1992–2008

Figure 2. Progression Rate of Severe Lower Urinary Tract Symptoms*, Health Professionals Follow-up Study, 1992–2008

Table 1
Characteristics of Men in the LUTS Incidence and Progression Cohorts, Health Professionals Follow-up Study

	LUTS Incidence Cohort*	LUTS Progression Cohort**
N	25,879	9,628
Age in years (mean ± sd)	57.3 ± 9.0	63.3 ± 8.9
Race (%)		
White	91.8	91.7
African-American	0.7	0.8
Asian-American	1.6	1.6
Other ancestry or unknown	5.9	5.9
IPSS (mean ± sd)	2.4 ± 2.0	9.9 ± 1.8
Percentiles		
10 th	0	8
25 th	1	8
Median	2	9
75 th	4	11
90 th	6	13
Irritative symptoms (mean ± sd)	1.7 ± 1.4	5.2 ± 2.2
Obstructive symptoms (mean ± sd)	0.7 ± 1.2	4.8 ± 2.3
Body mass index in kg/m ² (mean ± sd)	25.7 ± 3.4	26.0 ± 3.7
Height in inches (mean ± sd)	70.3 ± 2.6	70.0 ± 2.6
Waist circumference in inches (mean ± sd)	36.4 ± 3.4	36.6 ± 3.5
Physical activity in MET-hrs/week (mean ± sd)		
High intensity	15.5 ± 27.7	13.4 ± 26.2
Low intensity	21.8 ± 29.5	21.2 ± 28.3
History of diabetes mellitus (%)	3.7	7.0
Cumulative smoking in packyears (mean ± sd)	11.5 ± 17.5	13.7 ± 19.2

* Men entered follow-up in 1992 if they had an IPSS <8 and never had surgery to treat LUTS (see Methods for other entry criteria). Shown are characteristics in 1992.

** Men entered follow-up when they had an IPSS 8–14, but never had surgery or used medications to treat LUTS (see Methods for other entry criteria). Shown are characteristics from the time the men entered follow-up.

Table 2

Incidence Rate (IR) Per 1,000 Man-Years of Lower Urinary Tract Symptoms (LUTS)^{*}, Health Professionals Follow-up Study, 1992–2008

Age group (years)	Transition to surgery			Transition to medications			Transition to modest or worse LUTS ^{**}			Transition to moderate or worse LUTS ^{***}		
	Man-years	No. cases	IR 95% CI	Man-years	No. cases	IR 95% CI	Man-years	No. cases	IR 95% CI	Man-years	No. cases	IR 95% CI
40–54	71,542	83	1.2 0.9–1.4	71,573	173	2.4 2.1–2.8	68,014	1,674	24.6 23.4–25.8	71,541	451	6.3 5.7–6.9
55–59	65,090	202	3.1 2.7–3.5	65,158	320	4.9 4.4–5.4	58,250	1,502	25.8 24.5–27.1	65,104	682	10.5 9.7–11.3
60–64	64,816	521	8.0 7.3–8.7	65,004	430	6.6 6.0–7.2	56,867	2,434	42.8 41.1–44.5	64,855	1,207	18.6 17.6–19.7
65–69	50,540	619	12.2 11.3–13.2	50,753	434	8.6 7.7–9.4	43,095	2,159	50.1 48.0–52.2	50,588	1,180	23.3 22.0–24.7
70–74	39,090	641	16.4 15.1–17.7	39,266	377	9.6 8.6–10.6	32,089	1,845	57.5 54.9–60.1	39,138	1,116	28.5 26.8–30.2
75	36,169	882	24.4 22.8–26.0	36,437	469	12.9 11.7–14.0	27,866	1,738	62.4 59.4–65.3	36,228	1,422	39.3 37.2–41.3
Total P-trend	327,247	2,948	<0.0001	328,192	2,203	<0.0001	286,180	11,352	<0.0001	327,454	6,058	<0.0001
Age standardized IR 95% CI	9.0 8.7–9.3			6.7 6.4–7.0			40.5 39.7–41.2			18.5 18.0–19.0		

^{*} Among men who at baseline had an IPSS <8 and never had surgery to treat LUTS.

^{**} During follow-up, transitioned to an IPSS 8 or had surgery or used medications to treat LUTS, whichever came first

^{***} During follow-up, transitioned to an IPSS 15 or had surgery or used medications to treat LUTS, whichever came first

^{****} The age standard was the distribution of person time across age groups from the analytic cohort for transition to moderate or worse symptoms in this table.

Table 3

Progression Rate (IR) per 1,000 Man-Years of Lower Urinary Tract Symptoms*, Health Professionals Follow-up Study, 1992–2008

Age group (years)	Transition to surgery			Transition to medications			Transition to moderate or worse LUTS**			Transition to severe LUTS***		
	Man-years	No. cases	IR 95% CI	Man-years	No. cases	IR 95% CI	Man-years	No. cases	IR 95% CI	Man-years	No. cases	IR 95% CI
40–54	5,641	41	7.3 5.0–9.5	5,659	40	7.1 4.9–9.3	5,572	251	45.0 39.5–50.6	5,642	121	21.4 17.6–25.3
55–59	9,192	107	11.6 9.4–13.8	9,226	121	13.1 10.8–15.5	8,869	374	42.2 37.9–46.4	9,196	267	29.0 25.6–32.5
60–64	10,943	231	21.1 18.4–23.8	11,026	156	14.1 11.9–16.4	10,503	668	63.6 58.8–68.4	10,949	453	41.4 37.6–45.2
65–69	10,550	284	26.9 23.8–30.1	10,651	188	17.7 15.1–20.2	10,052	677	67.3 62.3–72.4	10,562	510	48.3 44.1–52.5
70–74	9,754	333	34.1 30.5–37.8	9,849	178	18.1 15.4–20.7	9,305	682	73.3 67.8–78.8	9,771	528	54.0 49.4–58.6
75	10,765	420	39.0 35.3–42.7	10,903	245	22.5 19.7–25.3	10,160	774	76.2 70.8–81.5	10,781	678	62.9 58.2–67.6
Total P-trend	56,845	1,416	<0.0001	57,314	928	<0.0001	54,460	3,426	<0.0001	56,901	2,557	<0.0001
Age standardized IR 95% CI	24.9 23.6–26.2			16.2 15.1–17.2			63.0 60.9–65.2			44.9 43.2–46.7		

* Among men who entered follow-up when they had an IPSS 8–14, but never had surgery or used medications to treat LUTS.

** During follow up, transitioned to an IPSS 15 or had surgery or used medications to treat LUTS, whichever came first

*** During follow-up, transitioned to an IPSS 20 or had surgery or used medications to treat LUTS, whichever came first

**** The age standard was the distribution of person time across age groups from the analytic cohort for transition to moderate or worse symptoms in this table.