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

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Abstract

Objective To evaluate the correlation between lower urinary tract symptoms, erectile dysfunction, and cardiovascular diseases in different male populations.

Data Sources PubMed (Medline), Clinical Evidence, Embase, Cochrane reviews, and articles from reference lists.

Selection Criteria Selection criteria in search databases were lower urinary tract symptoms, LUTS, Comorbidity (MESH), Impotence (MESH), Sexual Dysfunction, Aging, primary care (MESH) and Male. Studies on these subjects, and about men aged 40 years or older, were eligible for inclusion in this review. Both community based and clinical based studies were included.

Results 20 studies were eligible for inclusion, representing 71,322 men. These studies showed a significant positive correlation between lower urinary tract symptoms and erectile dysfunction. The Odds ratios varied from 1.4 to 9.74. All studies were community or clinical based. Just one study based on a primary care population was described. The association between erectile dysfunction and cardiovascular diseases is not proven in primary care.

Conclusions The evidence of a positive correlation between lower urinary tract symptoms and erectile dysfunction is significant in community and clinical based studies. It is at present unknown if these correlations are significant in the patient population of primary health care. We need more evidence to prompt the general practitioner to screen every man with the initial presentation of erectile dysfunction for standard cardiovascular risk factors and, as appropriate, start initiative cardioprotective interventions.
Introduction

With the increasing proportion of older people cardiovascular diseases, cancer, osteoporosis and frailty are the major health problems that will become more and more prevalent. Advancing age in men affects the lower urinary tract and therefore more men will present with lower urinary tract symptoms, prostate disease, and erectile dysfunction. All of these conditions are often dismissed as lifestyle issues. However these common ageing-related conditions significantly affect quality of life and may even be symptomatic of underlying cardiovascular or metabolic diseases.

In the mid 1990s, both male sexual dysfunction and lower urinary tract symptoms were known to be age dependent, although the association between these two conditions had not been investigated. In the last decade cross-sectional studies have collected data from large samples of men.

Worldwide, about 100 million men are affected by erectile dysfunction. The worldwide prevalence varies from 11-52%. In the Dutch population the prevalence of erectile dysfunction increases from 14% for men aged 41-50 years to 42% for men aged 71-80. Many studies describe erectile dysfunction as a somatic condition, with vasculopathy as the most common cause of erectile dysfunction. The ENIGMA study describes the prevalence of erectile dysfunction in the Dutch primary care. As well psychogenic as somatic erectile dysfunction is equally prevalent in men visiting their general practitioner for sexual dysfunction. In young men erectile dysfunction is mostly caused by a psychological condition, compared to older men, in whom a somatic cause is more common.

Erectile dysfunction is nowadays considered a readily treatable disorder and is described in several studies to be a powerful risk-marker for cardiovascular disease, because erectile dysfunction and cardiovascular diseases share aetiology and pathophysiology. Identification of erectile dysfunction as a predictive symptom for cardiovascular diseases could allow even earlier intervention, possibly further reducing morbidity and mortality due to the diseases.

The present review aims to assess the relationships between respectively lower urinary tract symptoms and erectile dysfunction, and between erectile dysfunction and cardiovascular disease. The second objective is to identify the differences of the previous mentioned relationships between populations from primary health care and urology clinics.
Methods

Two search strategies were used. Using key words, the following literature databases were searched: Embase, Cochrane, and Pubmed. Additionally, we made use of the so-called 'snowball method', whereby the reference sections of already selected articles were used to help locate other relevant articles. We selected articles written in English, Dutch or German. Articles from 1997 up to and including 2007 were included.

The inclusion criteria were: 1) The research populations were community based, clinical based or primary care based; 2) that the study was empirical; 3) that (part of) the study investigated the correlation between Lower Urinary Tract Symptoms and Erectile Dysfunction, or between Erectile Dysfunction and Cardiovascular Diseases; 4) that (part of) the population was male; and 5) at least 40 years of age; and 6) a research population of more than 100 subjects.

The key words were lower urinary tract symptoms, LUTS, Cardiovascular diseases (MESH), and Sexual Dysfunction (MESH). The combination of search terms were 1. ([LUTS OR Lower Urinary Tract Symptoms ] AND [Sexual Dysfunction]), 2. ([Sexual Dysfunction] AND [Cardiovascular Diseases]), 3. [1 AND 2]. Also the search terms were combined with Comorbidity (MESH), Impotence (MESH), Aging, and primary care (MESH). LUTS was defined as mild with an International Prostate Symptom Score (IPSS) of 0-7, moderate with an IPSS of 8-19, and Severe with an IPSS of 20-35.23

Data Extraction

Each potentially eligible study was assessed for inclusion and quality. The methodological quality of the studies was assessed by evaluating the design of the study, methods, reliable outcome measures, and also how patients lost to follow up were handled in the analysis. A checklist to obtain data on topics, study design, setting, number of participants, characteristics of the collaborative strategy, and relevant results, was used.

We could not use formal meta-analytical techniques because the studies used many different effect measures.

Results

The 562 articles resulting from our literature search were examined one by one. The abstracts of 196 articles which, at first glance, appeared to be relevant to our research question were analysed. Of these abstracts 115 were excluded, because closer reading revealed that they did not conform to the inclusion criteria. The full text was obtained
for the remaining 81 articles. 51 of the 81 articles did not meet the inclusion criteria. Two researchers, working independently, judged the remaining 30 articles according to the aforementioned methodological aspects. A third researcher was consulted when a difference of opinion came up, and his opinion decided the matter.

**The correlation between Lower Urinary Tract Symptoms and Erectile Dysfunction**

**Community and population based studies**

The Krimpen study from Blanker et al.\textsuperscript{24} showed a strong age dependency in erectile dysfunction. After multivariate logistic regression analysis the authors concluded that lower urinary tract symptoms are an independent risk factor for erectile dysfunction. The non-response study showed that the participants in the study were comparable with the nonresponders. The age dependency in erectile dysfunction is confirmed by the The Multinational Survey of the Aging Male (MSAM-7)\textsuperscript{27}. This is one of the largest studies to date describing the prevalence of lower urinary tract symptoms and sexual dysfunction in representative samples of aging male. Moderate to severe lower urinary tract symptoms seemed to be strongly related to age, ranging from 22% in men aged 50-59 years to 45% in men aged 70-80 years. Age and lower urinary tract symptoms severity showed a higher degree of association with erectile dysfunction than other comorbidities. Mariappan\textsuperscript{26} is the only one reporting a non significant relationship between lower urinary tract symptoms and erectile dysfunction when controlled for age.

Besides lower urinary tract symptoms and age, also comorbidities such as diabetes mellitus, hypertension, and previous pelvic operations are independent risk factors for the development of erectile dysfunction as concluded from The Cologne Male Survey from Braun et al.\textsuperscript{25}. The ‘Cross National Study on the Epidemiology of Erectile Dysfunction and its Correlates’\textsuperscript{37} showed that men with a heart disease, hypertension, diabetes, prostate diseases or surgery, depression, gastric or duodenal ulcer, or with hormonal treatment had a 1.64 times higher risk for erectile dysfunction compared with ‘healthy’ men, when controlled for age. Also the degree of physical activity, current smoking and educational level were significant predictors. A limit of this study may be that a proportion of the healthy men were undiagnosed with previous mentioned diseases.
Another Cross National study\textsuperscript{28} showed a significant relationship between International Prostate Symptom Score and lower urinary tract symptoms induced bother. Men with severe lower urinary tract symptoms had a noticeably higher degree of dissatisfaction (62\%) compared to those with moderate lower urinary tract symptoms (14\%). When compared with men without lower urinary tract symptoms, the incidence of erectile dysfunction is twice as high in men with moderate lower urinary tract symptoms and more than 3 times as high in those with severe lower urinary tract symptoms.\textsuperscript{28}

In the UrEpik study\textsuperscript{30} there was a strong difference among the four countries, in the attitude towards consultation for erectile dysfunction. Factors that influenced consulting a doctor were physical activity, diabetes, high blood pressure, heart attack, prostatitis, and benign prostatic hyperplasia. It is remarkable that just 4.8\% of men with erectile dysfunction visited a doctor because of their sexual dysfunction.

Overall, as can be seen in Table I, the results show that men with lower urinary tract symptoms have a higher risk of also having erectile dysfunction. The Odds ratios vary from 1.4 to 9.7.


table I. Evidence of a significant correlation between LUTS and male sexual dysfunction in community-/population-based studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study type</th>
<th>Country</th>
<th>Sample</th>
<th>Prevalence</th>
<th>Odd ratios (95% CI) No LUTS referent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blanker et al. 2001 (24)</td>
<td>community based</td>
<td>Netherlands</td>
<td>1688 men, aged 50-70</td>
<td>ED 11%</td>
<td>LUTS mild 1.8 (0.8-4.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LUTS moderate 3.4 (1.4-8.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LUTS severe 7.5 (2.5-22.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IPSS 8-35 1.39 (1.10-1.74)</td>
</tr>
<tr>
<td>Boyle et al. 2003 (20)</td>
<td>community based</td>
<td>UK, Netherlands, France, Korea</td>
<td>4800 men, aged 40-79</td>
<td>ED 21.1%</td>
<td></td>
</tr>
<tr>
<td>Braun et al. 2003 (25)</td>
<td>community based</td>
<td>Germany</td>
<td>4489 men, aged 30-80</td>
<td>LUTS 44%</td>
<td>LUTS 2.11 (1.75-2.55)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LUTS in pts with ED 72.2%</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LUTS in pts without ED 27.2% ED 19%</td>
<td></td>
</tr>
<tr>
<td>Holden et al. 2005 (1)</td>
<td>population based</td>
<td>Australia</td>
<td>5990 men,</td>
<td>LUTS 16%</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ED M/S 21%</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Study Design</td>
<td>Location</td>
<td>Men Count</td>
<td>Aged</td>
<td>LUTS %</td>
</tr>
<tr>
<td>-----------------------</td>
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</tr>
<tr>
<td>Li et al. 2005 (28)</td>
<td>community based</td>
<td>Asia</td>
<td>1155</td>
<td>aged &gt;40</td>
<td>LUTS 14-59</td>
</tr>
<tr>
<td>Mariappan et al. 2006</td>
<td>population based</td>
<td>Malaysia</td>
<td>353</td>
<td>aged &gt;40</td>
<td>LUTS 80%</td>
</tr>
<tr>
<td>Nicolosi et al. 2003</td>
<td>population based</td>
<td>Brazil, Italy, Japan, Malyasia</td>
<td>2412</td>
<td>aged 40-70</td>
<td>ED M/S 16.1</td>
</tr>
<tr>
<td>Rosen et al. 2003</td>
<td>population based</td>
<td>US, UK, France, NL, Italy, Germany, Spain</td>
<td>12815</td>
<td>aged 50-80</td>
<td>LUTS M/S 31%</td>
</tr>
<tr>
<td>Shabsigh et al. 2005</td>
<td>population based</td>
<td>USA</td>
<td>28691</td>
<td>aged 20-75</td>
<td>ED 19%</td>
</tr>
<tr>
<td>Shiri et al. 2005</td>
<td>population based</td>
<td>Finland</td>
<td>1126</td>
<td>aged 50, 60, and 70</td>
<td>NA</td>
</tr>
<tr>
<td>Stroberg et al. 2006</td>
<td>population based</td>
<td>Sweden</td>
<td>725</td>
<td>aged 60-70</td>
<td>LUTS 51%</td>
</tr>
</tbody>
</table>

LUTS: lower urinary tract symptoms; ED: erectile dysfunction; CI: confidence interval; IPSS: International Prostate Symptom Score (0-7 mild, 8-19 moderate, 20-35 severe symptoms of LUTS) (23); M/S: mild/severe; NA: not assessed.
**Clinic based and health screening studies**

Voiding symptoms correlated significantly with a declining score on the 5-item version of the international index of erectile dysfunction (IIEF-5). In multivariate analysis International Prostate Symptom Score, voiding symptoms, nocturia and bother score correlated significantly with the presence of erectile dysfunction. Overall, men with lower urinary tract symptoms had a two-fold greater risk of erectile dysfunction compared to those without lower urinary tract symptoms. The greatest Odds ratios were present in men aged 51-60 years.

**Table II. Evidence of a correlation between LUTS and male sexual dysfunction in clinic/health screening based studies.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Study type</th>
<th>Country</th>
<th>Sample</th>
<th>Prevalence</th>
<th>Odds ratios (95% CI)</th>
<th>No LUTS referent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atan et al. 2006 (40)</td>
<td>clinic</td>
<td>Turkey</td>
<td>307 men, aged 21-77</td>
<td>LUTS 52.8%</td>
<td>ED 76.8%</td>
<td>OR not stated</td>
</tr>
<tr>
<td>Chia-Chu Liu et al. 2006(41)</td>
<td>health screening</td>
<td>Taiwan</td>
<td>160 men, older than 45 years</td>
<td>ED 56.1-84.2%</td>
<td>OR not stated</td>
<td>LUTS mild referent LUTS M/S 3.27 (1.52-7.02)</td>
</tr>
<tr>
<td>Elliott et al. 2004 (37)</td>
<td>clinic</td>
<td>US</td>
<td>181 men, mean age 68.2 years</td>
<td>NA</td>
<td>OR not stated</td>
<td>yes for ED and obstructive LUTS or depression OR not stated</td>
</tr>
<tr>
<td>El-Sakka et al. 2005 (38)</td>
<td>office</td>
<td>Egypt</td>
<td>374 men, aged 45-63</td>
<td>LUTS 80.7%</td>
<td>ED 100%</td>
<td>OR not stated</td>
</tr>
<tr>
<td>Glina et al. 2005 (32)</td>
<td>clinic</td>
<td>Brazil</td>
<td>118 men, aged &gt;40</td>
<td>LUTS 16-40%</td>
<td>ED 11-29%</td>
<td>age adjusted (Pearson) -0.25</td>
</tr>
<tr>
<td>Ponholzer et al. 2004 (42)</td>
<td>health screening</td>
<td>Austria</td>
<td>2858 men, aged 20-80</td>
<td>LUTS 84%</td>
<td>ED 32%</td>
<td>LUTS 2.2 (1.8-2.8) nocturia 1.4 (1.1-1.7)</td>
</tr>
<tr>
<td>Terai et al. 2004 (33)</td>
<td>clinic</td>
<td>Japan</td>
<td>2084 men, aged &gt;18</td>
<td>ED 85.7%</td>
<td>OR not stated</td>
<td>mild LUTS referent LUTS M/S 1.52 (age adjusted)</td>
</tr>
<tr>
<td>Vallancien et al. 2003 (43)</td>
<td>clinic</td>
<td>France, Denmark, Netherlands, Switzerland, UK</td>
<td>927 men, aged 36-92</td>
<td>ED 62%</td>
<td>OR not stated</td>
<td>moderate LUTS 1.18 (0.7-2.0) severe LUTS 1.94 (1.09-3.46)</td>
</tr>
</tbody>
</table>

LUTS: lower urinary tract symptoms; ED: erectile dysfunction; CI: confidence interval; IPSS: International Prostate Symptom Score; M/S: mild/severe; NA: not assessed; SHIM: Sexual Health Inventory for Men (34).
The strong relationship between age, international prostate symptom score severity and erectile dysfunction is also concluded by Vallancien et al. Men aged 70 years old or older were nearly 6 times as likely to experience erectile dysfunction compared to those aged younger than 60 years. Men with severe lower urinary tract symptoms were about as twice as likely to have erectile dysfunction compared to those with mild lower urinary tract symptoms. At least 82% of men with erectile dysfunction were bothered by their sexual dysfunction. This bothersomeness significantly decreased with age, but significantly increased with lower urinary tract symptom severity. It needs to be considered that the men who took part in this study differs from men in the community based studies, because they all had exhibited some form of health seeking behaviour relating to lower urinary tract symptoms. Overall, as can be seen in table II, these studies show the similar results compared to the results from community- and population based studies: men with lower urinary tract symptoms have a higher risk of also having erectile dysfunction. The Odds ratios vary from 1.1 to 3.3. The patient population seen by a general practitioner was not specifically described in any of these studies.

**Relationship between Erectile Dysfunction and Cardiovascular Disease**

Endothelial dysfunction, in which damage to the lining of the arterial wall impairs the nitric oxide pathway and vasodilatation, is an important pathophysiologic factor underlying both erectile dysfunction and cardiovascular disease. Several risk factors, including inflammation, hypoxia, oxidative stress and homocysteinemia, are related to this endothelial dysfunction. The major cardiovascular risk factors as smoking, high body mass index, hypercholesterolemia, diabetes, and hypertension occur more often in individuals with erectile dysfunction. The prevalence of erectile dysfunction is also directly related to the number of cardiovascular risk factors present, being highest in individuals with more than three. One study showed that 19% of men with erectile dysfunction of vascular origin had angiographically documented silent coronary artery disease. In patients with erectile dysfunction who were referred to a clinic because of their erectile dysfunction, left ventricular dysfunction was an independent risk factor for erectile dysfunction, independent of heart failure symptoms. Moreover, symptoms of erectile dysfunction appeared 3.04 +/- 7.2 years prior to the cardiovascular event. Ponholzer found a 65% increased risk of developing coronary artery disease within 10 years in patients with erectile dysfunction compared with those without erectile dysfunction.

Data from the Prostate Cancer Prevention Trial (a prospective study in a clinical setting) showed that in 9457 men, aged 55 years and older, incidental erectile
dysfunction was statistically significantly associated with subsequent angina, myocardial infarction, and stroke. The unadjusted risk of an incidental cardiovascular event among men without erectile dysfunction at study entry was 1.5% per person-year compared with 2.4% per person-year for those with erectile dysfunction. Incidental erectile dysfunction had also an equal or greater effect on subsequent cardiovascular events of the same magnitude as a family history of myocardial infarction (HR 1.46; 95% CI 1.16-1.83), cigarette smoking (HR 1.46; 95% CI 1.07-1.97), or measures of hyperlipidemia (HR 1.03; 95% CI 0.98-1.08).40

A historical cohort study, using medical records of general practices in the Netherlands, concluded that erectile dysfunction could be seen as a marker for cardiovascular diseases before the introduction of Sildenafil (OR 1.7 (95%CI 0.9-3.3)) but not so clearly afterwards (OR 1.1 (95%CI 0.6-1.8)).50 However it is questionable if this is a significant difference. Both confidence intervals contain 1 and cannot be said to differ significantly from 1.

Ströberg et al.36 do not support the concept that erectile dysfunction is a clinically useful predictor of the more severe cardiovascular diseases, such as myocardial infarction. The incidence of erectile dysfunction was higher in the Myocardial Infarction group (32%) compared to the control group (18%). However the difference was not significant and 2/3 of the Myocardial Infarctions were not preceded by erectile dysfunction. Also Travison et al. concluded that erectile dysfunction is not a common predictor for cardiovascular diseases. Erectile dysfunction spontaneously disappeared in 35% of the study population (95% CI 30-40%).49

**Discussion**

Different studies describe the correlation between lower urinary tract symptoms and erectile dysfunction. Men with lower urinary tract symptoms have a higher risk of also having erectile dysfunction. The Odds ratios vary from 1.1 to 9.74. Studies differ in their study populations. As well clinical as community based studies are described. Also different kinds of questionnaires are used, and sometimes the results were obtained by direct interviews instead of self-administered questionnaires. Another difference is the way of statistical analysis: univariate and / or multivariate analysis. But even though there are differences in the way the previous described studies have been done, in both community and clinical based studies the conclusion was the same: men with lower urinary tract symptoms have a higher risk of also having erectile dysfunction. The
patient population seen by a general practitioner was however not specifically described in any of these studies.

Formerly dismissed as a psychological condition, urologists now assume that erectile dysfunction is a powerful risk-marker for cardiovascular diseases. Most studies mentioned previously are based on outclinic patient populations. The predictive value of erectile dysfunction for consequently cardiovascular diseases is confirmed by most of the studies, but not all. Also, it is almost not investigated in the patient population of a general practitioner.

There is a difference in cause of erectile dysfunction between the male population that visits the urologist, mostly somatic, and the male population of the general practitioner, where the distribution between somatic and psychological erectile dysfunction is almost equal. The prevalences concerning the causes of erectile dysfunction in primary care show a shift from a more psychological condition at younger age to a more somatic disorder in the elder men. But even though, it is often a mixture of psychological and somatic causes. This complicates the reasonable suggestion of screening for cardiovascular diseases in men with erectile dysfunction as early as possible. The Princeton consensus recommends screening for modifiable cardiovascular risk factors in patients with erectile dysfunction. By doing so, cardiovascular diseases can possibly be prevented. The Dutch guideline 'Erectile dysfunction' for the General Practitioner does not recommend screening for cardiovascular diseases in men with Erectile Dysfunction, until more follow up studies have been done.

Only few men contact their physician for their erectile dysfunction, varying from 5 to 24%. In the Netherlands, general practitioners perform specific case finding, but do not screen for risk factors in their total patient population. Most people who develop atherosclerotic cardiovascular disease have several risk factors which interact to produce their total fatal cardiovascular risk, which can be estimated directly by using the SCORE risk estimation system. General practitioners inquired about erectile dysfunction in less than 10% of their patients. If erectile dysfunction is to be a practically useful predictor, it must also be a reason for a man to seek medical attention, which was rarely the case in several study populations.

Correlations we investigated are studied mainly in clinical or community based populations. Data from patient populations in primary care must help health care providers decide if and when to screen for cardiovascular diseases in men with erectile dysfunction.
Conclusions

The evidence of a positive correlation between lower urinary tract symptoms and erectile dysfunction, as well as between erectile dysfunction and cardiovascular diseases is significant in community and clinical based studies. It is as yet not known if these correlations are significant in the patient population of primary health care. We need more evidence to prompt the general practitioner to screen every man with the initial presentation of erectile dysfunction for standard cardiovascular risk factors and, as appropriate, start initiative cardioprotective interventions.

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