Lower urinary tract symptoms in older men: does it predict the future?
Bouwman, Iris Ingeborg

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Publication date:
2015

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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Abstract

**Background** Although lower urinary tract symptoms (LUTS) seem to be related to erectile dysfunction (ED) in men, it is unclear whether this is a causal relationship, and if it is significant in the primary care population. In order to investigate this relationship, we used longitudinal data for establishing the possible causal relationship between LUTS and ED in a primary care population.

**Methods** We performed a registry study using data from the Registration Network Groningen (RNG). All data from men aged 50 years and older during the study period from 1 January 1998 up to 31 December 2011 were collected. Cox proportional hazard regression analysis was used to determine the association between LUTS and ED in our population.

**Results** Data from 5957 men were analysed. Of all men, 21.6% (n = 1284) reported LUTS. ED was reported in 16% of men with LUTS, compared to 7% of men without LUTS. The hazard ratio of LUTS for ED, compared to no LUTS, in the adjusted regression model, is significant: HR 1.41, 95%CI: 1.12-1.74; p=0.002.

**Conclusion** Based on the results, men with LUTS are more likely to develop ED, at any time, than men without LUTS in primary care.
Introduction

Lower urinary tract symptoms (LUTS) and erectile dysfunction (ED) are common problems in aging males, both more prevalent in older age.\textsuperscript{1} Men consulting their physician for either LUTS or ED are likely to have both conditions.\textsuperscript{2} The exact cause is unknown, but these conditions share common pathophysiological pathways, and both have a negative impact on quality of life.\textsuperscript{3–7} It is suggested that there appears to be a lack of awareness of the link between LUTS and ED in both primary and secondary care.\textsuperscript{2} Also, it is not known whether or not the relationship between LUTS and ED is a causal.\textsuperscript{8}

Cross-sectional studies showed that LUTS and sexual dysfunction are related (adjusted OR varying from 1.39-9.9).\textsuperscript{1,9–11} There is a limited number of longitudinal cohort studies, necessary for causal inferences, demonstrating a relationship between LUTS and ED.\textsuperscript{12–14} All longitudinal studies were conducted in community based- or selected study-populations, and had short follow-up times (2-5 years).\textsuperscript{12–14}. To date, no longitudinal studies have been conducted in primary care, although most men with LUTS and ED are treated by their GP.

The incidence of ED in primary care is low, i.e. 1.7/1000 man-years (vs. 26/1000 man-years in the community.\textsuperscript{12,15,16} Few patients consult their GP for ED (25% of men who sought help\textsuperscript{15}), and also the general practitioner not always asks for, nor registers ED as a reason for encounter.\textsuperscript{17} If there is a causal relationship between LUTS and ED in primary care, general practitioners should consider ED in patients with LUTS, its impact on quality of life, and explain this likelihood more often to their LUTS-patients.

The hypothesis that LUTS is associated with the development of ED still needs to be confirmed in primary care. Therefore, the objective of this study is to explore the presence of a causal relationship between LUTS and ED in a primary care population.

Methods

We performed a registry study using data from the Registration Network Groningen (RNG), one of several registration networks in the Netherlands. These registration networks conduct research on data derived from the electronic registration of daily patient care in their participating general practices. The Registration Network Groningen was established in 1989, and collects primary care data from three practices in the north of the Netherlands, with an annual population of approximately 30,000 patients.\textsuperscript{18}
In the Netherlands, the GP is the gatekeeper in the Dutch health-care system controlling access to specialized medical care. Virtually all Dutch citizens are registered with a GP and as a consequence the total practice population represents the general population.  

GPs working in the RNG-practices use a structured electronic medical record, in which all patient contacts are registered. This includes reason for encounter, medical diagnosis (according to the International Classification of Primary Care (ICPC)\(^ {20} \)), applied treatment (among which prescriptions, using the Anatomical Therapeutic Chemical (ATC) codes \(^ {21} \), and referrals), but also cause of death. The database also includes population dynamics, such as date of entry and departure from the database.

From the RNG registration, we selected all data from men aged 50 years and older (age at any time during the study period: 1 January 1998 - 31 December 2011). Patients with a history of Prostate Cancer, as well as men with a history of ED were excluded to enable a time dependent cause-effect relationship in the longitudinal analysis. Access to the patient’s medical history was a prerequisite. We collected the following information from the registration data: date of birth, date of entry in the study, date of and reason for leaving the registration, GP code, patient contacts (ICPC codes), prescriptions (ATC codes) and ICPC codes attached to these medications, and hospital referrals. From this information, we calculated age from date of birth and number of person years in study. All data were anonymised.

**Definitions**

Lower urinary tract symptoms (LUTS) encompasses all urinary symptoms, including storage, voiding, and post micturition symptoms.\(^ {22} \) There is no specific ICPC code for LUTS, therefore we defined LUTS by all relevant ICPC codes or use of LUTS medication (Table 1).

Erectile dysfunction is defined as the persistent inability to achieve or maintain an erection sufficient for sexual performance\(^ {3} \), in this study defined by the relevant ICPC codes (Table 1).

**Table 1. Definitions of study parameters and ICPC codes**

<table>
<thead>
<tr>
<th>Study parameter</th>
<th>ICPC code and definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower Urinary Tract</td>
<td>U01: strangury, U02: frequency, U05: other voiding symptoms, U07: other other symptoms, U13: other symptoms bladder, U29: other symptoms urinary tract, Y06: symptoms prostate, Y85: benign prostate hypertrophy</td>
</tr>
<tr>
<td>Erectile Dysfunction</td>
<td>Y07: symptoms sexual potential, P08.01: impotence</td>
</tr>
</tbody>
</table>

ICPC: International Classification of Primary Care
**Statistical Analysis**

Descriptive statistics were used to compare population characteristics. To allow comparisons with other cross-sectional studies, we tested the possible association between LUTS and ED at the start of the registration period, using the Chi-square test.

To determine the time-dependent association between ED (outcome) and LUTS in our population, we performed Cox regression analysis. Men with ED registered before or at the first observation of LUTS were excluded from analyses. Initially, an unadjusted analysis was performed. This association regression model was subsequently corrected for confounders. A covariate was considered a confounder in the event the beta coefficient of LUTS changed by 10% or more. In this open cohort, time to event (ED) was calculated from the patient’s date of birth to event (i.e. diagnosis of ED) or until death, or end of study in subjects without ED. The following possible confounders were added to the Cox regression models: COPD, hypertension, diabetes mellitus, obesity, dyslipidaemia, depression, smoking, heart disease, LUTS medication, diabetes medication, and antihypertensive medication (Table 2).

**Table 2. Definitions of study parameters ‘medication’ and ATC codes**

<table>
<thead>
<tr>
<th>Medication groups:</th>
<th>ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td>LUTS</td>
<td>α-1 receptor blockers: G04CA*</td>
</tr>
<tr>
<td></td>
<td>5α1 reductase inhibitors: G04CB*</td>
</tr>
<tr>
<td>Hypertension</td>
<td>β-blockers: C02*</td>
</tr>
<tr>
<td></td>
<td>(thiazide) diuretics: C03*</td>
</tr>
<tr>
<td></td>
<td>ACE-inhibitors: C07*</td>
</tr>
<tr>
<td></td>
<td>calcium antagonists: C08*</td>
</tr>
<tr>
<td></td>
<td>AT-II-inhibitors: C09*</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Antilipaemics: C10*</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>insulin and analogous: A10A*</td>
</tr>
<tr>
<td></td>
<td>oral therapy: A10B*</td>
</tr>
<tr>
<td></td>
<td>remaining: A10X*</td>
</tr>
<tr>
<td>Cardiaca</td>
<td>heart glycosides: C01*</td>
</tr>
<tr>
<td>Depression</td>
<td>Antidepressants: N06A*</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Anxiolytics: N05B*</td>
</tr>
<tr>
<td>Psychotic disorder</td>
<td>Antipsychotics: N05A*</td>
</tr>
</tbody>
</table>

ATCcode*: all medication subcodes are included
If meeting the 10% criterion, the variable was added to the regression model for correction only. Hazard ratios (HR) for the model variables are presented with 95%CIs. All analyses were performed using SPSS version 20 based on a two-sided 0.05 significance level.

**Results**

The total selected population consisted of 5957 men, contributing a total of 42,998.4 person-years to this dynamic cohort. Men with LUTS (21.6%, n=1284) were on average older than men without LUTS (p<0.001).

**Table 3.** Baseline characteristics; % (number) of patients suffering from the medical condition or registered for the use of medication

<table>
<thead>
<tr>
<th>medical condition / medication</th>
<th>total population (N=5957) % (n)</th>
<th>LUTS population (N=1284) % (n)</th>
<th>no LUTS population (N=4673) % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ED</td>
<td>8.5 (508)</td>
<td>15.6 (200)</td>
<td>6.6 (308)</td>
</tr>
<tr>
<td>Depression</td>
<td>11.8 (701)</td>
<td>16.4 (211)</td>
<td>10.5 (490)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>13.2 (786)</td>
<td>17.8 (228)</td>
<td>11.9 (558)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>25.2 (1502)</td>
<td>33.3 (427)</td>
<td>23.0 (1075)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>33.1 (1969)</td>
<td>44.9 (576)</td>
<td>29.8 (1393)</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>5.6 (333)</td>
<td>4.8 (62)</td>
<td>5.8 (271)</td>
</tr>
<tr>
<td>Obesity</td>
<td>6.2 (372)</td>
<td>7.1 (91)</td>
<td>6.0 (281)</td>
</tr>
<tr>
<td>Smoking</td>
<td>17.9 (1066)</td>
<td>18.4 (236)</td>
<td>17.8 (830)</td>
</tr>
<tr>
<td>Sleep disorder</td>
<td>14.0 (835)</td>
<td>21.6 (277)</td>
<td>11.9 (558)</td>
</tr>
<tr>
<td>UTI</td>
<td>13.2 (789)</td>
<td>30.7 (394)</td>
<td>8.5 (395)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>6.2 (371)</td>
<td>10.2 (131)</td>
<td>5.1 (240)</td>
</tr>
<tr>
<td>LUTS medication</td>
<td>9.2 (546)</td>
<td>39.4 (506)</td>
<td>0.9 (40)</td>
</tr>
<tr>
<td>Antihypertensive medication</td>
<td>42.2 (2514)</td>
<td>57.6 (740)</td>
<td>38.0 (1774)</td>
</tr>
<tr>
<td>Lipid lowering medication</td>
<td>25.1 (1493)</td>
<td>32.9 (423)</td>
<td>22.9 (1070)</td>
</tr>
<tr>
<td>Erectile dysfunction medication</td>
<td>7.4 (440)</td>
<td>13.2 (170)</td>
<td>5.8 (270)</td>
</tr>
<tr>
<td>Diabetes medication</td>
<td>10.0 (598)</td>
<td>12.6 (162)</td>
<td>9.3 (436)</td>
</tr>
<tr>
<td>Cardiaca</td>
<td>12.1 (719)</td>
<td>19.4 (249)</td>
<td>10.1 (470)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>14.4 (856)</td>
<td>20.0 (257)</td>
<td>12.8 (599)</td>
</tr>
<tr>
<td>Anxiolytics</td>
<td>27.9 (1660)</td>
<td>37.7 (484)</td>
<td>35.3 (1176)</td>
</tr>
<tr>
<td>Antipsychotic medication</td>
<td>5.0 (297)</td>
<td>6.5 (83)</td>
<td>4.6 (214)</td>
</tr>
</tbody>
</table>

ED: Erectile Dysfunction , UTI: Urinary tract infection
The mean age was 70.5±12 years in the LUTS group and 65.3±11.4 years in the population without LUTS. In the LUTS population 34.5% was >74 years and in the population without LUTS this was 17.8%. Erectile dysfunction was present in 16% of the LUTS group and in 7% of the No-LUTS group (Table 3).

Table 3 describes the characteristics of the study population. Participants with LUTS were more frequently diagnosed with hypertension, dyslipidaemia, heart failure, diabetes mellitus, and sleep disorders (all: p<0.001). Alcohol abuse, smoking, and obesity are not significant associated with LUTS.

All investigated groups of medication were significantly used more frequently in the LUTS group than in the no-LUTS group (Table 3). More than 50% of men with LUTS use antihypertensive medication. More than one third of the LUTS population use lipid lowering medication, LUTS medication, and anxiolytics. Men with ED registered often use medication for this condition: 78% (n=397) medication vs. 22 % no medication (n=111); p<0.001.

**Survival analysis**

Men with ED registered before or at the first observation of LUTS (n= 91) were excluded from the longitudinal analysis. There is a significant unadjusted univariate relationship between LUTS and ED (HR 0.65, 95%CI: 0.54-0.78; p<0.001). The hazard ratio of LUTS for ED, in the adjusted regression model, was significant but reversed (HR 1.41, 95%CI: 1.12-1.74; p=0.002). Therefore, men with LUTS were more likely to develop ED, at any time, than men without LUTS. LUTS medication was found to confound the relationship between LUTS and ED.

**Discussion**

To the best of our knowledge this is the first study that has been conducted to establish the relationship between LUTS and ED in a primary care population. This study suggests the presence of a time dependent relationship between LUTS and ED. Nowadays, when a patient consults his general practitioner for LUTS, the Dutch guideline LUTS recommends to inquire about the presence of ED. This study supports this recommendation, and suggests a possible causal relation.

Based on the results from our survival analyses, LUTS is related to ED. It supports the results found in the few longitudinal cohort studies. We found that only the use of medication for LUTS (α1 receptor blockers, or 5α reductase inhibitors) confounded the relationship between LUTS and ED. Before adjustment there is a 35% decreased change
of ED, after adjustment there is a 41% higher change of ED in men with LUTS. This effect of LUTS-medication on the relationship between LUTS and ED is also reported in earlier studies. Results are, however, conflicting. Two mechanisms have been proposed to explain patients’ improved sexual functioning after treatment for LUTS with a-blockers. First, as the symptoms become less bothersome, patients may feel less ‘disabled’ by their urinary symptoms and may thus be better able to enjoy other facets of life without feeling inhibited or limited. Alternatively, inhibition of the α1- and a1D-adrenoceptor subtypes that predominate in cavernosal smooth muscle should facilitate erection.

No other longitudinal studies reported the effect of LUTS medication on their results. The relationship between LUTS and ED in our study could not be accounted for by COPD, hypertension, diabetes mellitus, obesity, dyslipidaemia, depression, smoking, heart disease, and medication. However, we did not control for other possible confounders, such as: body mass index, physical activity, use of alcohol, diet, or surgical treatment for LUTS, because this information was not available in our data.

Despite similar conclusions, it is difficult to compare our study results with those in other studies, because study populations differ: studies were performed in a Chinese- Brazilian- and American populations. Open populations or a selected population of health care professionals. LUTS has not been categorized consistently among studies, different cut-off points were used, and results are presented in either OR, HR or RR. Moreira et al did not present results from the IPSS scores of 174 men from their study, earlier described in their study methods. Instead they presented men with BPH (n = 15) in the final predictive model for ED.

There are several explanations for the relationship between LUTS and ED, and its pathophysiology. For example, both LUTS and ED share similar risk factors that include age, medical conditions such as diabetes, hypertension, and depression. In terms of common pathophysiology, several hypotheses have been proposed to provide possible biological explanations for the observed association. These included: (i) Reduced production of nitric oxide synthase/nitric oxide in the pelvis as the pathophysiological mechanism that was responsible for both ED and LUTS; (ii) Pelvic atherosclerosis which results in diffuse atherosclerosis of prostate, penis and bladder that impacts both LUTS and ED; and (iii) “Alternate Pathways” of smooth muscle relaxation and contraction that may be responsible for the association between bladder outlet obstruction and ED. Also, it is suggested that the psychological impact of LUTS could cause ED. It is suggested that ED in men with LUTS is strongly associated with both the severity of LUTS symptoms and the degree of experienced bothersomeness. The
authors emphasize the potential of psychological mechanisms of ED. They show that urinary bothersomeness of mild LUTS account for the risk of ED more strongly than mild LUTS themselves.29

Strengths of this study include a large primary care based sample across a wide age range (50-91 years old) and the extended follow-up time (median 6.63 years(range 1-14 years), compared to 2-5 years in previous longitudinal studies.12,13,32 The prevalence of LUTS in this study is comparable to the prevalence in the (open) Dutch population15,33, although it is likely that LUTS is underreported because it is known that not all patients who suffer from LUTS consult the GP for this reason.34 The data collected within RNG are extensive, enabling to examine many potential predictors for LUTS and ED. The RNG study population is representative of the Dutch population.35 The RNG supports the need for qualitatively good data.36 It is important to collect data complete and correct, to code all episodes of care with ICPC codes. There should not be bulk episodes, individual complaints or disorders are recorded under different episodes of care. So, all reported LUTS and ED is recorded with ICPC codes.

Another strength of this study is the possibility to correct for the use of medication in the analysis since treatment for LUTS may affect ED outcome, as we showed in our results.

This study was carried out based on a primary care population in the north-eastern part of Netherlands. Most studies describe LUTS patients in a secondary care or in a community setting, using the IPSS questionnaire and defining a score >8 as having LUTS. We defined LUTS as having consulted the GP for at least one voiding symptom, as LUTS is not covered by the ICPC coding system. We cannot differentiate between mild, moderate or severe symptoms. As a consequence, comparing our results with those of other studies is problematic. Also, we were unable to differentiate between storage- and voiding symptoms.

For the lifestyle factors, such as smoking, underreport is very likely. Probably, smoking is only registered as ICPC code P17 in case of the intention to quit smoking. When compared to the prevalence of smoking in the Dutch population (23%) we would expect a higher rate of smoking men ≥50 years than the observed 236 (4%) within the LUTS population, because not all smokers have the intention to quit smoking, let alone with the help of GPs or practice nurses. For future research it would be better to improve the registration of lifestyle factors.
We were not able to include all cardiovascular problems in our analysis. This may have biased the results of our study. It is still questionable if the relationship between LUTS and ED is causal. Not many studies have established longitudinal or survival analysis. Possibly, this relationship may depend on other confounding factors than considered in our data. However, despite differences in study methods, populations, definitions of study variables, etc. all longitudinal studies reported a positive relationship between LUTS and ED. Future prospective longitudinal cohort studies may further clarify this possible causal relationship, and its pathophysiological mechanisms. More prospective data, as well as more standardised methods, including registration of life style factors as possible confounders, will need to be also considered.

Conclusion
Our results suggest that lower urinary tract symptoms and erectile dysfunction are time-related. For the general practitioner it is worthwhile to inquire about ED symptoms in men with LUTS and to be aware that men with LUTS are more likely to have ED in the future.

Acknowledgments
We thank Dr. Marco Blanker, General Practitioner and epidemiologist for his comments on this article.

References


