Lower urinary tract symptoms in older men: does it predict the future?
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The main objective of this thesis was to improve our knowledge of the epidemiology of comorbidities in men with lower urinary tract symptoms (LUTS). We focussed especially on the relation between LUTS and erectile dysfunction (ED). Furthermore on the relation between LUTS and cardiovascular diseases (CVD). We aimed to discover if the time-dependent relations found between LUTS and ED could be confirmed in primary care. Since there were just a few studies available on the relation between LUTS and CVD, we conducted research on time-dependent relationships between LUTS and CVD in both community care and primary care.

We conducted registry studies using data from the Registration Network Groningen, and the Krimpen study, as well as a systematic review and meta-analysis. In this chapter we will summarise the independent chapters of this thesis. Then we will discuss the results and consider the importance of addressing LUTS and its comorbidities. We will also focus on the shared care of LUTS and the epidemiological differences of relations between LUTS and comorbidities. Furthermore we will reflect on the broader context of clinical practice and possible further implications.

**Summary**

After the introduction in Chapter 1, Chapter 2 reviews the information about the relation between LUTS, ED, and CVD in different male population groups in the period 1997-2007. In this review article 20 studies were included, representing 71,322 men. There were almost no results from primary care population based studies. All studies were either community or clinical based. We found a significant relation between LUTS and ED in population based and community based studies. The odds ratios varied from 1.4 to 9.74. Just one study based on a primary care population was described. No longitudinal results were available. The results describing the relation between ED and CVD are conflicting, and most studies had population bias, and were cross sectional. Just one primary care based study was found. ¹

In Chapter 2 we conclude that it remains unknown whether the relation between LUTS and ED is causal. Furthermore, we conclude that a causal association between erectile dysfunction and cardiovascular diseases is not proven in primary care.

We conducted a primary care based cohort study to find out if a time-dependent relation between LUTS and ED is present in primary care (Chapter 3). Data from the Registration Network Groningen were used. The total study population consisted of 5957 men, aged 50 years and older, of whom 1284 (21.6%) were registered with LUTS.
Erectile dysfunction was present in 508 men (8.5%), of whom 16% (N=200) in the LUTS group, and 7% (N=308) in the non-LUTS group (p<0.001). In a posthoc longitudinal analysis (follow-up time 1-14 years, median 6.63) we found a time-dependent relation between LUTS and ED (adjusted HR: 1.41, 95%CI 1.12-1.74). Therefore, men from this cohort, with LUTS, were more likely to develop ED, at any time, than men without LUTS.

In Chapter 4 the time dependent relation between LUTS and CVD in a primary care setting is described. We used the data from the Registration Network Groningen for the period January 1998 to December 2008. In a registry study, results from a primary care male patient population with a follow-up period of 11 years were described, including 6614 men aged 50 years and older, contributing 54,250 studied person-years in total (mean 8.2py, SE 0.04py). In the study period, 1165 (17.6%) men aged 50 years and older had LUTS registered. In that same period 1539 men (23%) reported CVD: 41% in men with LUTS versus 20% in men without LUTS (p<0.01). In the longitudinal analysis we found a significant result in men with LUTS for subsequent CVD if we did not adjust for confounders (HR 1.16, 95% CI: 1.035 - 1.291; p=0.010). After adjustment for confounders there was no longer a significant relation between LUTS and future CVD (HR=0.921, 95%CI: 0.824 - 1.030; p=0.150). In conclusion: in this primary care study men with LUTS are no more likely to develop CVD at any time compared to men without LUTS.

Since only cross-sectional studies were found, and just one study on the longitudinal relation between LUTS and CVD (see Chapter 2), we decided to examine not only the relation between LUTS and CVD in a primary care setting, but also to conduct a study in a community based setting. We did posthoc analyses on the data from the large Krimpen study (Chapter 5). In our analyses, 1610 men with LUTS could be included aged 50-75 years. The follow-up period for data on cardiovascular diseases was 8 years: 1995-2003. In our cross-sectional analyses we found a significant relation between LUTS and CVD: OR 2.04 (unadjusted, 95%CI 1.58-2.63) without adjustment for confounders, OR 1.86 after adjustment for age (95%CI 1.53-2.41), and OR 1.81 (95%CI 1.38-2.37) in the multivariate analysis. 1248 Men were selected for the longitudinal analyses, with a mean follow-up time of 6.55 years. We found no significant relation between LUTS and CVD in this longitudinal analysis: unadjusted HR 0.98 (95%CI 0.52-1.86), and adjusted HR 1.08 (95%CI 0.57-2.07). We conclude that LUTS and CVD commonly coincide, and that men with LUTS are not more likely to develop subsequent CVD.
Chapter 6 presented a systematic review and a meta-analysis on the relation between LUTS and CVD described in longitudinal studies that have been conducted so far. Five studies with 6027 men with follow-up times varying from 5-17 years described the relation between LUTS and CVD. The pooled effect size: HR 1.09 (95% CI 0.90-1.31); p=0.40. Another two studies described the relation between nocturia and CVD mortality. Despite the observed association between LUTS and CVD in cross sectional studies, this systematic review cannot confirm a time-dependent relation between LUTS and CVD.

General discussion

By conducting this research we want to contribute to an appropriate use of healthcare focussed on the needs of elderly men, and explore the differences between primary care and clinical care on this subject. We have a special interest in the primary care because the GP has a central role as gatekeeper to all further secondary care and an increasingly central role in preventive medicine. Since all Dutch inhabitants are registered with a GP, and about 77% of all people consult their GP every year, the GP is in an ideal position to deliver preventive medicine.

Evidence for causal relationships between LUTS and mentioned erectile dysfunction / cardiovascular disease could influence mortality and quality of life in patients with LUTS. Is the general practitioner obliged to start preventive therapy for cardiovascular diseases in men with LUTS? Or is he/she supposed to inform patients about higher incidence of erectile dysfunction in men with LUTS?

LUTS: shifting the focus from prostate to bladder

During this study, a paradigm shift in the clinical understanding and evaluation of LUTS has started. This has effects on study designs and definitions of study variables. As we already mentioned in the Introduction, it is not only the prostate that seems to be responsible for the LUTS symptoms. Indeed there is increasing recognition that LUTS may be due to bladder abnormalities, urethral abnormalities and/or polyuria of various types. Also LUTS are not sex specific: storage symptoms increase with age in both male and female patients. There is a similar distribution of both storage and voiding symptoms in both men and women. This shift of paradigm also has changed the view on prevalence, and pathophysiological mechanisms of comorbidities in men/women with LUTS. In Figure 1, the multifactorial causes of LUTS are combined with an overview of pathophysiological mechanisms and interactions between these different causes of LUTS. It illustrates the relations between LUTS and multifactorial causes, and its pathophysiological mechanisms.
Fig 1. LUTS: shifting the focus from the prostate to the bladder.

Multifactorial causes of LUTS and its pathophysiological mechanisms. BPO: benign prostate obstruction; other*: polyuria of various types, urethral abnormalities, bladder abnormalities. Vascular risk factors #: Obesity, hyperinsulinaemia, physical inactivity, smoking, dyslipidaemia.

Relation between LUTS and ED

In our review we discovered that the relation between LUTS and ED was predominantly found in cross-sectional studies, and in just a few longitudinal ones. In our primary care based, open cohort study we found that LUTS and ED are time-related, so new ED in men with LUTS is more likely than in men without LUTS, at any moment in time. We confirm the advice from the Dutch guideline LUTS 6 to ask for co-diagnosis of ED in men with LUTS. We suggest informing patients that ED is more prevalent in men with LUTS and that they also have more chance of developing ED. We believe our results are clinically
relevant, despite a low HR (1.41, 95%CI 1.12-1.74). However it is important to state that just a fraction of the true number of ED cases are presented to the general practitioner, versus above 50% of LUTS cases. Since quality of life (QOL) is affected in most men with ED, awareness of GPs that patients with LUTS are more likely to have ED at any moment in time compared to patients without LUTS can possibly lead to better QOL of for patients with ED.

The association between LUTS and ED could not be accounted for by the risk factors common to both conditions and described earlier in Chapter 3, when we specifically adjusted the HRs of ED by LUTS for hypertension, diabetes mellitus, obesity, dyslipidaemia, depression, smoking, heart disease, LUTS medication, diabetes medication, and antihypertensive medication. The association between LUTS and ED may be due to biological or psychosocial factors, and LUTS is probably an early sign of shared underlying pathophysiological mechanisms.

Relation between ED and CVD
We did not search for the relation between ED and CVD in our primary care database, as there were limited numbers of patients with registered ED. A lack of study power would make the results of such a study non-significant, and has no implications for clinical practice. In a longitudinal, community based study, men with ED were found to be a higher risk for cardiovascular disease (adjusted HR: 2.6 (95%CI1.3-5.2)). A suggestion was made that a cardiovascular risk profile assessment should be considered in men aged 50 years and over presenting with an erectile dysfunction. However it is still not known if the found relation between ED and CVD can also be found in primary care.

Relation between LUTS and CVD
Since there were very limited results from longitudinal studies, we studied the relation between LUTS and CVD in both community care and primary care settings. The longitudinal studies, with long follow-up periods and large study groups showed a relation between LUTS and CVD, but could not prove a time-dependant relation, after adjustment for confounders. We concluded that LUTS and CVD seem to coincide often and do not have a causal relation. So this means that in men with LUTS a cardiovascular risk assessment should not be considered. To relate our study results to more recent longitudinal studies on this subject, we conducted a systematic literature search, and a meta-analysis, of all results on the relation between LUTS and CVD from these longitudinal studies. The meta-analysis results did not show a causal relation between LUTS and CVD. Longitudinal studies in high-risk patients are lacking, and surprisingly, no data from secondary or tertiary care settings were found. As we stated earlier, one of
the consequences of different definitions/aetiologies of LUTS (and CVD in this case) could have made it impossible to find an association in our review. We think that other possible causes of CVD should also be considered in studying the association between LUTS and CVD, such as nicotine abuse, hyperlipidaemia, BMI, and alcohol abuse. Not all cardiovascular risk factors were included in the longitudinal studies. This might have had impact on the results of the studies.

In Figure 2, we summarise the results from our thesis, illustrated in a triangle LUTS – ED – CVD. The arrows show the temporal sequences we studied, if significant relations were found, and if these relations were found in primary care, secondary care, or in community based studies.

![Diagram showing time-dependent relations between LUTS, ED, and CVD](image)

**Fig 2.** Time-dependent relations between LUTS – ED – CVD in different populations.

*CB: community based studies, PC: primary care studies, CP: clinical practice studies, LUTS: lower urinary tract symptoms, ED: erectile dysfunction, CVD: cardiovascular disease*

As can be seen from Figure 2, we conclude that LUTS, ED, and CVD are related. Time-dependent relations are found for LUTS – ED, and ED-CVD in community care and
secondary care settings. For LUTS – ED this is found in primary care as well. For LUTS-CVD, however, we conclude that these conditions coincide. Longitudinal studies on all three described relations are surprising scarce, especially in primary care. These longitudinal studies are needed to prove causal relations.

With our study outcomes, and after reviewing the literature, we want to emphasise that alertness is needed when suggestions are made for more preventive measurements and/or preventive medical interventions. General practitioners and clinicians have to be aware of the differences between study populations. Still, suggestions for GPs' policy are made in articles from small longitudinal studies – and even from cross-sectional studies - that are not representative for patients from primary care. 9,10

Strengths and limitations
The strengths and weaknesses of the individual studies included in this thesis have been described in the corresponding chapters. However, the major overall strength of this thesis is the huge amount of data from large populations we had access to and the long follow-up periods. We believe primary care has a unique position in longitudinal research settings.

There are also some limitations of this thesis that should be mentioned. Our first review was not complete by just mentioning definitions for LUTS, and not for ED or CVD.

Secondly, data used from the Registration Network Groningen are not collected periodically. The registration network is a continuous morbidity registration, so data are registered structurally. In a more ideal situation, we would use more standardised data. Also we could not use all variables describing lifestyle factors in our analyses, as these are not collected for all patients in the registration. Therefore it was not possible to search for relations in both the contexts of diseases and symptoms/lifestyle. In the studies using data from Registration Network Groningen, we could not exclude under-registration of cardiovascular risk factors. Therefore additional searches into medical files could yield some of the unknown information about these cardiovascular risk factors.

Next, in the two RNG studies (Chapter 3 and 4), we assumed the presence of LUTS if one or more LUTS-like ICPC codes were identified. 11 Unfortunately, this did not always agree with the LUTS definition from other studies, so studies were more difficult to compare. However, the found results and conclusions were comparable with the results
from the Krimpen study, in which we also used the IPSS. We were not able to differentiate between the different categories of LUTS (mild/moderate/severe) due to small subgroups (Krimpen study, Chapter 5) or the use of ICPC codes. Differentiating between these severity groups (especially in the large RNG study groups) would have led to better comparison with other longitudinal studies.

**Registration networks, primary care and research**

In relation to this study, in which we focussed on primary care data, we want to make some comments about research in primary care, and the use of data from general practice registration networks (GPRNs).

The family physician has a unique medical role in care for unrestricted health problems in all patient groups. Diagnosis and the diagnostic process take centre stage, as most morbidity is presented and identified in primary care. Research in primary care can improve patient care, further understanding of diseases and comorbidities, and increases insight into the effectiveness of interventions.

A particular strength of GPRNs is their ability to tap into continuity of patient care, and extend the timeframe of research from the couple of years that usually can be covered in projects. This opens the possibility to obtain data on the long-term natural history of outcome of care of disease and is essential in assessing the effectiveness of interventions in family practice. GPRNs have the potential of producing large amounts of data and allowing searches for comorbidities and possibilities for prevention.

We used data from the Registration Network Groningen, one of the eleven GPRNs in primary care. All networks collectively support the need for qualitatively good data. It is important to collect data completely and correctly and 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.

RNG is a ‘contact’ and ‘problem’ list-based GPRN. The database contains information about the health problems of a patient that are permanent, chronic, or recurrent. Also information about all patients’ health complaints and diagnoses from all contact with the practice is stored. Extras are the storage of out of hours contacts, and contacts with the assistant or physician assistant etc., leading to a more complete dataset. There is, however, no control of data after extraction.
Researchers using data lack information not recorded and not coded, such as free text in the medical records. Conducting the studies with use of RNG data, we were not sure if all health problems were coded by ICPC, especially when two or more problems were presented in one contact with the GP. We had to make the assumption that all health problems were coded in a structured way; every medical issue registered with a separate ICPC code.

There is no international standard approach to coding and classification.\(^\text{15}\) Many countries use ICPC (international Classification for Primary Care), developed by the WONCA international classification committee.\(^\text{16}\) The ICPC, also used in the GPRNs, offers 400 codes for coding reason for encounter, diagnostic and therapeutic procedures and diagnoses for directed health problems with a prevalence of 1.0 or more per 1000 patients. It is the smallest (offering fewest coding alternatives) compared with ICD-10, and CT v3.

**Implications for clinical practice, research, and education**

For a start, this thesis implicates that for men with LUTS, the GP must inform them about the co-incidence of LUTS and ED as well as about more future ED in men with LUTS, since ED affects quality of life. The GP does not have to search for cardiovascular risk factors or start preventive treatments to prevent subsequent cardiovascular diseases in men with LUTS. For some patients this is a positive outcome. Nowadays, GPs have to increasingly focus on the implementation of prevention programmes for chronic diseases, such as hypertension, diabetes mellitus, and cardiovascular diseases. The GP has an important function in finding patients at risk. Subsequently more people become ‘patients’ at a younger age. It should not be forgotten that on average life expectancy is higher than ever before.\(^\text{17}\) More interventions/therapy should lead to significant better QOL and less morbidity. We have to be careful as preventive healthcare can be an important reason of polypharmacy, especially in older people.\(^\text{18}\)

We aimed for appropriate use of healthcare focussed on the needs of elderly men. Life expectancy in men is lower than women.\(^\text{19}\) Although men have more chronic diseases and risk factors, they visit the GP less often than women.\(^\text{20}\) This implicates that there are men who could benefit from further research in reducing this disparity between men and women. In addition, consideration of preventive and early detection / intervention programmes may improve men’s health.\(^\text{19}\) Based on this thesis we cannot recommend starting cardiovascular prevention programmes for men consulting their GP for LUTS.
Implications for clinical practice and further research also consider the insufficient definition of LUTS by the current ICPC codes. Appropriate coding is important for awareness of the paradigm shift described earlier, and there should be a code for LUTS with sub-codes for voiding, storage, or post-micturition symptoms (both for men and women, U-codes, not Y-codes). Results from studies still generate theories about the pathophysiology of LUTS and its comorbidities. Future research in large longitudinal settings, using more standardised definitions, will support this process. Primary care studies are also needed on this subject LUTS. They can provide large studies on longitudinal data and further improve ‘shared care’. This is necessary, since there are epidemiological differences between populations from primary and clinical care.

More research in primary care, using data from large primary care databases, has implications for education of GPRN GPs and students. Training of GPs (GP trainees, doctors’ assistants) in using a classification system, e.g. ICPC, is essential for the quality of coding. For future education of GPs and/or trainees, this thesis implicates the need to create awareness of LUTS being non-sex specific conditions with different subcategories and possible clinically relevant comorbidities. GPs learning about this change of definitions may alter the treatment options for both women and men. The recently updated Dutch GP guideline on this subject already emphasises the previously mentioned paradigm shift.

**General conclusion**

This study has improved the knowledge of LUTS and comorbidities, especially the relation between LUTS, ED, and CVD. We conclude that LUTS is related to ED and CVD in both primary care and community based settings. There is a time-dependent relation between LUTS and ED, also in primary care. A causal relation between LUTS and future CVD is not proven yet in primary care or community settings.

General practitioners do have to inform their patients with LUTS about the higher risk of developing ED at any time, compared to men without LUTS. However, there is no evidence to recommend general practitioners screening automatically for cardiovascular risk factors or starting early treatments to prevent subsequent cardiovascular diseases in men with LUTS.
References


