Normal values and determinants of urogenital tract (dys)function in older men: The Krimpen Study

Normaalwaarden en determinanten van (dis)functie van de tractus urogenitalis bij oudere mannen: De Krimpen Studie

Cover illustration: Hollandsche IJssel dam, Krimpen aan den IJssel, the Netherlands (first part of the Dutch Deltaworks)
Printed by Optima Grafische Communicatie, Rotterdam

The research described in this thesis was financially supported by the Foundation for Urological Research (SUWO), Rotterdam, the Netherlands.

ISBN 90-6734-007-3

Normal values and determinants of urogenital tract (dys)function in older men: The Krimpen Study.

Normal values and determinants of urogenital tract (dys)function in older men: The Krimpen Study

Normaalwaarden en determinanten van (dis)functie van de tractus urogenitalis bij oudere mannen: De Krimpen Studie

Proefschrift

ter verkrijging van de graad van doctor
aan de Erasmus Universiteit Rotterdam
op gezag van de Rector Magnificus
Prof.dr.ir. J.H. van Bemmel
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
woensdag 9 oktober 2002 om 15.45 uur

door

Marcus Hendrikus Blanker

geboren te Rotterdam.

Promotiecommissie

Promotoren

Prof.dr. J.L.H.R. Bosch

Prof.dr. S. Thomas

Copromotor

Dr. A.M. Bohnen

Overige leden

Prof.dr. M.W. Hengeveld

Prof.dr. A.W. Hoes

Dr. F.P.M.J. Groeneveld

Paranimfen

Michiel den Oudendammer

Mischa Thiele

Iemand met veel vrienden moet zelf wel een vriend zijn.

Voor onze vriend Kadri
Voor Simone en mijn ouders

Contents

Part VI Appendix

Part I

Introduction, aim and design of study

Chapter 1

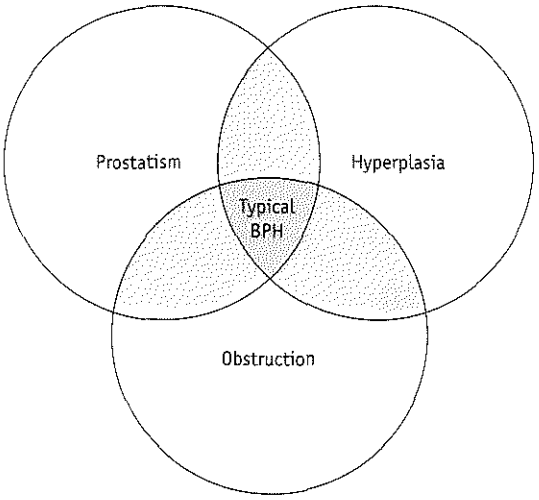
General introduction

Although symptoms of the lower urogenital tract are common and bothersome in older men,[1-3] it seems that only a small percentage of men visit their general practitioner for these symptoms.[4,5] With the ageing of the population, the number of men consulting their physician will increase significantly, with a related demand on health care resources. There are various guidelines for the evaluation and treatment of such symptoms,[6-8] but these all suffer from a common drawback: in the evaluation of lower urogenital tract symptoms physicians are still hampered by a lack of consensus on definitions and normal values, by a lack of insight into their natural history and, consequently, by the lack of unambiguous diagnostic and therapeutic tools.
This thesis addresses some of these problems by applying basic epidemiologic research methods to the following topics.

Lower urinary tract symptoms (LUTS)

Benign prostatic hyperplasia is reported to be the main cause of LUTS in older men.[1,9-13] Consequently, physicians are traditionally educated to classify LUTS as "prostate-related" in men and, in contrast, as "bladder-related" in women. Clinical benign prostatic hyperplasia is mostly defined by the concept proposed by Hald,[14] in which the presence of LUTS, prostate enlargement and bladder outflow obstruction are considered together, as presented in Figure 1.1.
Depending on the definitions used for symptoms, bladder outflow obstruction and prostate enlargement, the overlap of the three circles may vary and, consequently the prevalence of benign prostatic hyperplasia may also vary considerably.[1,11,15]
In epidemiologic research, it has been shown that there is only a weak association between LUTS, benign enlargement of the prostate, and bladder outflow obstruction.[15,16] Many older men have an enlarged prostate without LUTS or bladder outflow obstruction, whereas others have severe LUTS without an enlarged prostate or bladder outflow obstruction. To avoid the suggestion of diagnostic accuracy in such cases, Abrams suggested to use other terms[17]: The term "lower urinary tract symptoms" is the most accurate to describe a patient's symptoms, without implying their cause. "Benign prostatic enlargement, BPE" is preferred to the use of "benign prostatic hyperplasia" as the latter is a precise histological term and not a parameter that can be clinically and epidemiologically

Figure 1.1. *Relation between lower urinary tract symptoms, prostate enlargement and infravesical obstruction according to Hald[14] (BPH; benign prostatic hyperplasia)*



assessed, for instance by digital rectal examination and transrectal ultrasound. The term "benign prostatic obstruction, BPO" has similar advantages, if used in cases where objective evidence of obstruction exists such as reduced urinary flow rate or raised voiding pressures in combination with low flow rates.[17] "Bladder outflow obstruction, BOO" may also be present in men with no LUTS or without prostate enlargement.

Natural history of LUTS

Few data on the natural history of LUTS are available that are based on longitudinal findings in the general population,[9,18-20] whereas more information is available from studies in selected populations.[10,21] Population-based studies addressing the natural history of LUTS are an essential part of treatment outcome research.[22] Moreover, these data are necessary to define populations at risk for complications (e.g. acute urinary retention and urinary tract infections) and for clinical decision making.

Sexual dysfunction

Sexual dysfunction in older men mainly consists of problems with erection, ejaculation, libido and decreased sexual activity. Erectile dysfunction is common in older men,[23-27] with all studies showing a distinct increase of this problem with advancing age. However, the prevalence rates in these studies vary considerably, probably due to the different definitions used.

Traditionally, erectile dysfunction has been related to the diagnosis and treatment of benign prostatic hyperplasia. Most importantly, it has been described as one of the complications of operative treatment.[28] Alternatively, it has been suggested that erectile dysfunction improves

with the treatment of LUTS and hypertension by alpha-blockers.[29,30] Age-specific data on erectile function in the population are needed to accurately judge the value of treatment outcome studies in populations of older men.

Only a few studies describe related factors for erectile dysfunction in a population sample of older men.[23,25,31] In these studies, however, the age of the responders was low, a clear definition of erectile dysfunction was lacking,[23] or response rates were low.[23,31] Thus, a clear picture of determinants for erectile dysfunction in community-dwelling older men is lacking.

With the introduction of new classes of drugs for erectile dysfunction and the ageing of the population, it is expected that more men will visit their physician for this problem. Therefore, there is a need for more accurate information on this condition, collected from population-based surveys.

Ejaculatory dysfunction has only been studied in a small survey in England.[32] In a French survey, "ejaculatory difficulty" was studied but the researchers did not clearly define this problem.[33] The epidemiologic database on ejaculatory dysfunction is therefore very limited.

Little is known about the sexual activity of older men, especially in relation to erectile and ejaculatory dysfunction.[34-38] Most of these studies are restricted to married men. As marital status itself may influence sexual activity and erectile and ejaculatory dysfunction, this restriction seems inappropriate.

Health status in men with lower urogenital tract symptoms

Both LUTS and genital tract dysfunction (erectile and ejaculatory dysfunction) have been reported as important determinants of reduced perceived health status.[24,26,39,40] In other studies on correlates for health status, the impact of urogenital tract dysfunction was not considered.[41-43]

Generally, health status can be considered in two ways. First, disease-specific health status can be assessed. For this purpose several instruments were developed to evaluate urogenital tract dysfunction,[44-46] and studies on this topic were reported.[32,47] Secondly, general health status can be determined using questionnaires such as the Sickness Impact Profile,[48] the MOS Short Form-36[49] and the Inventory of Subjective Health.[50] Use of such questionnaires allows general health status to be determined in relation to specific diseases or other conditions.[40,51-53] Both aspects of health status (i.e. disease-specific and general health) are important for medical care in general, and for patients with specific diseases in particular. When considering health status it should be recognised that it is a multifactorial entity. Therefore, when considering the effect of selected medical conditions, such as LUTS and genital tract dysfunction, the concurrent effect of other conditions and sociodemographic factors should also be taken into account.[42]

Study aims

The main research questions addressed in this work are:

1. What is the prevalence of LUTS in the Dutch community?
2. What is the prevalence and incidence of clinical benign prostatic hyperplasia, according to different definitions?
3. What are the normal values for the various components of lower urinary tract function, such as nocturnal and diurnal voiding frequency, urine production patterns, nocturnal urine production, average and functional bladder capacity, 24-hour voided volumes, prostate size, uroflowmetry and post void residual urine volumes?
4. What are appropriate definitions of abnormality for these parameters, especially in relation to LUTS or other conditions?
5. What is the natural history of LUTS, clinical benign prostatic hyperplasia and other urogenital tract parameters?
6. What is the prevalence and incidence of erectile and ejaculatory dysfunction?
7. What are the main determinants of these conditions?
8. What is the relation between LUTS and erectile and ejaculatory dysfunction?
9. What is the prevalence of sexual activity in relation to erectile and ejaculatory dysfunction?
10. How do LUTS and erectile and ejaculatory dysfunction relate to health status, separately and in conjunction with other medical conditions and sociodemographic factors?

To address these questions, the Krimpen Study on male urogenital tract dysfunction and general wellbeing is being conducted.

References

1. Garraway WM, Collins GN and Lee RJ: High prevalence of benign prostatic hypertrophy in the community. *Lancet* 1991;338:469-71.
2. Ouslander JG: Aging and the lower urinary tract. *Am J Med Sci* 1997;314:214-8.
3. Peters TJ, Donovan JL, Kay HE, *et al.*: The International Continence Society "Benign Prostatic Hyperplasia" Study: the bothersomeness of urinary symptoms. *J Urol* 1997;157:885-9.
4. Wolfs GG, Knottnerus JA, Van der Horst FG, Visser AP and Janknegt RA: Determinants of doctor consultation for micturition problems in an elderly male population. *Eur Urol* 1998;33:1-10.
5. Ansong KS, Lewis C, Jenkins P and Bell J: Epidemiology of erectile dysfunction: a community-based study in rural New York State. *Ann Epidemiol* 2000;10:293-6.
6. Klomp MLF, Gercama AJ, De Jonge-Wubben JGM, *et al.*: [Dutch College for General Practitioners Guideline for lower urinary tract symptoms in older men.] NHG-standaard Bemoeilijkte mictie bij oudere mannen (eerste herziening) [Dutch]. *Huisarts Wet* 1997;40:114-124.
7. Ralph D and McNicholas T: UK management guidelines for erectile dysfunction. *BMJ* 2000;321:499-503.
8. Benign prostatic hyperplasia: diagnosis and treatment. Benign Prostatic Hyperplasia Guideline Panel. Agency for Health Care Policy and Research. *Am Fam Physician* 1994;49:1157-65.
9. Arrighi HM, Metter EJ, Guess HA and Fozzard JL: Natural history of benign prostatic hyperplasia and risk of prostatectomy. The Baltimore Longitudinal Study of Aging. *Urology* 1991;38:4-8.
10. Barry MJ, Fowler Jr FJ, Bin L, *et al.*: The natural history of patients with benign prostatic hyperplasia as diagnosed by North American urologists. *J Urol* 1997;157:10-4.
11. Bosch JL, Hop WC, Kirkels WJ and Schröder FH: Natural history of benign prostatic hyperplasia: appropriate case definition and estimation of its prevalence in the community. *Urology* 1995;46:34-40.
12. Glynn RJ, Campion EW, Bouchard GR and Silbert JE: The development of benign prostatic hyperplasia among volunteers in the Normative Aging Study. *Am J Epidemiol* 1985;121:78-90.
13. Tsang KK and Garraway WM: Impact of benign prostatic hyperplasia on general well-being of men. *Prostate* 1993;23:1-7.
14. Hald T: Urodynamics in benign prostatic hyperplasia: a survey. *Prostate Suppl* 1989;2:69-77.
15. Girman CJ, Jacobsen SJ, Guess HA, *et al.*: Natural history of prostatism: relationship among symptoms, prostate volume and peak urinary flow rate. *J Urol* 1995;153:1510-5.
16. Barry MJ, Cockett AT, Holtgrewe HL, *et al.*: Relationship of symptoms of prostatism to commonly used physiological and anatomical measures of the severity of benign prostatic hyperplasia. *J Urol* 1993;150:351-8.
17. Abrams P: New words for old: lower urinary tract symptoms for "prostatism" [editorial]. *BMJ* 1994;308:929-30.
18. Lee AJ, Garraway WM, Simpson RJ, Fisher W and King D: The natural history of untreated lower urinary tract symptoms in middle-aged and elderly men over a period of five years. *Eur Urol* 1998;34:325-32.
19. Jacobsen SJ, Jacobson DJ, Girman CJ, *et al.*: Natural history of prostatism: risk factors for acute urinary retention. *J Urol* 1997;158:481-7.
20. Jacobsen SJ, Girman CJ, Guess HA, *et al.*: Natural history of prostatism: longitudinal changes in voiding symptoms in community dwelling men. *J Urol* 1996;155:595-600.
21. Ball AJ, Feneley RC and Abrams PH: The natural history of untreated "prostatism". *Br J Urol* 1981;53:613-6.
22. Guess HA, Jacobsen SJ, Girman CJ, *et al.*: The role of community-based longitudinal studies in evaluating treatment effects. Example: benign prostatic hyperplasia. *Med Care* 1995;33:AS26-35.
23. Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ and McKinlay JB: Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. *J Urol* 1994;151:54-61.
24. Panser LA, Rhodes T, Girman CJ, *et al.*: Sexual function of men aged 40 to 79 years: the Olmsted County Study of Urinary Symptoms and Health Status Among Men. *J Am Ger Soc* 1995;43:1107-11.

25. Laumann EO, Paik A and Rosen RC: Sexual dysfunction in the United States: prevalence and predictors. *JAMA* 1999;281:537-44.

26. Masumori N, Tsukamoto T, Kumamoto Y, *et al.*: Decline of sexual function with age in Japanese men compared with American men-results of two community-based studies. *Urology* 1999;54:335-44.

27. Helgason AR, Adolfsson J, Dickman P, *et al.*: Sexual desire, erection, orgasm and ejaculatory functions and their importance to elderly Swedish men: a population-based study. *Age Ageing* 1996;25:285-91.

28. Catalona WJ, Carvalhal GF, Mager DE and Smith DS: Potency, continence and complication rates in 1,870 consecutive radical retropubic prostatectomies. *J Urol* 1999;162:433-8.

29. Grimm RH, Jr., Grandits GA, Prineas RJ, *et al.*: Long-term effects on sexual function of five antihypertensive drugs and nutritional hygienic treatment in hypertensive men and women. Treatment of Mild Hypertension Study (TOMHS). *Hypertension* 1997;29:8-14.

30. Vallancien G: Alpha-blockers in benign prostatic hyperplasia. *Urology* 1999;54:773-5.

31. Pinnock CB, Stapleton AM and Marshall VR: Erectile dysfunction in the community: a prevalence study. *Med J Aust* 1999;171:353-7.

32. Frankel SJ, Donovan JL, Peters TI, *et al.*: Sexual dysfunction in men with lower urinary tract symptoms. *J Clin Epidemiol* 1998;51:677-85.

33. Macfarlane GJ, Botto H, Sagnier PP, *et al.*: The relationship between sexual life and urinary condition in the French community. *J Clin Epidemiol* 1996;49:1171-6.

34. Johannes CB and Avis NE: Gender differences in sexual activity among mid-aged adults in Massachusetts. *Maturitas* 1997;26:175-84.

35. Steinke EE: Knowledge and attitudes of older adults about sexuality in ageing: a comparison of two studies. *J Adv Nurs* 1994;19:477-85.

36. Mulligan T and Moss CR: Sexuality and aging in male veterans: a cross-sectional study of interest, ability, and activity. *Arch Sex Behav* 1991;20:17-25.

37. Schiavi RC, Schreiner-Engel P, Mandeli J, Schanzer H and Cohen E: Healthy aging and male sexual function. *Am J Psychiatry* 1990;147:766-71.

38. Diokno AC, Brown MB and Herzog AR: Sexual function in the elderly. *Arch Intern Med* 1990;150:197-200.

39. Roberts RO, Jacobsen SJ, Rhodes T, *et al.*: Natural history of prostatism: impaired health states in men with lower urinary tract symptoms. *J Urol* 1997;157:1711-7.

40. Mozes B, Maor Y and Shmueli A: The competing effects of disease states on quality of life of the elderly: the case of urinary symptoms in men. *Qual Life Res* 1999;8:93-9.

41. Stewart AL, Greenfield S, Hays RD, *et al.*: Functional status and well-being of patients with chronic conditions. Results from the Medical Outcomes Study. *JAMA* 1989;262:907-13.

42. Kempen GI, Ormel J, Brilman EI and Relyveld J: Adaptive responses among Dutch elderly: the impact of eight chronic medical conditions on health-related quality of life. *Am J Public Health* 1997;87:38-44.

43. Lam CL and Lauder IJ: The impact of chronic diseases on the health-related quality of life (HRQOL) of Chinese patients in primary care. *Fam Pract* 2000;17:159-66.

44. Donovan JL, Kay HE, Peters TJ, *et al.*: Using the ICSQoL to measure the impact of lower urinary tract symptoms on quality of life: evidence from the ICS-'BPH' Study. International Continence Society-Benign Prostatic Hyperplasia. *Br J Urol* 1997;80:712-21.

45. Barry MJ, Fowler Jr FJ, O'Leary MP, *et al.*: The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. *J Urol* 1992;148: 1549-57.

46. Barry MJ, Fowler Jr FJ, O'Leary MP, *et al.*: Measuring disease-specific health status in men with benign prostatic hyperplasia. Measurement Committee of The American Urological Association. *Med Care* 1995;33: AS145-55.

47. Sagnier PP, MacFarlane G, Teillac P, *et al.*: Impact of symptoms of prostatism on level of bother and quality of life of men in the French community. *J Urol* 1995;153:669-73.

48. Bergner M, Bobbitt RA, Pollard WE, Martin DP and Gilson BS: The sickness impact profile: validation of a health status measure. *Med Care* 1976;14:57-67.

49. Ware JE, Jr. and Sherbourne CD: The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30:473-83.
50. Visser APh: De betekenis van de VOEG: enkele gegevens over de begripsvaliditeit [Dutch]. *Gezondheid en Samenleving* 1983;4:177-188.
51. Groeneveld FP, Bareman FP, Barentsen R, *et al.*: The climacteric and well-being. *J Psychosom Obstet Gynaecol* 1993;14:127-43.
52. Hartgers C, Van den Hoek JA, Coutinho RA and Van der Pligt J: Psychopathology, stress and HIV-risk injecting behaviour among drug users. *Br J Addict* 1992;87:857-65.
53. Lawrence WF, Fryback DG, Martin PA, Klein R and Klein BE: Health status and hypertension: a population-based study. *J Clin Epidemiol* 1996;49:1239-45.

Chapter 2

Study design

A longitudinal population-based study in men aged 50 to 75 years is being conducted: "The Krimpen Study."

Population

Names and addresses of all registered 3.924 men aged 50 to 75 years were obtained (reference date June 1995) from all general practices of Krimpen aan den IJssel, a commuter suburb near Rotterdam (the Netherlands) with approximately 28.000 inhabitants. In the Netherlands, almost every person is registered at a general practice.[1]

Men who had not undergone radical prostatectomy and had not had prostate or bladder cancer, neurogenic bladder disease or a negative advice from their general practitioner (GP), and who were able to complete questionnaires and visit the health centre were found eligible. In all cases, the GP decided whether the patient could enter the study before invitation. The GP's reasons for excluding any patient were checked by the researchers in the electronic medical records. Recruitment took place from August 1995 to January 1998.

Flow chart of study

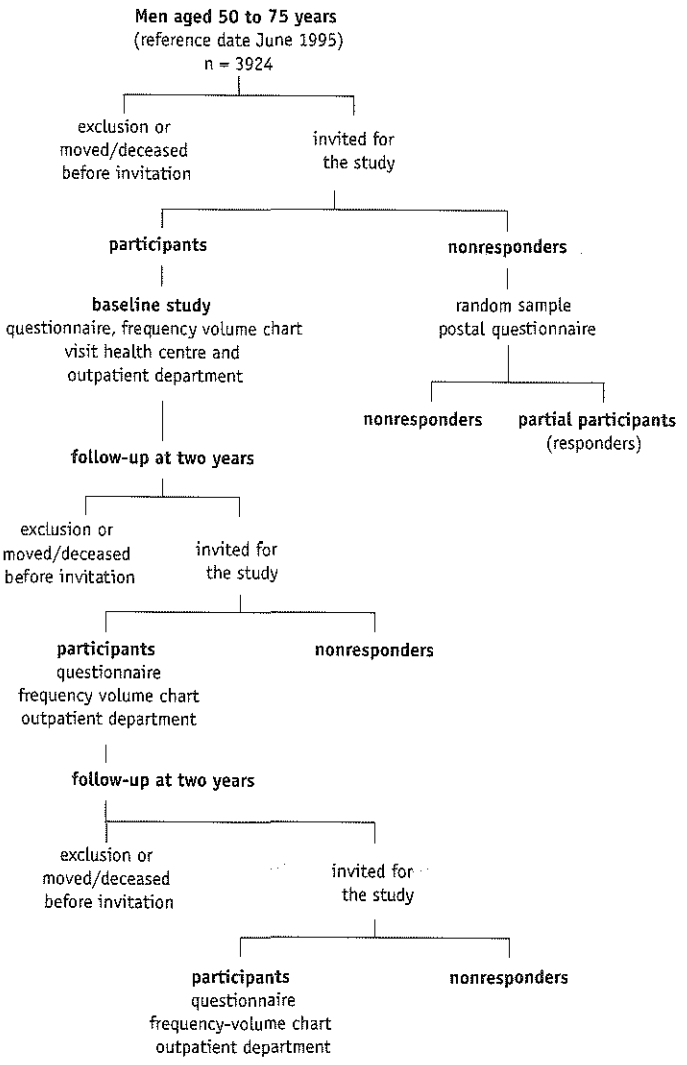
A flow chart of the study design is presented in Figure 2.1. The baseline study consisted of two phases. In the first phase, participants were asked to complete a self-administered 113-item questionnaire and to attend the health centre in Krimpen aan den IJssel. In the second phase, participants were asked to complete a 3-day frequency volume chart and to attend the urology outpatient department of the University Hospital Rotterdam-Dijkzigt.

The study received approval from the Medical Ethical Committee of the Erasmus University Rotterdam and the University Hospital Rotterdam.

Questionnaire: urogenital tract dysfunction

To study the presence of urogenital dysfunction and related bother, the questionnaire included the International Prostate Symptom Score (IPSS),[2] the BPH impact score,[3] and sexuality related questions of the International Continence Society "BPH" Study (ICS*sex* questionnaire).[4,5]

Figure 2.1. *Flow chart of the Krimpen Study*



The IPSS consists of the AUA-7 symptom index with the addition of a disease-specific quality of life question; the latter question results in a separate quality of life score.[2] The IPSS (AUA-7 symptom index) was used to rate the severity of LUTS.[2] The AUA-7 symptom index consists of seven questions, with six possible answers, resulting in a total score range from zero to 35. Severity ratings are as follows: 0, no LUTS; 1 to 8, mild LUTS; 8 to 19, moderate LUTS; 19 or more, severe LUTS.[2]

The BPH impact index includes four questions on the bothersomeness of LUTS and the impact of LUTS on physical distress, health concerns and interference with daily activities.[3]

The ICS*sex* questionnaire covers four items, each with a bother score ranging from no problem to a serious problem on a four-point scale. In addition, the men were asked whether they were sexually active and, if not, how long ago their sexual activities ceased.[4,5]

Questionnaire: health status

To study health status, the questionnaire included two validated inventories, namely the Dutch validated version of the Sickness Impact Profile (SIP)[6-8] and the Inventory of Subjective Health (ISH).[9] The latter questionnaire proved to be a sensitive instrument to describe general health status,[10] and several Dutch surveys have used it to quantify subjective health status.[9,11-14] In the current study a short 13-item version of the ISH was used.[15] On every item the respondent is asked whether he has experienced it during the past 2 weeks. All items must be answered "yes" or "no." The sum score of all responses is computed, the maximum score being 13.

The four categories of the SIP used in our survey were "emotions, feelings and sensations" (grouped as "emotions"), "leisure pastimes and recreation" ("recreation"), "social interaction" ("social"), and "usual daily work". For each category, a weighted score was computed, providing scores ranging from zero to 100 with higher scores indicating lower levels of health status.[6]

Questionnaire: medical conditions and sociodemographic factors

The questionnaire also included questions on treatment for chronic diseases (e.g. cardiovascular problems, hypertension, diabetes mellitus, Parkinson's disease, chronic obstructive pulmonary disease (COPD), chronic urinary tract infections and liver disease), history of transurethral resection of the prostate, family history of prostate cancer, smoking habits and alcohol consumption, marital status and educational level.

Frequency-volume charts

The participants were asked to complete a 3-day frequency-volume chart on which each micturition was recorded in one-hour time units. On the third day, the volume of each voiding was recorded. Bedtime and time of rising were also recorded on the charts. The number of voids during patient-reported waking/sleeping hours was estimated.

Recordings on the frequency-volume charts are used to determine: nocturnal and diurnal voiding frequency, 24-hour voided volume, average volume per void (24-hour volume/frequency), functional bladder capacity (defined as the largest voided volume) and hourly urine production.

Measurements: health centre

At the health centre, two study physicians checked the questionnaires and completed these with data on current medication use (using the Anatomical Therapeutical Chemical classification).[16] Urinalysis was performed using dipstick (including levels of leukocytes, nitrate and glucose), mainly to exclude lower urinary tract infection. Erythrocyte levels were not assessed to avoid unnecessary investigations in men with microscopic haematuria.[17,18] Finally, systolic and diastolic blood pressure, height and bodyweight were measured.

Measurements: urology outpatient department

At the urology outpatient department, the following measurements were obtained: digital rectal examination (DRE), transrectal ultrasound (TRUS), uroflowmetry, post void residual urine volume and serum prostate specific antigen (PSA).

On DRE, the volume of the prostate was estimated and the location of possible nodules was noted. TRUS was performed with a 7 MHz Bruel and Kjaer multiplane sector scanning probe. The planimetric technique of volume measurement was used.[19] This method involves measuring the surface area of transverse sections taken through the prostate at 5-mm intervals. The average of two intervals multiplied by 5 mm provides the volume for each step and the cumulative volume allows the total prostatic volume (cm^3) to be derived. The same method was used to determine the volume of the central prostate (transitional zone). Moreover, the following items were recorded: width, height, length, perimeter and area of the prostate and the transitional zone of the prostate.

Uroflowmetry was done using a flowmeter (Dantec Urodyn 1000, Copenhagen, Denmark). The following parameters were recorded: peak flow rate (Q_{max}), average flow rate (Q_{ave}), delay time (T_{delay}), total voiding time (T_{100}), total flow time (T_Q) and the voided volume. The men were asked to visit the clinic with a full bladder and were instructed not to void in a toilet before that time.

The post void residual urine volume (ml) in the bladder was computed by transabdominal ultrasound, using an Aloka machine with a 3.5 MHz handheld probe using the formula $\pi/6$ x (width) x (height) x (depth).[20] The post void residual was not computed if a man was unable to void in the flowmeter. The initial pre-micturition bladder volume was calculated by summing the voided volume and the residual volume. The initial bladder volume was 100 ml or more in 72% of the men, and 150 ml or more in 53% of the men. No flow rates were discarded because of relatively low initial bladder volume.

A blood sample was obtained through venapuncture. From this sample, the serum PSA level was determined using the Tandem-R method (Hybritech, San Diego, USA). Three portions of 3 ml each from the blood sample were stored.

Prostate biopsies

The following protocol was used to detect prostatic carcinoma: Prostate biopsies were performed (i) always at PSA values above 10 ng/ml, (ii) at PSA values between 2 and 10 ng/ml in case of abnormal findings on DRE or TRUS (i.e. suspect for carcinoma) and (iii) at PSA values of 1 to 2 ng/ml only if DRE was abnormal. No biopsies were taken to confirm the histopathologic diagnosis BPH.

Nonresponse study

A random stratified sample proportional to the number of nonresponders per general practice (n = 500) was taken from the list of nonresponders to evaluate whether the responders were representative. These nonresponders were invited to complete a short mailed questionnaire, which included the Inventory of Subjective Health, IPSS, and questions on treatment for chronic diseases, social status, smoking and drinking habits and current medication use. Questionnaires were sent

in October 1997 and had to be returned within six weeks. Those returning the questionnaires were indicated as partial participants.

Follow-up

All men who completed the second part of the baseline study and who were not diagnosed with prostatic cancer and had no previous operation for benign prostatic hyperplasia will be re-evaluated after two and four years. In this follow-up the same procedures will be done, with the exception of a visit to the health centre.

In addition, the electronic medical record of all participants will be reviewed and data on all prescribed drugs during the study period will be obtained from the pharmacists' database.

References

1. de Bruyn NJM, Bickel BCJ and Prins A: Cervixscreening in huisartsenpraktijken [Dutch]. *Medisch Contact* 1990;40:1277-8.
2. Barry MJ, Fowler Jr FJ, O'Leary MP, *et al.*: The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. *J Urol* 1992;148: 1549-57.
3. Barry MJ, Fowler Jr FJ, O'Leary MP, *et al.*: Measuring disease-specific health status in men with benign prostatic hyperplasia. Measurement Committee of The American Urological Association. *Med Care* 1995;33: AS145-55.
4. Denis L, Griffiths K, Khoury S, *et al.*, editors. Measuring the symptoms and health impact of benign prostatic hyperplasia and its treatments. Proceedings of the 4th International Consultation on BPH; 1998; Paris. Plymouth, UK, Health Publication Ltd.
5. Frankel SJ, Donovan JL, Peters TI, *et al.*: Sexual dysfunction in men with lower urinary tract symptoms. *J Clin Epidemiol* 1998;51:677-85.
6. Pollard WE, Bobbitt RA, Bergner M, Martin DP and Gilson BS: The Sickness Impact Profile: reliability of a health status measure. *Med Care* 1976;14:146-55.
7. Jacobs HM, Luttik A, Touw-Otten FW and de Melker RA: [The sickness impact profile; results of an evaluation study of the Dutch version] De 'sickness impact profile'; resultaten van een valideringsonderzoek van de Nederlandse versie [Dutch]. *Ned Tijdschr Geneeskd* 1990;134:1950-4.
8. de Melker RA, Touw-Otten F, Jacobs HM and Luttik A: [Value of the sickness impact profile as outcome measure] De waarde van de 'sickness impact profile' als uitkomstmeting [Dutch]. *Ned Tijdschr Geneeskd* 1990;134:946-8.
9. Visser APh: De betekenis van de VOEG: enkele gegevens over de begripsvaliditeit [Dutch]. *Gezondheid en Samenleving* 1983;4:177-188.
10. Joosten J and Drop MJ: De betrouwbaarheid en de vergelijkbaarheid van de drie versies van de VOEG [Dutch]. *Gezondheid & Samenleving* 1987;8:251-252.
11. van Reek J, Diederiks J, Philipsen H, van Zutphen W and Seelen T: Subjective complaints and blood pressure. *J Psychosom Res* 1982;26:155-65.
12. Huygen FJ, Mokkink HG, Smits AJ, *et al.*: Relationship between the working styles of general practitioners and the health status of their patients. *Br J Gen Pract* 1992;42:141-4.
13. Groeneveld FP, Bareman FP, Barentsen R, *et al.*: The climacteric and well-being. *J Psychosom Obstet Gynaecol* 1993;14:127-43.
14. Hartgers C, Van den Hoek JA, Coutinho RA and Van der Pligt J: Psychopathology, stress and HIV-risk injecting behaviour among drug users. *Br J Addict* 1992;87:857-65.
15. Jansen ME and Sikkel D: Verkorte versies van de VOEG-schaal [Dutch]. *Gezondheid en Samenleving* 1981;1: 78-82.
16. Miller GC and Britt H: A new drug classification for computer systems: the ATC extension code. *Int J Biomed Comput* 1995;40:121-4.
17. Britton JP, Dowell AC and Whelan P: Dipstick haematuria and bladder cancer in men over 60: results of a community study. *BMJ* 1989;299:1010-2.
18. Froom P, Froom J and Ribak J: Asymptomatic microscopic hematuria–is investigation necessary? *J Clin Epidemiol* 1997;50:1197-200.
19. Torp-Pedersen S, Juul N and Jakobsen H: Transrectal prostatic ultrasonography. Equipment, normal findings, benign hyperplasia and cancer. *Scand J Urol Nephrol Suppl* 1988;107:19-25.
20. Roehrborn CG and Peters PC: Can transabdominal ultrasound estimation of postvoiding residual (PVR) replace catheterization? *Urology* 1988;31:445-9.

Part II

Lower urinary tract (dys)function

Chapter 3

Prevalence of lower urinary tract dysfunction and benign prostatic hyperplasia in the community: the effect of age, definition and nonresponse bias

Abstract

Objective. To estimate the prevalence of benign prostatic hyperplasia (BPH) in the community, and study the influence of BPH definition, age and response bias on prevalence rates.

Subjects and methods. A community-based longitudinal study on 3924 men aged 50 to 75 years was conducted in a Dutch municipality (Krimpen) near Rotterdam. Data from those responding were collected using self-administered questionnaires, and during visits to the health centre and outpatient clinic of the urology department. The questionnaires included symptom scores on general well being (Inventory of Subjective Health; ISH) and lower urinary tract symptoms (International Prostate Symptom Score; IPSS). A short version of the questionnaire (including IPSS and ISH) was sent to a random sample of those not responding. All subjects participating fully underwent physical examination, uroflowmetry, transrectal ultrasound of the prostate, and had their prostate specific antigen level measured.

Age-specific prevalence rates of BPH were estimated using different definitions, based on one or more of symptom severity, prostate volume and maximum flow rate. The influence of response bias was estimated using the questionnaires.

Results. The response rate was 50% (full participants). Of those not responding, 55% completed a short version of the questionnaire (partial participants). Compared with full participants, partial participants had a lower IPSS and slightly lower ISH.

The prevalence rates of clinical BPH in the study population ranged from 9 to 20% (95% confidence interval: 8-11% to 22-27%) depending on the definition used. After adjustment for nonresponse bias, the age-group specific prevalences for 5-year age groups are 1.1 to 1.8 times lower for all BPH definitions used.

Conclusions. Prevalence rates of clinical BPH depend largely on the definition used and increase strongly with age. The effect of age is stronger when more parameters are included in the definition. Adjustment for response bias results in substantially lower prevalence rates.

Introduction

Clinical benign prostatic hyperplasia (BPH) is a common diagnosis in older men but the reported prevalence of this condition varies considerably. Garraway *et al* reported a prevalence of 25% in men aged 40 to 79 years, whereas Bosch *et al* found rates of 4 to 19% using different definitions for BPH.[1,2]

The study of the natural history of BPH has been hampered by three major problems. First, there is a lack of consensus about the definition of BPH. Most definitions are based on the concept of Hald, which combines lower urinary tract symptoms (LUTS), prostate volume and objective proof of difficult micturition.[3] To describe these properties various studies have used different parameters and different threshold values of these variables. Second, as most community studies have not considered nonresponse bias, it is not known whether they are truly representative. One preliminary study on potential nonresponse bias, the Olmsted County Study (OCS), suggested that response might have been affected by concern about urologic disease.[4] Third, there is a paucity of data on the natural history of BPH based on longitudinal community studies.

To gain information on male urogenital tract dysfunction, and the prevalence and incidence of clinical BPH (and its determinants) in men aged over 50 years, a prospective community-based study was designed, i.e. the Krimpen study of male urogenital tract problems and general health status. The aim of this study was to investigate prevalence rates of BPH in the community using various definitions, and to study the influence of age and non-response bias on these prevalences.

Subjects and methods

Population

From all general practices in Krimpen aan den IJssel (a commuter suburb near Rotterdam with approximately 28,000 inhabitants) the names and addresses of all 3924 registered men aged 50 to 75 years were obtained (reference date June 1995). In The Netherlands, almost every person is registered with a general practice.[5]

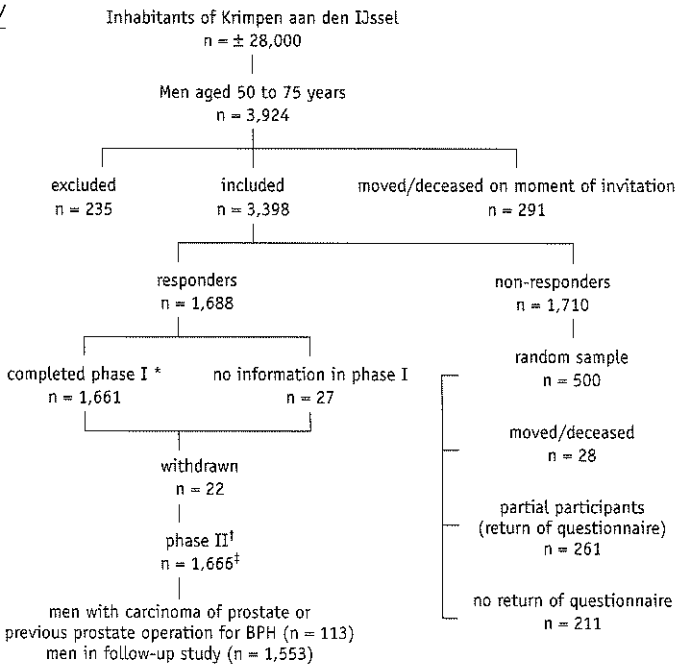
Recruitment took place between August 1995 and January 1998; reasons for exclusion are given in Table 3.1. Men previously operated for BPH (n = 64) were not excluded but were analysed separately. In all cases the GP decided whether or not the patient could enter the first phase of the study; GPs' reasons for exclusion were checked by the investigators in the electronical medical records.

Table 3.1. *Reasons for exclusion from the first phase of the study*

Reason	Number of men		(%)
Radical prostatectomy	11		(5)
Known prostatic or bladder cancer	34		(14)
Under treatment by urologist	14		(6)
Neurogenic bladder disease	26		(11)
Inability to complete questionnaire (dementia, mental retardation, language problem)	32		(14)
Inability to attend health centre	7		(3)
Negative advice by patient's general practitioner	105		(45)
Cardiac disease	23	(10)	
Pulmonary disease	14	(6)	
Malignancy	27	(11)	
Not specified	41	(17)	
Unknown	6		(3)
Total	**235**		**(100)**

Figure 3.1 presents an overview of the study scheme. All 3,398 enrolled men were invited by mail to complete a self-administered questionnaire and to attend the health centre. During the recruitment period about 40 men were invited weekly. In this period, 152 men passed the age of 75 years but were nevertheless enrolled. A total of 1688 men agreed to participate (a response rate of 50%).

Figure 3.1. *flow chart of the study*



* self administered questionnaire † see text ‡ 1592 men completed phase II, 69 men visited the clinic without a completed voiding diary and five men completed the voiding diary but did not visit the clinic.

Procedures

The questionnaire included: two inventories on general well being, i.e. the Sickness Impact Profile (SIP)[6,7] and a 13-item version of the Inventory of Subjective Health (ISH)[8]; the IPSS[9]; the BPH impact score[10]; and ICS*sex* questionnaire.[11] In addition, information on marital status, educational level, treatment for chronic diseases, smoking and drinking habits was collected.

At the health centre, two study physicians checked the questionnaires and completed these with data on the present medication use using the Anatomical Therapeutical Chemical (ATC) classification.[12] Urine was analysed using a dipstick test, mainly to exclude lower urinary tract infection, and the subjects' blood pressure, height and bodyweight were measured.

The second part of the study took place at the urology outpatient department of the University Hospital Rotterdam. Before attendance, participants were asked to complete a 3-day frequency-volume chart. The following measurements were obtained: digital rectal examination (DRE); transrectal ultrasound (TRUS) performed with a 7 MHz Bruel and Kjaer multiplane sector scanning probe to measure volumes, using the planimetric technique of volume measurement[13]; uroflowmetry, recording of peak flow rate (Q_{max}) and other parameters with a Dantec Urodyn 1000 flowmeter; post void residual urine volume determined by transabdominal ultrasound; and the serum PSA level (Tandem-R method, Hybritech, San Diego, CA, USA).

The following protocol was used to detect prostatic carcinoma. Prostate biopsies were taken (i) from all men with PSA values of > 10 ng/ml; (ii) from men with a PSA level of 2 to 10 ng/ml if there were abnormal findings on DRE or TRUS (i.e. suspect for carcinoma); and (iii) in men with a PSA level of 1 to 2 ng/ml only if the DRE was abnormal. No biopsies were taken to confirm the histopathologic diagnosis BPH. A total of 57 men were found to have prostatic cancer and were analysed separately; eight of these had been operated previously for BPH.

Partial participants and complete nonresponders

A random sample (n = 500), stratified proportional to the number of nonresponders per general practice, was taken from the list of nonresponders to evaluate whether the responders were representative. These nonresponders were invited to complete a short mailed questionnaire which included the ISH, IPSS, and questions on treatment for chronic diseases, marital status, educational level, smoking and drinking habits and current medication use. Questionnaires were sent in October 1997 and had to be returned within six weeks. Of those not responding, 261 returned the questionnaires (response rate 55%) and became "partial participants."

All men who completed the second part of the study and who were not diagnosed with prostatic cancer and had no previous operation for BPH (n = 1553) will be re-evaluated after two and after four years.

Prevalence of BPH and estimation of response bias

The age-specific prevalence of BPH is estimated using different definitions: the definition used by Garraway *et al* and three different definitions reported to be the most valid ones by Bosch *et al.*[1,2] The variables used in these definitions were the IPSS, Q_{max} and prostate volume.

To adjust for response-bias, age-group specific prevalences of men with an IPSS of > 7 were estimated as the weighted average of the prevalence in the full participant group and the estimated prevalence in the nonresponders group. We assumed that the IPSS of the partial participants represented the IPSS of all nonresponders, and that the other variables used in the definitions of BPH are independent of the IPSS and equally distributed among full and partial participants.
If the total nonresponders had either lower or higher prevalences than the partial participants (in contrast to our assumption) the adjusted prevalences of those with an IPSS of > 7 in the population would differ. A sensitivity analysis was conducted to evaluate the effect of variation in IPSS in the total nonresponders group, ranging from a best case to a worst case scenario, on the adjusted prevalence rates of men with an IPSS of > 7 in the total population.

Statistical analysis

Full and partial participants were compared for items on the short questionnaire by means of multivariate logistic regression, t-test, chi-square test and the Mantel-Haenszel test as applicable. The relation between age and prevalence rates of BPH and its determinants was tested by means of univariate regression (because of assumptions of normality, dependent variables were transformed), chi-square test and the Mantel-Haenszel test. Correlation between these variables was estimated by means of Spearman's rho.
The study received approval from the Medical Ethical Committee of the Erasmus University Rotterdam and the University Hospital Rotterdam. All participants gave written informed consent.

Results

Age groups of responders and nonresponders and age-group specific response rates are given in Table 3.2. There was a slight under-representation of men aged 50 to 55 years and of men aged > 70 years and a slight overrepresentation of those aged 60 to 65 years. Age of the partial participants did not differ from age of the total nonresponders (62.7 years, standard deviation, SD, 7.4 years, compared to 62.3 years, SD 7.6 years, p = 0.6). Age group specific response rates in the random sample are also given in Table 3.2.

Table 3.2. *Age groups and age-group specific response rates*

Age, years (n)*	Number of included men	Number of responders	Response rate (%)	Response rate in random sample (%)
50 to 54 (859)	788 (91%)	356	45.2	50.4
55 to 59 (891)	813 (91%)	432	53.1	57.4
60 to 64 (798)	720 (90%)	398	55.3	55.8
65 to 69 (711)	622 (88%)	318	51.1	54.0
70 to 78 (659)	452 (68%)	184	40.7	57.5
Total (3924)	**3398† (87%)**	**1688**	**49.7**	**55.3**

* age on date of invitation, n = number of men in age group † age calculation of three men is missing

Table 3.3 shows the characteristics of the included men: full participants were slightly younger than the partial participants.

Table 3.3. *Characteristics of the men included in the study*

	Full participants (n = 1688)	Partial participants (n = 261)	p-value
Age (years)* ; mean (SD)	61.2 (6.7)	62.7 (7.4)	<0.001‡
Marital status:			0.06
Married	91.4 %	88.1 %	
Unmarried	2.3 %	3.6 %	
Co-habitation	3.1 %	2.4 %	
Divorced	1.0 %	2.8 %	
Widower	2.2 %	3.2 %	
Educational level			0.43
No education/ Primary school	13 %	16 %	
Secondary education	61 %	63 %	
University	26 %	21 %	
Smoking habits			0.24
Never smoked	19 %	20 %	
Stopped smoking	50 %	57 %	
Current smoker	31 %	23 %	
Drinking habits			0.57
No alcohol	23 %	27 %	
Average 1 to 2 units per day	59 %	56 %	
Average over 2 units per day	18 %	17 %	
Under treatment for chronic diseases			
Diabetes mellitus	3.4 %	5.3 %	0.11
Hypertension	15.9 %	18.7 %	0.25
COPD	4.5 %	4.6 %	0.96
Parkinson's disease	0.1 %	0.8 %	0.03
Cardiac disease	6.2 %	8.8 %	0.11
Chronic urinary tract infection	0.8 %	1.5 %	0.28
Liver disease	0.7 %	0 %	0.29
One or more of the above	25 %	32 %	<0.01
Prostatic cancer in 1st degree family member	91 %	94 %	0.11
ISH questionnaire; mean score (SD)	2.02 (2.34)	1.55 (2.15)	<0.003‡
International Prostate Symptom Score (IPSS)			<0.001
No symptoms	10 %	19 %	
Minor	65 %	66 %	
Moderate	22 %	14 %	
Severe	3 %	1 %	
IPSS quality of life			<0.001
Delighted to mostly satisfied	83 %	92 %	
Mixed, to terrible	17 %	8 %	

* age on date of invitation † p-value refers to chi-square test. ‡ Marked p-value refers to t-test. ISH, Inventory of Subjective Health

Multivariate logistic regression, adjusted for age, shows that full participants had less treatment for chronic diseases (odds ratio, OR, 0.60, $p < 0.001$), marginally higher mini-ISH scores (OR 1.08, $p = 0.06$), and a higher percentage had an IPSS above 7 (OR 1.70, $p < 0.02$). The effect of IPSS quality of life (QoL) question in the multivariate logistic regression was similar to the effect of IPSS above 7 when separately included in the model. When both IPSS and QoL were included in the model, the effect of these variables was much weaker, because of their strong correlation (Pearson's correlation coefficient = 0.68, $p < 0.001$).

Prevalence of BPH

Table 3.4 gives the median score and 25 to 75th percentiles of the variables used to estimate the prevalence of BPH according to different definitions. IPSS and prostate volume increased with age, and Q_{max} decreased with age ($p < 0.001$ for all three). The variables were weakly correlated: IPSS vs. prostate volume, Spearman's rho = 0.13; IPSS vs. Q_{max}, rho = -0.20; prostate volume vs. Q_{max}, rho = -0.13 ($p < 0.001$, all values).

Table 3.4. *Median scores and percentiles of IPSS, maximum urinary flow rate (Q_{max}) and prostate volume (VolT).*

	IPSS		Q_{max}		VolT	
Age (years)*	N	Median (percentiles)†	N	Median (percentiles)†	N	Median (percentiles)†
50 to 54	325	3 (1-6)	288	12.4 (7.6-17.6)	325	27.4 (23.6-31.7)
55 to 59	397	3 (1-6)	360	10.9 (7.5-15.9)	395	30.3 (24.4-35.2)
60 to 64	362	4 (2-7)	328	9.5 (5.8-13.3)	362	31.9 (25.5-40.5)
65 to 69	284	4 (2-9)	261	8.7 (5.9-13.1)	288	32.6 (25.8-40.8)
70 to 78	155	5 (3-10)	136	7.7 (4.9-11.1)	155	38.7 (29.4-50.1)
Total	1523	4 (1-7)	1373	10.0 (6.3-14.7)	1525	30.4 (25.0-38.3)
p-value‡		<0.001		<0.001		<0.001

* age on day of attendance at clinic † 25th to 75th percentiles are shown in parenthesis. ‡ p-value refers to tests for trend on transformed variables (arc-sin-square root for IPSS; square root for Qmax; log transformation for VolT).

Prevalence rates of BPH according to different definitions and with adjustment for response bias are given in Table 3.5. Different definitions of BPH resulted in substantially different prevalence rates. Definitions, taking all three parameters (IPSS, prostate volume and Qmax) into consideration, showed a larger effect of age on the prevalence than definitions including only one or two parameters. All (corrected and uncorrected) prevalence rates showed a significant increase with age. In three of the five definitions, there was a small decrease in prevalence in the age group 70 to 78 years, after adjustment for response bias. Adjustment for response bias resulted in lower prevalence rates for all definitions and across all age groups.

In estimating the adjusted prevalences of IPSS above 7, we assumed that the partial participants represented the nonresponders group. Effect of the sensitivity analysis on the adjusted prevalence rates of IPSS above 7 is given in Table 3.6.

Table 3.5. *Prevalence rates of BPH according to different definitions, with adjustment for response bias.*

		Age (years)*					
Prevalence (CI95%)	**N†**	**50 to 54**	**55 to 59**	**60 to 64**	**65 to 69**	**70 to 78**	**total**
IPSS>7‡	1523						
Unadjusted		21 (16-25)	19 (15-23)	24 (20-29)	31 (26-37)	37 (29-45)	25 (22-27)
Adjusted		12 (8-16)	15 (11-20)	23 (17-30)	29 (20-37)	24 (17-32)	20 (14-26)
IPSS>7 + VolT>30‡	1499						
Unadjusted		7 (4-10)	7 (5-11)	15 (12-20)	22 (17-27)	28 (21-36)	14 (12-16)
Adjusted		4 (3-5)	6 (4-8)	15 (11-19)	22 (16-27)	19 (14-25)	12 (9-15)
IPSS>7 + VolT>30 + Q_{max}<15‡	1330						
Unadjusted		6 (4-10)	6 (4-9)	13 (10-17)	20 (15-25)	27 (19-35)	12 (11-14)
Adjusted		4 (3-5)	4 (3-6)	13 (10-16)	18 (13-22)	18 (13-23)	10 (8-13)
IPSS>7 + VolT>30 + Q_{max}<10‡	1330						
Unadjusted		4 (2-6)	4 (2-7)	9 (6-13)	14 (11-20)	23 (17-32)	9 (8-11)
Adjusted		2 (1-3)	3 (2-4)	9 (7-11)	14 (10-17)	16 (12-20)	8 (6-9)
IPSS>7 + VolT>20 + Q_{max}<15‡	1330						
Unadjusted		14 (10-18)	14 (11-19)	20 (16-25)	26 (21-32)	32 (24-40)	20 (18-22)
Adjusted		8 (5-11)	11 (8-14)	20 (15-25)	24 (17-31)	22 (15-28)	17 (13-22)

* age on day of attendance at clinic † numbers differ per definition, missing values were not counted ‡ $p < 0.001$ for all, Mantel-Haenszel test IPSS, international prostate symptom score; VolT, prostate volume on transrectal ultrasound (cc); Q_{max}, maximum urinary flow rate (ml/sec)

Table 3.6. *The effect of sensitivity analysis on prevalence rates of men with IPSS of > 7 in the total population.*

	adjusted prevalence rates of men with IPSS of > 7		
Age (years)	**best case scenario***	**presented in Table 3.5**	**worst case scenario***
50 – 54	10.4%	11.7%	37.6%
55 – 59	13.3%	15.4%	33.3%
60 – 64	18.8%	23.3%	38.5%
65 – 69	22.3%	28.5%	44.9%
70 – 78	19.6%	24.1%	44.9%
Totals	**16.1%**	**19.8%**	**38.3%**

* best case scenario: none of the total nonresponders has IPSS above 7 worst case scenario: all of the total nonresponders have IPSS above 7

Discussion

Considering the effort required from the responders and the number of invasive tests performed, the present 50% response rate was remarkably high. It was higher than that of two other Dutch studies on the prevalence of BPH: Bosch *et al* reported an age-group specific response rate of 33 to 36% and Wolfs *et al* reported a 39% overall response rate.[14,15] In Scotland, Garraway *et al* reported an overall response rate of 65%,[1] whereas the Olmsted County Study (OCS) reported 48%.[16] In the OCS home visits were made to complete the questionnaire and uroflowmetry; only a quarter of the responding men (randomly sampled) was invited for further evaluation at a urology clinic.[16] Garraway *et al* performed TRUS only in men with signs and symptoms of prostatic dysfunction (symptom scores and Q_{max}).[1]

In the present study, all the objective measures were obtained in all full participants, allowing an estimate of community-based age-specific reference values for prostate size, uroflowmetry and PSA level. Furthermore, the prevalence of BPH can be estimated using different definitions.

In this community-based study, the prevalence rates of BPH were 9 to 25% in men aged 50 to 78 years. These rates may be an underestimate because men previously operated for BPH were not included in the estimation; however, this latter group represents only about 4% of the responders.

The full participants were comparable with the partial participants for educational and marital status, smoking and drinking habits. Full participants were slightly younger and were less often treated for one or more chronic diseases but had higher ISH scores. Partial participants were more often "delighted to mostly satisfied" about their current voiding symptoms. Although different methods were used in an evaluation of nonresponse in the OCS, the present results were comparable with those in the OCS;[4] however, prevalence rates of BPH from the OCS were not adjusted for this bias.

In the present study, the GP decided whether to propose a patient for enrolment; this may be considered a potential limitation to the study. In retrospect, that almost 15% of the excluded men had died within one month to 2 years after exclusion suggests that the GPs' decision on eligibility was valid.

The prevalence of men with an IPSS of > 7 was lower in those not responding. When estimating prevalence rates of BPH, using the IPSS as part of the definition, it is important to adjust for this bias. In the present study, this adjustment resulted in substantially lower prevalence rates, particularly in the youngest and oldest age groups.

The adjusted prevalence rates of IPSS > 7 would be overestimated if the partial participants had a higher IPSS than the total nonresponders. However, this overestimation is not large (3.7%) even if we assume that none of the total nonresponders had an IPSS of > 7. In the OCS study, the total nonresponders had lower prevalence rates for BPH and other urologic diagnoses than had partial responders.[4] Therefore, the worst case scenario is unlikely. It seems to be more realistic to assume that the true prevalence of IPSS of > 7 will be 16 to 20%.

In conclusion, the prevalence of BPH depends largely on age and the definition used. The age effect is stronger when more variables are included in the definition of BPH. Future prevalence studies and models using prevalence rates of BPH should use various definitions, and should adjust for nonresponse bias with subdivision into age groups.

References

1. Garraway WM, Collins GN and Lee RJ: High prevalence of benign prostatic hypertrophy in the community. *Lancet* 1991;338:469-71.
2. Bosch JL, Hop WC, Kirkels WJ and Schröder FH: Natural history of benign prostatic hyperplasia: appropriate case definition and estimation of its prevalence in the community. *Urology* 1995;46:34-40.
3. Hald T: Urodynamics in benign prostatic hyperplasia: a survey. *Prostate Suppl* 1989;2:69-77.
4. Panser LA, Chute CG, Guess HA, *et al.*: The natural history of prostatism: the effects of non-response bias. *Int J Epidemiol* 1994;23:1198-205.
5. de Bruyn NJM, Bickel BCJ and Prins A: Cervixscreening in huisartsenpraktijken. *Medisch Contact* 1990;40: 1277-8.
6. Pollard WE, Bobbitt RA, Bergner M, Martin DP and Gilson BS: The Sickness Impact Profile: reliability of a health status measure. *Med Care* 1976;14:146-55.
7. Jacobs HM, Luttik A, Touw-Otten FW and de Melker RA: [The sickness impact profile; results of an evaluation study of the Dutch version] De 'sickness impact profile'; resultaten van een valideringsonderzoek van de Nederlandse versie [Dutch]. *Ned Tijdschr Geneeskd* 1990;134:1950-4.
8. Jansen ME and Sikkel D: Verkorte versies van de VOEG-schaal [Dutch]. *Gezondheid en Samenleving* 1981;1: 78-82.
9. Barry MJ, Fowler Jr FJ, O'Leary MP, *et al.*: The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. *J Urol* 1992;148: 1549-57.
10. Barry MJ, Fowler Jr FJ, O'Leary MP, *et al.*: Measuring disease-specific health status in men with benign prostatic hyperplasia. Measurement Committee of The American Urological Association. *Med Care* 1995;33: AS145-55.
11. Frankel SJ, Donovan JL, Peters TJ, *et al.*: Sexual dysfunction in men with lower urinary tract symptoms. *J Clin Epidemiol* 1998;51:677-85.
12. Miller GC and Britt H: A new drug classification for computer systems: the ATC extension code. *Int J Biomed Comput* 1995;40:121-4.
13. Torp-Pedersen S, Juul N and Jakobsen H: Transrectal prostatic ultrasonography. Equipment, normal findings, benign hyperplasia and cancer. *Scand J Urol Nephrol Suppl* 1988;107:19-25.
14. Bosch JL, Hop WC, Kirkels WJ and Schröder FH: The International Prostate Symptom Score in a community-based sample of men between 55 and 74 years of age: prevalence and correlation of symptoms with age, prostate volume, flow rate and residual urine volume. *Br J Urol* 1995;75:622-30.
15. Wolfs GG, Knottnerus JA and Janknegt RA: Prevalence and detection of micturition problems among 2,734 elderly men. *J Urol* 1994;152:1467-70.
16. Girman CJ, Jacobsen SJ, Guess HA, *et al.*: Natural history of prostatism: relationship among symptoms, prostate volume and peak urinary flow rate. *J Urol* 1995;153:1510-5.

Chapter 4

Normal voiding patterns and determinants for increased diurnal and nocturnal voiding frequency in older men

Abstract

Objective. To determine normal values of diurnal and nocturnal voiding frequency and its determinants in a population-based sample of older men.

Subjects and methods. We collected data from 1688 men aged 50 to 78 years old recruited from the population of Krimpen, The Netherlands. Measurements consisted of self-administered questionnaires, including the International Prostate Symptom Score (IPSS), a 3-day frequency-volume chart, transrectal prostatic ultrasound, uroflowmetry and post-void residual volume measurement.

Results. Diurnal voiding frequency is independent of age (median 5 voids, interquartile range 4 to 6), and higher in men with benign prostatic hyperplasia (BPH). Nocturia 2 or more times is present in 30% of men aged 50 to 54 years and in 60% of those 70 to 78 years old, while nocturia 3 or more times is present in 4% and 20%, respectively. In addition, nocturia is strongly associated with BPH and nocturnal polyuria but apparently not with cardiovascular symptoms, hypertension or diabetes mellitus. We noted poor agreement of the responses on the frequency-volume charts and the IPSS question on nocturia. Using the IPSS leads to a higher prevalence of nocturia.

Conclusions. Diurnal frequency is independent of age but higher in men with BPH. Nocturia increases with advancing age and is more frequent in men with nocturnal polyuria. BPH is an independent risk factor for nocturia and increased diurnal voiding frequency. In those with nocturia, there is a great difference in subjective symptoms and objective data, indicating that the weight of the IPSS question on nocturia in treatment decisions should be reconsidered.

Introduction

Increased diurnal and nocturnal voiding frequency are common and bothersome symptoms in older men.[1,2] Urinary frequency interferes with daily activities,[3] whereas nocturia may result in sleep disturbance, daytime fatigue, a lower level of general well-being and is a risk factor for nightly falls.[4] In addition to the association with urological conditions, such as prostate enlargement, diurnal and nocturnal urinary frequency are reported as symptoms of various diseases.[5]

With growing attention to urologic problems and the increasing number of older men, it is expected that physicians will see more men with these problems. When evaluating these patients, physicians are hampered by a lack of sound population-based data on normal voiding patterns and related factors.

Previously reported normal voiding patterns were determined with the use of questionnaires, which are generally influenced by recall bias.[6] Frequency-volume charts are not subject to this type of bias and, therefore, they are a more valid tool for measuring urinary frequency.[7] To our knowledge, these have not been previously used in a community-based study, to establish normal values in older men. Reports on the agreement between chart data and questionnaires are contradictory.[8,9]

We used frequency-volume charts to determine normal voiding frequency values and their determinants in older men. The current series is part of the large ongoing Krimpen study of male urogenital tract problems. We describe age group specific normal values of diurnal and nocturnal voiding frequencies, and the effect of urological parameters and general medical conditions on these frequencies. Moreover, we tested the influence of the definition of sleeping hours on nocturnal frequency, and the level of agreement between frequency-volume chart with questionnaire data regarding nocturia in the same study group.

Subjects and methods

The data presented here were collected as part of a large, ongoing, community-based Krimpen study on male urogenital tract problems and general health status, as previously described in detail.[10] Briefly, in the Krimpen study all 3924 men aged 50 to 75 years residing in a Dutch municipality near Rotterdam were evaluated to gain information on male urogenital tract dysfunction, and the prevalence and determinants of clinical benign prostatic hyperplasia (BPH). The study consisted of phase 1, in which data of 1688 responders (50% of all eligible men) were collected by way of self-administered questionnaires and during a visit to a health centre and phase 2, in which 1661 men (98.4% of the participants) visited a urology outpatient clinic. All men entering the study provided written informed consent.

The questionnaire included the International Prostate Symptom Score (IPSS) and questions on chronic disease history such as cardiovascular symptoms, hypertension and diabetes mellitus, smoking habits, alcohol consumption and current medication use. Measurements at the health centre included: height, body weight, systolic and diastolic blood pressure, and urinalysis by a dipstick test. At the urology outpatient department other measurements were made: serum prostate specific

antigen, digital rectal examination and transrectal prostatic ultrasound, uroflowmetry, and post-void residual urine volume.

A 3-day frequency-volume chart was completed by 1597 participants (95%), on which each micturition was recorded in one-hour time units. On day 3 each voided volume was recorded. The time of rising and bedtime were noted on the chart by participants. Diurnal and nocturnal urinary frequency was determined from the time of rising on the first day until time of rising on the third day.

We estimated 24-hour urinary frequency as the mean during three days or two when one was missing. The number of voids during patient-reported waking and sleeping hours was estimated as the mean of two or the frequency of one day and night, respectively, when the other was missing. Voiding at the time of arising and just before bedtime was considered diurnal frequency.[11]

We defined nocturia as voiding for which sleep was interrupted and designated two or more, and three or more such voids as, *nocturia-2* and *-3*, respectively. Men with 1.5 and 2.5 voids in two nights on the frequency-volume chart were included in the *nocturia-2* and *nocturia-3* groups, respectively. The nocturnal urinary volume was determined from midnight until time of rising.[11] The initial daytime voiding within one hour after rising was included into nocturnal urinary volume. Nocturnal polyuria was defined as nocturnal urinary volume greater than 35% of the 24-hr total urine volume.[11] Clinical BPH was defined as having moderate to severe voiding symptoms (IPSS greater than 7 points) with prostate enlargement (volume greater than 30 cc) and a reduced urinary peak flow rate (less than 15 ml per second).[12]

We compared the number of voids during patient-reported and arbitrarily defined sleeping hours: 11 p.m. to 7 a.m., 11 p.m. to 8 am, midnight to 7 a.m. or midnight to 8 a.m.

Statistical analysis

We excluded men with newly diagnosed prostate cancer or previous prostate operation for BPH (n = 106) from all analyses because we evaluated the natural history of lower urinary tract symptoms and BPH. Age group specific normal values are expressed as median and interquartile range of voiding frequencies. We compared the number of sleeping hours per age group by means of analysis of variance test for trend.

To investigate the possible effect of different variables on the diurnal voiding frequency, we performed bivariate linear regression analyses for repeated measurements.[13] Certain characteristics were entered into the model individually, including age group, diabetes mellitus (yes or no), cardiovascular symptoms (yes or no), hypertension indicated by diastolic and systolic blood pressure greater than 94 and 159 mm Hg respectively, or antihypertensive drug use, diuretic use (yes or no), alcohol consumption (no alcohol, 1 to 2 units per day or more than 2 units per day), smoking habits (yes or no), post void residual volume of > 50 ml, nocturnal polyuria (yes or no), clinical BPH (yes or no), IPSS groups (no, mild, moderate or severe symptoms), prostate enlargement (yes or no), and reduced urinary peak flow rate (yes or no). To assess the possible effect of variables in the *nocturia-2* and *nocturia-3* group, bivariate logistic regression for repeated measurements was done.[13]

In both the linear and logistic regression analyses variables with a p-value < 0.25 entered multivariate models with diurnal voiding frequency and nocturia as dependent variables. We tested

two models: one with clinical BPH (model A) and one with IPSS, prostate enlargement and reduced urinary peak flow rate as separate parameters (model B). Final analyses were performed using variables with a p-value < 0.05 in the multivariate models.

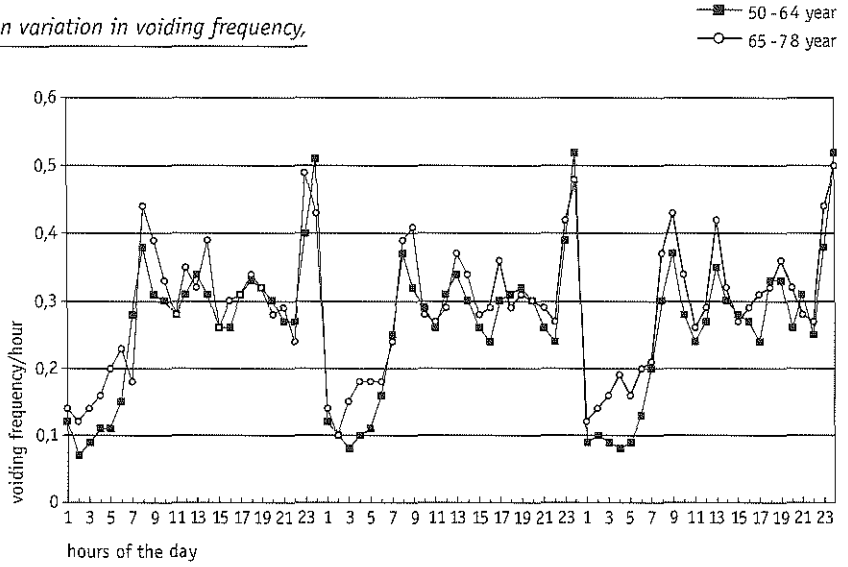
The linear regression approach enabled us to estimate diurnal voiding frequency in men with a certain characteristic relative to those without this characteristic, while controlling for other factors. The logistic regression approach produced adjusted odds ratios (ORs), indicating the probability of nocturia in men with a certain characteristic in regard to a reference group, while controlling for other characteristics.

As a measure of agreement between responses to the IPSS question on nocturia and the frequency-volume chart data, we calculated the intraclass correlation. A correlation coefficient of 1 indicated perfect agreement, a correlation of zero indicates no agreement at all.[14] A p-value of 0.05 was considered significant.

Results

A total of 1597 men (95% of the responders) completed the 3-day frequency-volume chart. Two charts were excluded from analysis due to inadequate completion and 41 charts had missing values on one of the three days. Because of missing data on time of rising and bedtime, diurnal and nocturnal voiding was only estimated in 1211 men (76% of the completed charts). The rate of missing values on time of rising and bedtime differed among age groups. It was highest and lowest in men aged 50 to 54 years and 70 to 78 years (43% and 18%, respectively). There were no differences in men with and without recorded waking and sleeping hours concerning 24-hour voiding frequency and IPSS scores.

Figure 4.1. *Circadian variation in voiding frequency,*



gray blocks: time period in which 80-90% of the men are "getting up" and "going to bed"

Figure 4.1 shows the circadian variation in urinary frequency during three days. Results in the three youngest and the two oldest age groups were similar. Therefore, the data were combined to age groups; 50 to 64 years and 65 years and older.

Table 4.1 shows 24-hour, diurnal and nocturnal voiding frequency in 5-year age groups. The mean duration of the sleeping time differed between the age groups. It was least and greatest in the 55 to 59 and 70 to 78-year old groups (8.1 versus 8.6 hours, analysis of variance test for trend, $p < 0.001$). These differences were corrected as the number of voids per patient-reported sleeping hour (Table 4.1).

Table 4.1. *Voiding frequency in population sample of men aged 50 to 78 years.*

	voiding frequency			number of voids per patient
	24 hour* (n = 1489)	diurnal† (n = 1140)	nocturnal† (n = 1138)	reported sleeping hour‡ (n = 1138)
age group (yr)	median (IQR)	median (IQR)	median (IQR)	median (IQR)
50 to 54	5.7 (5.0 – 7.0)	5.0 (4.0 – 6.0)	1.0 (0.3 – 1.5)	0.11 (0 – 0.17)
55 to 59	6.0 (4.7 – 7.0)	5.0 (4.0 – 6.0)	1.0 (0 – 1.5)	0.13 (0 – 0.18)
60 to 64	6.3 (5.3 – 7.7)	5.0 (4.0 – 6.5)	1.0 (0.5 – 2.0)	0.13 (0.06 – 0.22)
65 to 69	6.5 (5.7 – 8.0)	5.0 (4.0 – 6.0)	1.5 (1.0 – 2.0)	0.16 (0.10 – 0.22)
70 to 78	7.0 (5.7 – 8.3)	5.0 (4.0 – 6.5)	1.5 (1.0 – 2.0)	0.18 (0.11 – 0.25)
all (50 to 78)	**6.3 (5.0 – 7.5)**	**5.0 (4.0 – 6.0)**	**1.5 (1.0 – 2.0)**	**0.13 (0.06 – 0.21)**

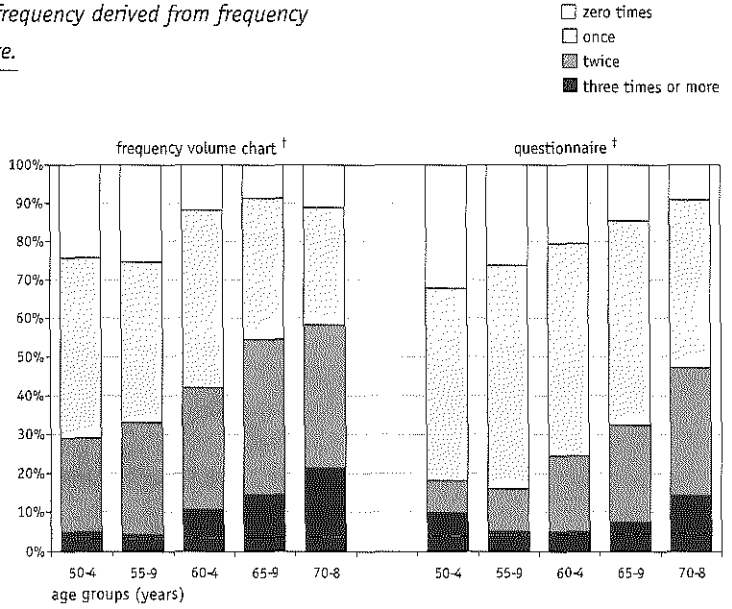
* Mean frequency on 3 days or two days (if 1 day is missing); † Mean number of voids on 2 days/nights or number of voids on 1 day/night (if other is missing), estimated with use of patient reported sleeping hours. Voiding on time of rising included in diurnal frequency; ‡ Number of voids during sleeping hours / number of sleeping hours (patient reported); n Number of men in estimation. Differences in the numbers are due to missing data on sleeping/waking times; IQR Interquartile Range

Bivariate linear regression revealed that certain variables had a significant positive correlation with mean diurnal voiding frequency, including clinical BPH, cardiovascular symptoms, hypertension, post void residual of greater than 50 ml, IPSS, prostate enlargement and decreased maximum urinary flow. In the two multivariate models including these parameters only clinical BPH and IPSS independently influenced diurnal urinary frequency. Men with clinical BPH voided a mean of 1.2 times more than those without BPH (6.2 versus 5.0). Men with mild, moderate and severe symptoms voided a mean of 0.7, 2.0 and 2.5 more times, respectively, than men without symptoms who voided 4.5 times.

Figure 4.2 shows the percent of nocturnal voids for the 5-year age groups, as estimated by frequency-volume charts and IPSS nocturia question. Frequency-volume charts indicated a higher percent of *nocturia-2* and *-3* than the IPSS question. For all ages intraclass correlation of responses to the IPSS nocturia question with frequency-volume chart data was 0.30 (95% confidence interval [CI] 0.25 to 0.35) for all ages. It ranged from 0.08 (CI95% 0 to 0.21) to 0.36 (0.36 to 0.57) in men 55 to 59 and 60 to 69 years old, respectively, with only minor agreement between the two methods for estimating nocturia.

Table 4.2 represents an overview of logistic regression analyses on *nocturia-2* and *–3* groups. Results indicate that each condition depended on age and the presence of BPH. Moreover, nocturnal polyuria

FIGURE 4.2. *Nocturnal voiding frequency derived from frequency volume chart and questionnaire.*



† sleeping hours in two nights or one night (if other missing). ‡ Question from International Prostate Symptom Score: For the past month, how many times did you most typically get up to urinate from the time you went to bed until the time you got up in the morning?, none, 1 time, ... 5 or more times.

was independently associated with *nocturia-3*, whereas it had no significant relation with *nocturia-2*. The opposite was true for diuretics use. The effect of age is greater for *nocturia-3*.

When the parameters involved in the definition of BPH were entered separately into model B, prostate enlargement did not contribute significantly to the effect. The odds ratio increased strongly with higher IPSS-scores for *nocturia-2* and *-3*. In the analyses of *nocturia-3*, the odds ratio of the IPSS groups was not uniquely estimated, and so IPSS greater than 7 points was used. Decreased maximum urinary flow had a positive effect on *nocturia-2* but no significant correlation with *nocturia-3*.

Only 4% and 22% of men were adequately categorised when the arbitrarily defined sleeping hours of midnight to 7 a.m. and 11 p.m. to 8 a.m., respectively, were used for estimating nocturia. These times would have resulted in substantially different data on nocturnal voiding frequency.

Discussion

To our knowledge our study is the first to use frequency-volume charts for evaluating normal voiding patterns in a large community-based sample of men 50 years old or older.

The response rate of 50% in the Krimpen study is remarkably high considering the effort required from the responders and the number of invasive tests performed. Moreover, a nonresponse study showed that the participants were comparable to nonresponders with respect to age, educational and marital status and for smoking and drinking habits.[10] The participants had higher IPSS-scores

Table 4.2. *Logistic regression analyses on nocturia "twice and more" and nocturia "three times and more"*

	bivariate logistic regression		multivariate logistic regression							
			Model A				Model B			
	nocturia-2	nocturia-3	nocturia-2		nocturia-3		nocturia-2		nocturia-3	
	OR	OR	OR#	$CI_{95\%}$	OR#	$CI_{95\%}$	OR#	$CI_{95\%}$	OR#	$CI_{95\%}$
age group (yr)										
50 to 54	referent	referent	referent		referent		referent		referent	
55 to 59	1.1***	1.1*	1.3	0.9-1.9	1.6	0.6-4.4	1.2	0.8-1.9	1.2	0.5-2.8
60 to 64	1.8*	2.9*	2.0	1.3-2.9	4.1	1.6-10.5	1.9	1.2-2.8	3.2	1.5-6.9
65 to 69	2.9*	4.6*	3.4	2.3-5.1	5.8	2.3-15.0	2.8	1.9-4.2	4.6	2.1-10.0
70 to 78	3.4*	6.8*	3.5	2.2-5.5	6.6	2.5-17.3	3.0	1.9-4.7	5.6	2.5-12.4
diabetes history	0.6**	1.0***	NS		NA		NS		NA	
cardiovascular symptoms	2.2*	2.8*	NS		NS		NS		NS	
hypertension	1.4*	1.7*	NS		NS		NS		NS	
diuretics use	2.0*	2.2*	2.0	1.2-3.2	NS		1.5	1.0-2.4	NS	
alcohol consumption										
no	referent	referent								
1 to 2 /day	0.9***	0.8**								
> 2/day	0.7*	0.7**	NS		NS		NS		NS	
smoking	0.7*	0.6***	NS		NA		NS		NA	
residual volume > 50 ml	1.4**	1.9*	NS		NS		NS		NS	
nocturnal polyuria	1.3*	2.1*	NS		1.9	1.3-3.0	NS		2.3	1.5-3.4
benign prostatic hyperplasia†	2.3*	3.9*	1.7	1.2-2.4	3.1	1.9-5.0	NA		NA	
IPSS group										
no symptoms	referent	NA	NA		NA		referent		NA	
mild (1 to 7 points)	8.7*						6.8	3.5-13.3		
moderate (8 to 19)	16.6*						11.3	5.6-22.9		
severe (> 19)	20.0*						17.1	6.7-43.6		
IPSS > 7	NA	3.1*	NA		NA		NA		2.9	1.9-4.3
prostate enlargement†	1.1***	1.8**	NA		NA		NA		NS	
reduced urinary peak flow rate§	1.8*	2.4*	NA		NA		1.3	1.0-1.7	NS	

Nocturia-2, nocturia "twice or more"; Nocturia-3, nocturia "three times or more"; OR, odds ratio; * p-value < 0.05, ** 0.05 < p < 0.25, *** p > 0.25; CI95%, 95% confidence interval for odds ratio; IPSS, International Prostate Symptom Score; NA, not applicable (variable not used in the model); NS, no significant influence of variable (p > 0.05), presented values of OR resulted from final analyses of variables with significant influence (i.e., nonsignificant variables omitted); † defined as moderate to severe urinary symptoms (IPSS greater than 7) with prostate enlargement and reduced urinary peak flow rate; ‡ prostate volume ≥ 30 cc (measured by transrectal ultrasound); § urinary peak flow rate < 15 ml/sec

and a slightly lower level of general wellbeing than the nonresponders. This result may have caused overestimation of the diurnal and nocturnal voiding frequency indicated by the frequency-volume chart since a higher IPSS-score corresponded with increased diurnal frequency and higher nocturia odds ratios. Data from the American study of Panser *et al* had the same pattern of response bias,[15] implying that this bias may have influenced other studies. These considerations indicate that normal values in the general population may be slightly lower than those in our sample but they do not refute our general finding that voiding two times during sleeping hours is so common that it may be considered normal.

In the current study clinical BPH and IPSS voiding symptoms were the only two factors with an influence on diurnal voiding frequency. Participant age, cardiovascular symptoms, hypertension, post-void residual urine volume, prostate enlargement and decreased maximum urinary flow did not influence diurnal frequency independent of these two factors. In a previous community-based study Wolfs *et al* reported lower diurnal frequency but no determinants were mentioned.[16] The difference in those results and ours may be due to the different measuring tool (questionnaire versus frequency-volume chart).

The present study shows that nocturia is common in older men, increasing strongly with increasing age (Figure 4.2). Previous community-based studies using questionnaires reported one or more and two or more episodes of nocturia in 32% to 78% and 24% to 30% of older men, respectively.[1,2,16-20] Most reported prevalences are substantially lower than those obtained from our frequency-volume charts but similar to our results from the IPSS nocturia question. The prevalence of nocturia one or more times reported by Garraway *et al* was similar to our frequency-volume chart prevalence of 78% but they reported no age-specific prevalences.[1]

The results of the current population-based study do not support the previously reported correlation of nocturia with diabetes mellitus, heart disease and hypertension, as described by Barker and Mitteness.[5] However, they do confirm the association of nocturia with age and clinical BPH. According to the parameters involved in the definition of BPH prostate enlargement does not seem to correlate with nocturia. In men with higher level of voiding symptoms or decreased maximum urinary flow the odds ratio for nocturia is greater. Nocturnal polyuria only has a role in more severe nocturia, such as three voidings or more nightly. Diuretics use only has a role when there are two or more voids nightly.

Although 28% of reports on "sleeping hours" were missing, we prefer the use of these patient-reported hours to the use of arbitrarily defined hours, because the latter method is highly inaccurate. Due to the lower number of missing reports on "sleeping hours" in elderly subjects there was a relative over-representation of this group in the estimation of the nocturnal urinary frequency for the study population overall, which may have led to an overestimating of nocturia. We have no explanation for the significant difference in percentage of missing values on time of rising and bedtime between the young and old age group.

In line with our results McCormack *et al* reported poor agreement of frequency-volume chart with questionnaire results.[8] More recently, Donovan *et al* for the International Continence Society-BPH Study reported moderate to good agreement between these two methods (exact agreement 68% with

corresponding kappa 0.57).[21] However, it is not advisable to use the kappa statistic for this purpose but rather a weighted kappa equivalent to an intraclass correlation coefficient.[22]

Conclusions

This population-based study provides normal values for diurnal and nocturnal voiding frequency in older men. Diurnal frequency is higher in men with clinical BPH, whereas age has no influence. Nocturnal frequency has a strong positive relation with age, clinical BPH, diuretics use and nocturnal polyuria but does not seem to be associated with cardiovascular symptoms, diabetes mellitus or hypertension. This means that interventions on nocturia in older patients, if needed at all, may be justified by urologic considerations.

We stress that questionnaires underestimate the prevalence of nocturia. In individuals there is a lack of agreement between subjective (questionnaire and history taking) and objective prospectively collected (frequency-volume chart) data on nocturnal frequency. The weight of the IPSS question on nocturia in treatment decisions should be reconsidered. Frequency-volume charts are the most valid instrument for diagnosing nocturia in older men and should be used for evaluating treatment strategies for nocturia and increased diurnal voiding frequency.

References

1. Garraway WM, Collins GN and Lee RJ: High prevalence of benign prostatic hypertrophy in the community. *Lancet* 1991;338:469-71.
2. Chute CG, Panser LA, Girman CJ, *et al.*: The prevalence of prostatism: a population-based survey of urinary symptoms. *J Urol* 1993;150:85-9.
3. Burgio KL, Engel BT and Locher JL: Normative patterns of diurnal urination across 6 age decades. *J Urol* 1991;145:728-31.
4. Asplund R and Aberg H: Health of the elderly with regard to sleep and nocturnal micturition. *Scand J Prim Health Care* 1992;10:98-104.
5. Barker JC and Mitteness LS: Nocturia in the elderly. *Gerontologist* 1988;28:99-104.
6. Coughlin SS: Recall bias in epidemiologic studies. *J Clin Epidemiol* 1990;43:87-91.
7. Abrams P and Klevmark B: Frequency volume charts: an indispensable part of lower urinary tract assessment. *Scand J Urol Nephrol Suppl* 1996;179:47-53.
8. McCormack M, Infante-Rivard C and Schick E: Agreement between clinical methods of measurement of urinary frequency and functional bladder capacity. *Br J Urol* 1992;69:17-21.
9. Donovan JL, Abrams P, Peters TJ, *et al.*: The ICS-'BPH' Study: the psychometric validity and reliability of the ICSmale questionnaire. *Br J Urol* 1996;77:554-62.
10. Blanker MH, Groeneveld FPMJ, Prins A, *et al.*: Strong effects of definition and nonresponse bias on prevalence rates of clinical benign prostatic hyperplasia: the Krimpen study of male urogenital tract problems and general health status. *BJU Int* 2000;85:665-71.
11. Weiss JP and Blaivas JG: Nocturia. *J Urol* 2000;163:5-12.
12. Bosch JL, Hop WC, Kirkels WJ and Schröder FH: Natural history of benign prostatic hyperplasia: appropriate case definition and estimation of its prevalence in the community. *Urology* 1995;46:34-40.
13. Diggle PJ, Liang KY and Zeger SL: *Analysis of Longitudinal Data*. Oxford: Clarendon Press, 1994.
14. Fisher RA: *Statistical Methods, Experimental Design, and Scientific Inference*. Oxford: Oxford University Press, 1990.
15. Panser LA, Chute CG, Guess HA, *et al.*: The natural history of prostatism: the effects of non-response bias. *Int J Epidemiol* 1994;23:1198-205.
16. Wolfs GG, Knottnerus JA and Janknegt RA: Prevalence and detection of micturition problems among 2,734 elderly men. *J Urol* 1994;152:1467-70.
17. Norman RW, Nickel JC, Fish D and Pickett SN: 'Prostate-related symptoms' in Canadian men 50 years of age or older: prevalence and relationships among symptoms. *Br J Urol* 1994;74:542-50.
18. Bosch JL, Hop WC, Kirkels WJ and Schröder FH: The International Prostate Symptom Score in a community-based sample of men between 55 and 74 years of age: prevalence and correlation of symptoms with age, prostate volume, flow rate and residual urine volume. *Br J Urol* 1995;75:622-30.
19. Sagnier PP, MacFarlane G, Richard F, *et al.*: Results of an epidemiological survey using a modified American Urological Association symptom index for benign prostatic hyperplasia in France. *J Urol* 1994;151:1266-70.
20. Britton JP, Dowell AC and Whelan P: Prevalence of urinary symptoms in men aged over 60. *Br J Urol* 1990;66: 175-6.
21. Donovan JL, Kay HE, Peters TJ, *et al.*: Using the ICSQoL to measure the impact of lower urinary tract symptoms on quality of life: evidence from the ICS-'BPH' Study. International Continence Society-Benign Prostatic Hyperplasia. *Br J Urol* 1997;80:712-21.
22. Maclure M and Willett WC: Misinterpretation and misuse of the kappa statistic. *Am J Epidemiol* 1987;126:161-9.

Chapter 5

Relation between nocturnal voiding frequency and nocturnal urine production in older men

Abstract

Objective. To describe normal values for nocturnal urine production and its determinants as well as the relation between nocturnal urine production and voiding frequency.

Subjects and methods. Data were collected from 1688 men 50 to 78 years old without bladder or prostate cancer, radical prostatectomy, neurogenic bladder dysfunction or a negative advice from their general practitioner. Measurements included self-administered questionnaires, a 3-day frequency volume chart, transrectal ultrasonography of the prostate, uroflowmetry and post void residual measurement.

Mean nocturnal urine production was computed from the frequency-volume charts. Linear regression analyses were performed to determine associated factors for nocturnal urine production. Areas under the receiver operating characteristic curves (ROC area) were used to describe the discriminative value of nocturnal urine production on nocturnal voiding frequency. A cut-off value for 'increased' nocturnal urine production was defined using logistic regression analyses.

Results. The nocturnal urine production was 60.6 ml/hr for the total study population, which increased with age and was significantly higher in men with 24-hour polyuria. Nocturnal urine production is on average higher in men with increased nocturnal voiding frequency, but has only a reasonable discriminative value on nocturnal voiding frequency (ROC area 0.71 and 0.76). A nocturnal urine production exceeding 90 ml/hr is suggested as abnormal.

Conclusions. On average, nocturnal voiding frequency is indicative of nocturnal urine production. However, nocturnal urine production is only a modest discriminator for increased nocturnal voiding frequency. Therefore, the use of nocturnal urine production as an explanatory variable for nocturnal voiding frequency in daily practice is of little value.

Introduction

Increased nocturnal voiding frequency is common in older men.[1] Many physicians consider it a sign of increased nocturnal urine production, which may represent a pathologic condition reflective of congestive heart failure, venous stasis or hormonal changes with aging, or a condition reflective of lower urinary tract symptoms.[2-4] The relationship between (increased) nocturnal voiding frequency and urine production has, however, not been well established. Moreover, normal values on nocturnal urine production in older men are lacking.

Besides the relation to nocturnal urine production, nocturnal voiding frequency has been described as a result of diuretic use and awakenings for other reasons such as sleep disorders or anxiety.[3,5]

We have previously published our analyses on nocturia in a large population-based sample of men aged 50 to 78 years.[1] In this study population, nocturia increased strongly with age, was strongly associated with clinical benign prostatic hyperplasia and nocturnal polyuria, but was apparently not related with cardiovascular symptoms, hypertension or diabetes mellitus.

In the assessment of nocturnal polyuria, the nocturnal polyuria index was used. The value of this index, as well as other suggested definitions of nocturnal polyuria remains, however, debatable.[3,4,6-12] In general, the suggested definitions of 'abnormal' were not based on normal distributions and were not properly validated. Most definitions of 'nocturnal polyuria' refer to a day/night ratio in urine production.[3,8] Although mathematically related, the nocturnal urine production and day/night ratio have only a poor agreement: men with a significantly increased nocturnal urine production can easily have a normal day/night ratio, whereas men with a normal nocturnal urine production can have a significantly disturbed day/night ratio. In definitions using nocturnal voided volumes only,[4,10] it is assumed that volumes voided at night are produced during the night. In our opinion, this seems incorrect. When analysing nocturnal voiding frequency, attention should focus on urine production during nighttime.

This study describes normal values for nocturnal urine production in older men, based on recordings on frequency-volume charts in a population-based study. Additionally, associated factors and the quantitative association between nocturnal urine production and nocturnal voiding frequency are described, and a new definition of nocturnal polyuria is given.

Subjects and Methods

The data presented here were collected as part of the Krimpen study, described in detail elsewhere.[13] Briefly, the Krimpen study was performed to gain information on male urogenital tract dysfunction and general well being among Dutch men aged 50 to 75 years. Men without radical prostatectomy, prostate or bladder cancer, neurogenic bladder disease or negative advice from their general practitioner, who were able to complete questionnaires and attend the health centre, were invited for the study. All 1688 participants (response rate 50%) provided written informed consent. The Medical Ethical Committee of the Erasmus Medical Centre Rotterdam, the Netherlands, approved the study.

Data were collected via self-administered questionnaires (including the International Prostate Symptom Score (IPSS)[14] and questions on history of chronic disease, smoking habits, alcohol

consumption and current medication use) and during visits to the local health centre and the outpatient clinic of a urology department. Measurements included blood pressure, serum prostate specific antigen (PSA), digital rectal examination (DRE), prostate volume through transrectal ultrasonography (TRUS), uroflowmetry and post voiding residual measurement. To exclude men with prostate carcinoma, biopsies were taken according to a previously described protocol, based on DRE, PSA and TRUS.[13]

Of the participants, 1597 (95%) recorded each micturition in one-hour time units and 'bedtime' and 'time of rising' on a three-day frequency-volume chart. On the third day, the volume of each voiding was recorded.

We computed urine production for each hour of the day according to the method described by Van Mastrigt & Eijskoot[15]: urine production was assumed constant between two voidings and hourly urine production was estimated as the volume of each micturition divided by the number of hours that passed since the previous micturition.[15] Nocturnal urine production was estimated as the mean hourly urine production (ml/hr) from 1 a.m. to 6 a.m. This period was chosen because (approximately) 90% of the men were 'asleep' in this period. Nocturnal voiding frequency was estimated using patient reported sleeping times. A 24-hour voided volume greater than 2,500 ml was defined as '24-hour polyuria'.

Bladder voiding efficiency was defined as the voided volume during uroflowmetry divided by the initial urine volume (voided volume plus the post-void residual).[16]

We previously described that the participants were similar to those not responding for age, smoking and drinking habits and chronic diseases; participants more often had moderate to severe lower urinary tract symptoms.[13]

Statistical analyses

Men with newly diagnosed prostate cancer or previous operation for benign prostatic hyperplasia (n = 106, one without a frequency-volume chart) were excluded from the analyses. Of the remaining men, 60 completed the frequency-volume chart inadequately and were therefore excluded; thus, 1432 men constitute the basis for this report.

We performed linear regression analyses on nocturnal urine production to explore possible determinants. In these analyses, only variables with a previously described or hypothetical effect on nocturnal urine production were included. Variables with a p-value < 0.25 were entered in multivariate analyses. A p-value < 0.05 was considered significant. A final analysis was performed using the significant variables only.

As, in daily practice, physicians may regard voiding frequency as an indicator for urine production, we present nocturnal urine production according to the nocturnal voiding frequency.

In the analyses on the relation between urine production and voiding frequency, the latter is considered as the dependent variable, as changes in nocturnal urine production may lead to changes in nocturnal voiding frequency, rather than be a result of it. In these analyses, data of men that reported sleeping times (n = 1124) are used. Nocturnal urine production did not differ between these men and those who did not reported sleeping times (mean 60.2 and 61.4 ml/hr, respectively).

We assessed whether nocturnal urine production is discriminative for nocturnal voiding frequency (two or more and three or more episodes) using the area under the receiver operating characteristic curves (ROC area).[17] The ROC area is a suitable parameter to summarize the overall discriminative or diagnostic value of a model and can range from 0.5 (like flipping a coin, useless model) to 1.0 (perfect discrimination).[17] A value over 0.7 can be interpreted as reasonable and over 0.8 as good.[18] As diagnostic tests are used in addition to other available information, such as patient characteristics and physical examination,[18] we tested the value of nocturnal urine production in addition to the other previously described determinants of nocturnal voiding frequency.[1] Different cut-off values of nocturnal urine production were added to the logistic regression models with these determinants. Moreover, we corrected for the number of sleeping hours reported by the individuals and tested the effect of bladder voiding efficiency on nocturnal voiding frequency. The model with the highest percentage of explained variance ($R^2_{nagelkerke}$) was determined as best model.[19] For the cut-off value of nocturnal urine production in these best models, the test characteristics (true positive rate, TPR, and false positive rate, FPR) are derived from the ROC curves.

Results

Mean nocturnal urine production was 60.6 ml/hr (standard deviation 32.6). Univariate linear regression analyses yielded that alcohol consumption, body weight, post void residual, number of sleeping hours, prostate enlargement and diabetes mellitus were non-significant ($p > 0.25$). In the multivariate analyses, the effect of hypertension, cardiac symptoms, reduced urinary flow rate and medication use was lost; significant determinants are presented in Table 5.1.

Table 5.1. *Determinants of nocturnal urine production**

		nocturnal urine production†, ml/hr (mean and difference from reference)
Reference‡		53.4 ‡
Age groups (years)	50-54	Ref
	55-59	0.8
	60-64	4.9
	65-69	9.4
	70-78	13.2
Smoking	No	Ref
	Yes	-5.9
24-hour polyuria (voided volume > 2,500 ml)	No	Ref
	Yes	47.5

* results from multivariate linear regression analyses † Nocturnal urine production was estimated as the mean hourly urine production (ml/hr) from 1 a.m. to 6 a.m. ‡ Reference: non-smoking men aged 50 to 54 years, without 24-hour polyuria. Only values for determinants with $p<0.05$ in multivariate analyses are presented.

Figure 5.1 shows that increased voiding frequency is indicative of increased nocturnal urine production.

FIGURE 5.1. *Nocturnal urine production according to nocturnal voiding frequency*

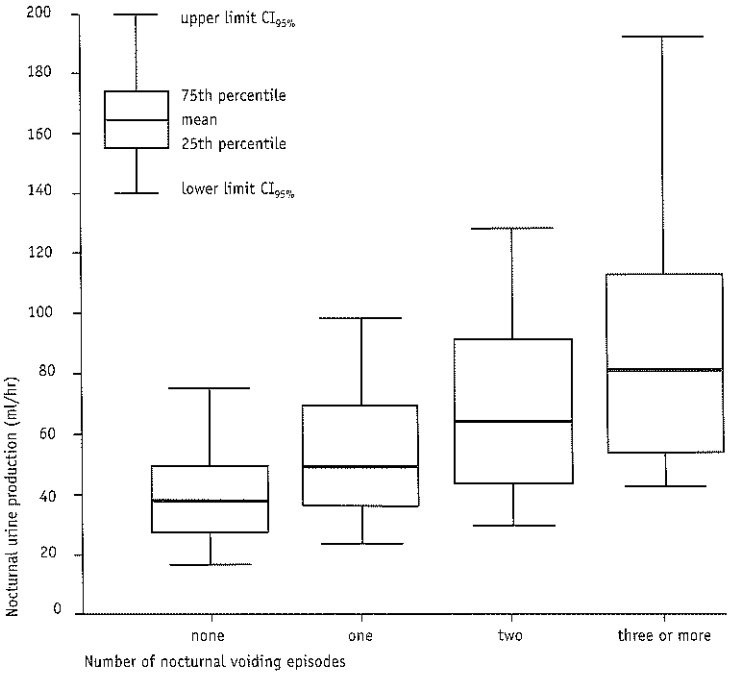


Figure 5.2 and 5.3 present the ROC curves for the discriminative value of nocturnal urine production on voiding frequency. The ROC areas were 0.71 ($CI_{95\%}$ 0.68-0.75) and 0.76 ($CI_{95\%}$ 0.71-0.81) for, respectively, two or more and three or more nocturnal voidings (i.e. reasonable discrimination). Bladder voiding efficiency was not significantly related to nocturnal voiding frequency in the multivariate models, in contrast to the other included parameters.

$R^2_{nagelkerke}$ was 0.231 for the basic model on two or more nocturnal voids (including age, lower urinary tract symptom severity, diuretics use, reduced urinary flow rate and number of sleeping hours), and 0.182 for the model on three or more voids (including age, lower urinary tract symptom severity and number of sleeping hours). Adding a cut-off value of 90 ml/hr for nocturnal urine production resulted in $R^2_{nagelkerke}$ of 0.365 and 0.288, respectively. In both models, this cut-off value resulted in the highest $R^2_{nagelkerke}$. The difference between the basic and complete models was significant (likelihood ratio test, 1 df, $p < 0.001$). In these analyses, age appeared not to be a confounding variable, or an effect modifier.

Using the cut-off value of 90 ml/hr, 32% of the men with two or more voiding episodes would be classified correctly (TPR 0.32), whereas 6% of the men without two or more voiding episodes would be incorrectly classified (FPR 0.06). For three or more voiding episodes the TPR and FPR are 0.46 and 0.12, respectively.

Figure 5.2. *Receiver operating characteristic curve based on nocturnal urine production as a discriminative variable for two or more nocturnal voiding episodes*

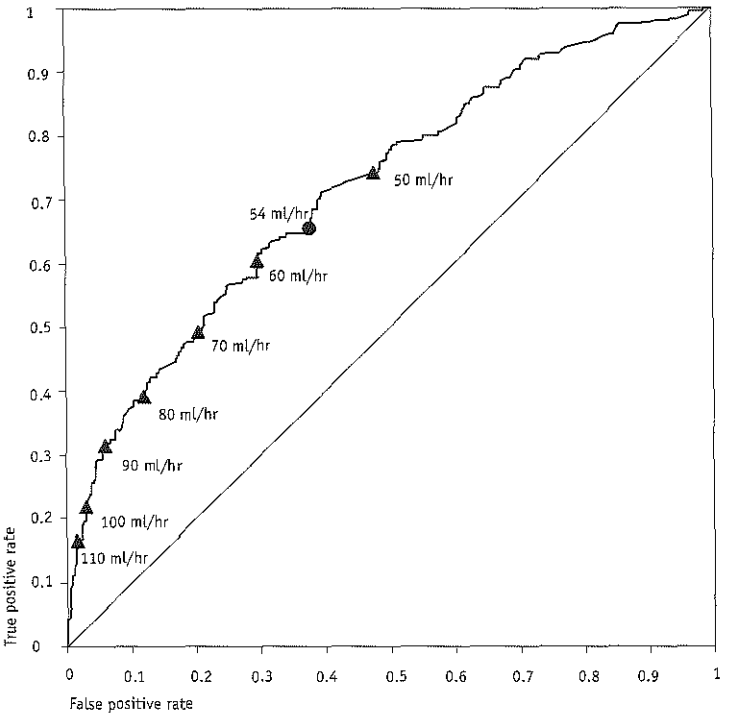
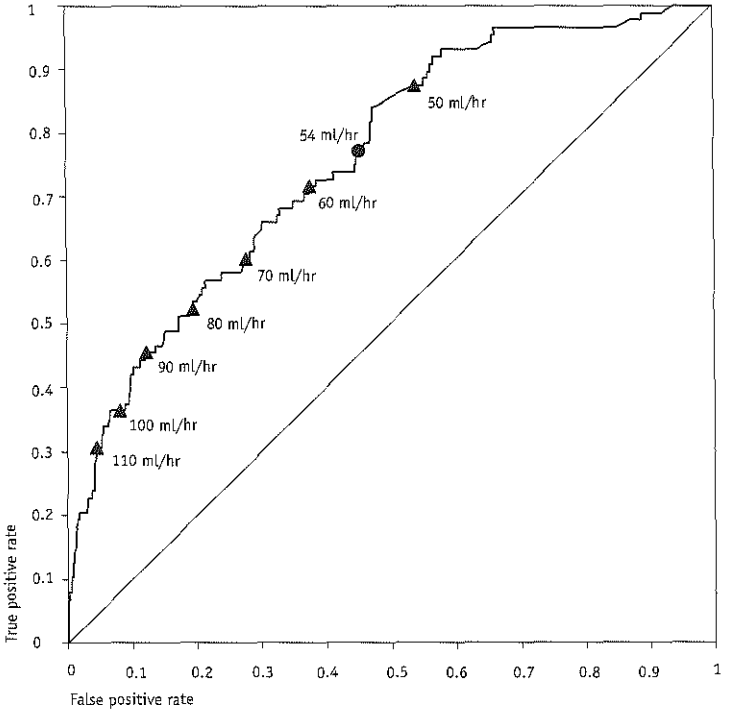


Figure 5.3. *Receiver operating characteristic curve based on nocturnal urine production as a discriminative variable for three or more nocturnal voiding episodes*



Discussion

The availability of frequency-volume charts from a large population-based sample of older men allowed to describe nocturnal urine production and associated factors in a natural environment.[20,21] In the present study, nocturnal urine production and nocturnal voiding frequency are clearly related, i.e. increased nocturnal voiding frequency is indicative of higher nocturnal urine production. It is, however, difficult to separate men with and without increased voiding frequency based on nocturnal urine production.

We have used patient-reported sleeping hours in the analyses of voiding frequency, because using fixed time periods to estimate voiding frequency is highly inaccurate.[1] The use of a fixed time period for the estimation of nocturnal urine production seems appropriate as changing this period did not significantly change the nocturnal urine production estimates (data not presented).

This study indicates that nocturnal urine production is significantly higher in men with 24-hour polyuria, which may result from habitually high fluid intake. Men who smoke have a slightly lower nocturnal urine production. The effect of age may be due to changes in hormonal status, such as atrial natriuretic peptide and antidiuretic hormones,[22,23] or may be a result of changes in nightly excreted potassium, sodium and solutes.[24] Moreover, subclinical heart failure or venous stasis may be present more often in the older men (aged 65 to 78 years) than in the younger men (aged 50 to 64 years).

Based on our analyses we suggest that a nocturnal urine production exceeding 90 ml/hr is abnormal. It should be stressed, however, that even this new definition predicts nocturnal voiding frequency only reasonably. Moreover, about one third of the men with 'increased' nocturnal urine production also have 24-hour polyuria, most probably explaining the increased production.

A previously suggested cut-off value of 54 ml/hr for increased nocturnal urine production was based on the mean nocturnal diuresis of men aged 25 to 35 years.[9,24] In our opinion, these younger subjects cannot serve as reference for older men. Moreover, using this cut-off value in the current study population would lead to a TPR of 0.67 and 0.77 and a FPR of 0.38 and 0.44 for, respectively, men with two or more and three or more nocturnal voidings (see Figures 5.2 and 5.3).

Based on the above-mentioned definitions, the effect of several drugs on 'nocturnal polyuria' as a treatment option for increased nocturnal frequency was studied.[6,9,25,26] The interpretation of those study results is, however, limited, due to the limitations of the used definitions. In our opinion, future studies on medical treatment for 'nocturnal polyuria' should first include patients with severe nocturia (e.g. nocturnal frequency of three times or more) and increased nocturnal urine production according to our new definition. In such studies, patients with 24-hour polyuria, based on habitually excessive fluid intake, should be excluded. This suggestion is supported by a report of a phase III study on desmopressin in the treatment of nocturia in men.[27] In that study, it appeared that patients with nocturia who are treated for a polyuric factor respond better to treatment if nocturnal voiding frequency is three times or more.

Conclusions

This large population-based study on Dutch older men provides normal values and determinants for nocturnal urine production. Mean nocturnal urine production was 60.6 ml/hr and increased considerably with advancing age and 24-hour polyuria.

We conclude that the nocturnal voiding frequency is, on average, indicative of nocturnal urine production. However, nocturnal urine production is a modest discriminator for increased nocturnal frequency. Therefore, the use of nocturnal urine production as an explanatory variable for nocturnal voiding frequency in daily practice is of little value.

References

1. Blanker MH, Bohnen AM, Groeneveld FP, *et al.*: Normal voiding patterns and determinants of increased diurnal and nocturnal voiding frequency in elderly men. *J Urol* 2000;164:1201-5.
2. Brendler CB. Evaluation of the urologic patient. In: Walsh PC, Retik AB, Stamey TA and Vaughan ED, editors. *Campbell's Urology*. 7th ed. Philadelphia: Saunders, 1998:134.
3. Weiss JP, Blaivas JG, Stember DS and Brooks MM: Nocturia in adults: etiology and classification. *Neurourol Urodyn* 1998;17:467-72.
4. Matthiesen TB, Rittig S, Norgaard JP, Pedersen EB and Djurhuus JC: Nocturnal polyuria and natriuresis in male patients with nocturia and lower urinary tract symptoms. *J Urol* 1996;156:1292-9.
5. Barker JC and Mitteness LS: Nocturia in the elderly. *Gerontologist* 1988;28:99-104.
6. Reynard JM, Cannon A, Yang Q and Abrams P: A novel therapy for nocturnal polyuria: a double-blind randomized trial of frusemide against placebo. *Br J Urol* 1998;81:215-8.
7. Matthiesen TB, Rittig S, Mortensen JT and Djurhuus JC: Nocturia and polyuria in men referred with lower urinary tract symptoms, assessed using a 7-day frequency-volume chart. *BJU Int* 1999;83:1017-22.
8. Saito M, Kondo A, Kato T and Yamada Y: Frequency-volume charts: comparison of frequency between elderly and adult patients. *Br J Urol* 1993;72:38-41.
9. Asplund R, Sundberg B and Bengtsson P: Desmopressin for the treatment of nocturnal polyuria in the elderly: a dose titration study. *Br J Urol* 1998;82:642-6.
10. Homma Y, Yamaguchi O, Kageyama S, *et al.*: Nocturia in the adult: classification on the basis of largest voided volume and nocturnal urine production. *J Urol* 2000;163:777-81.
11. Weiss JP, Blaivas JG, Stember DS and Chaikin DC: Evaluation of the etiology of nocturia in men: the nocturia and nocturnal bladder capacity indices. *Neurourol Urodyn* 1999;18:559-65.
12. Weiss JP and Blaivas JG: Nocturia. *J Urol* 2000;163:5-12.
13. Blanker MH, Groeneveld FPMJ, Prins A, *et al.*: Strong effects of definition and nonresponse bias on prevalence rates of clinical benign prostatic hyperplasia: the Krimpen study of male urogenital tract problems and general health status. *BJU Int* 2000;85:665-71.
14. Barry MJ, Fowler Jr FJ, O'Leary MP, *et al.*: The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. *J Urol* 1992;148: 1549-57.
15. van Mastrigt R and Eijskoot F: Analysis of voided urine volumes measured using a small electronic pocket balance. *Scand J Urol Nephrol* 1996;30:257-63.
16. Abrams P: Bladder outlet obstruction index, bladder contractility index and bladder voiding efficiency: three simple indices to define bladder voiding function. *BJU Int* 1999;84:14-5.
17. Hanley JA and McNeil BJ: The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* 1982;143:29-36.
18. Moons KG, van Es GA, Michel BC, *et al.*: Redundancy of single diagnostic test evaluation. *Epidemiology* 1999;10:276-81.
19. Nagelkerke NJD: A note on a general definition of the coefficient of determination. *Biometrika* 1991;78:691-2.
20. Palnaes Hansen C and Klarskov P: The accuracy of the frequency-volume chart: comparison of self-reported and measured volumes. *Br J Urol* 1998;81:709-11.
21. Larsson G and Victor A: Micturition patterns in a healthy female population, studied with a frequency/volume chart. *Scand J Urol Nephrol Suppl* 1988;114:53-7.
22. Bodo G, Gontero P, Casetta G, *et al.*: Circadian antidiuretic hormone variation in elderly men complaining of persistent nocturia after urinary flow obstruction removal. *Scand J Urol Nephrol* 1998;32:320-4.
23. Carter PG, Cannon A, McConnell AA and Abrams P: Role of atrial natriuretic peptide in nocturnal polyuria in elderly males. *Eur Urol* 1999;36:213-20.
24. Kirkland JL, Lye M, Levy DW and Banerjee AK: Patterns of urine flow and electrolyte excretion in healthy elderly people. *Br Med J (Clin Res Ed)* 1983;287:1665-7.

25. Cannon A, Carter PG, McConnell AA and Abrams P: Desmopressin in the treatment of nocturnal polyuria in the male. *BJU Int* 1999;84:20-4.

26. Pedersen PA and Johansen PB: Prophylactic treatment of adult nocturia with bumetanide. *Br J Urol* 1988;62: 145-7.

27. Abrams P, Weiss J, Mattiasson A, *et al.*: The efficacy and safety of oral desmopressin in the treatment of nocturia in men. *Neurourol Urodyn* 2001;20:456-7.

Chapter 6

Voided volumes: normal values and relation to lower urinary tract symptoms in older men

Abstract

Objectives. To determine normal values of voided volumes and explore the relation between bladder capacity and lower urinary tract symptoms (LUTS) in older men.

Subjects and Methods. Data were collected from 1688 men 50 to 78 years old recruited from the population of Krimpen aan den IJssel, The Netherlands. Measurements included self-administered questionnaires (including the International Prostate Symptom Score), a 3-day frequency-volume chart, transrectal ultrasound of the prostate, uroflowmetry and post void residual volume determination.

Results. The 24-hour voided volumes were independent of age (median 1506 ml; 25^{th}-75^{th} percentiles 1160 to 1950). Average volume per void and functional bladder capacity (FBC, defined as the largest single voided volume) declined with advancing age. Moreover, FBC was lower in men with reduced maximum flow rate (less than 15 ml/sec) and independent of the post void residual volume. Multivariate analyses showed no significant effect of prostate enlargement on FBC.

FBC was strongly related to LUTS: a low FBC coincided with higher International Prostate Symptom Scores. Multivariate logistic regression analyses revealed that the presence of moderate to severe symptoms (International Prostate Symptom Score greater than 7) was independent of prostate volume but dependent on age, a reduced flow rate, post void residual and FBC.

Conclusions. Prospective studies are needed to establish the causal relation between FBC and LUTS. Frequency-volume charts are a valid, easy to use, non-invasive method to determine FBC as an aspect of urinary tract (dys-)function in the evaluation of men with LUTS and to determine treatment options for LUTS.

Introduction

Lower urinary tract symptoms (LUTS) are common and bothersome symptoms in the older population.[1-3] Traditionally, doctors are educated to classify these symptoms as "bladder-related" in women and "prostate-related" in men. In the latter group, attention has been focused on prostate volume and urinary outflow obstruction. It has been emphasised, however, that the relation between these parameters and LUTS is modest[1,4,5]; many symptomatic men have normal findings, whereas many symptom-free men have abnormal findings. Nevertheless, only little attention is given to other determinants, such as the bladder capacity.

Studies of bladder capacity in men are performed in selected populations[6,7] or "healthy" subjects,[8] or inpatient monitoring of subjects was used.[7] The results from these studies cannot be generalised to the general population. The frequency-volume chart is a valid instrument to measure voiding frequencies and voided volumes in a natural environment.[9,10] To date these have not been used to determine the normal values of voided volumes in a general population of older men.

As part of a large population-based survey, we have studied the frequency-volume charts of 1597 men 50 to 78 years old. Previously we reported the normative data on urinary frequency derived from these charts.[11] The aim of this report was to describe the normal values of voided volumes (24-hour volumes, average volume per void and functional bladder capacity [FBC], defined as maximum single-voided volume) and the influence of age, anatomic and physiologic parameters (prostate volume, maximum urinary flow rate, post void residual volume) and general medical conditions on these volumes. We also describe the relation between FBC and LUTS.

Subjects and Methods

The data presented were collected as part of the Krimpen study on male urogenital tract problems and general health status. The design of this community-based study has been described in detail elsewhere.[12] In brief, the Krimpen study was performed in a population of 3924 men 50 to 75 years old in a Dutch municipality near Rotterdam, to gain information on male urogenital tract dysfunction and the prevalence of clinical benign prostatic hyperplasia and its determinants. Men who had not undergone radical prostatectomy and had not had prostate or bladder cancer, neurogenic bladder disease or negative advice from their general practitioner, and who were able to complete questionnaires and visit the health centre were eligible and were invited to participate in the study. Recruitment took place between August 1995 and January 1998. In this period, 152 men had passed the age of 75 years but were nevertheless enrolled. All men entering the study provided written informed consent.

The data of 1688 responders (response rate 50%) were collected by way of self-administered questionnaires and during visits to the local health centre (first phase) and outpatient clinic of a urology department (second phase).

The questionnaire included the International Prostate Symptom Score (IPSS)[13] and questions on history of chronic disease (e.g. diabetes mellitus, cardiac symptoms, chronic obstructive

pulmonary disease [COPD]), smoking habits, alcohol consumption, and current medication use. The measurements at the health centre and urology outpatient clinic included height, weight, blood pressure, digital rectal examination, transrectal ultrasound, uroflowmetry and post void residual urine volume measurement.

Non response study

A random sample (n = 500) of the nonresponders were invited to complete a short, mailed questionnaire, which included the IPSS and questions on their history of chronic disease, marital status, educational level, smoking and drinking habits, and current medication use. Of those not responding, 261 (55%) returned the short questionnaire. Participants were comparable to nonresponders for age, educational and marital status, and for smoking and drinking habits. The prevalence of an IPSS greater than 7 was higher in the participants (25% versus 15% in nonresponders).[12]

Frequency-volume charts

Of the participants, 1597 (95%) completed a 3-day frequency-volume chart on which each micturition was recorded in 1-hour time units. On the third day, the volume of each voiding was recorded. Bedtime and time of rising were recorded on the charts. The number of voids during patient-reported waking/sleeping hours was estimated.

From the frequency-volume chart, the following was determined: 24-hour volume, average volume per void (24-hour volume/frequency). The FBC was defined as the largest voided volume of the day. At time of uroflowmetry, the initial bladder volume was determined as the voided volume plus the post void residual volume; 73% and 54% of the men had an initial bladder volume of 100 ml or more and 150 ml or more, respectively. No flow rates were discarded because of relatively low initial bladder volume. We defined reduced flow rate as having a maximum urinary flow rate of less than 15 ml/sec. Prostate enlargement was defined as a prostate volume exceeding 30 ml on transrectal ultrasound scanning.

Statistical analyses

Men with newly diagnosed prostate cancer or who had undergone a previous prostate operation for benign prostatic hyperplasia (n = 106, one without a frequency-volume chart) were excluded from the analyses. Of the remaining men, 2 completed the frequency-volume chart inadequately, 35 did not measure volumes on the third day and 9 reported a 24-hour volume of less than 500 ml and were therefore excluded. The remaining 1446 men constitute the basis for this report.

Men were categorised into the following age groups: 50 to 54, 55 to 59, 60 to 64, 65 to 69 and 70 to 78 years. The 24-hour voided volume, average volume per void and FBC are presented as median values with 25th and 75th percentiles, for the different age groups. The differences in 24-hour volumes between the age groups were tested with the analysis of variances test for linear trend.

Correlates of FBC and average volume per void

To explore the possible effects of the different variables on FBC and average volume per void, we performed bivariate linear regression analyses. The following variables entered these analyses independently: age groups, prostate enlargement, reduced flow rate, post void residual greater than 50 ml, alcohol consumption (no, 1 to 2, more than 2 units [glasses] per day), smoking habits (yes/no), body mass index, COPD (yes/no), diabetes mellitus (yes/no), cardiac symptoms (yes/no), hypertension (diastolic blood pressure greater than 94 mm Hg, systolic blood pressure greater than 159 mm Hg, or use of antihypertensive drugs; yes/no). Variables with a p-value of less than 0.25 were entered in multivariate analyses. Final analyses was performed using variables with a p-value of less than 0.05.

Correlates of LUTS

To determine the effect of FBC on LUTS, we divided the men into categories on the basis of the quartiles of FBC value. Age and total IPSS were compared between the FBC categories by means of analysis of variances test for trend. The presence of single voiding symptoms (IPSS questions; responses "not at all" and "less than 1 time in 5" were considered as "symptom insignificant"; other responses were considered as "symptom significant") was determined for the FBC categories. The differences were tested by chi-square test for linear trend.

Finally, we performed bivariate and multivariate logistic regression analyses to test the influence of age and anatomic and physiologic parameters on LUTS, with moderate to severe symptoms (IPSS greater than 7) as the dependent variable. Age groups, reduced flow rate, post void residual greater than 50 ml, prostate enlargement and FBC (quartiles) were used as independent variables. A p-value of 0.05 was considered statistically significant.

Results

Table 6.1. *24-hour voided volumes, average volume per void and functional bladder capacity by age groups*

	age groups (years)					
	50 to 54 (n = 301)	55 to 59 (n = 373)	60 to 64 (n = 343)	65 to 69 (n = 279)	70 to 78 (n = 146)	total (n = 1446)
24 hr voided volume						
median (ml)	1500	1400	1550	1530	1563	1506*
(percentiles)	(1118-2000)	(1095-1900)	(1180-1950)	(1200-2025)	(1200-1902)	(1160-1950)
Average volume per void						
median (ml)	267	250	248	238	224	246
(percentiles)	(210-346)	(198-331)	(193-316)	(172-300)	(183-271)	(192-349)
Functional bladder capacity						
median (ml)	420	400	400	375	350	400
(percentiles)	(305-518)	(300-548)	(300-500)	(280-500)	(300-450)	(300-500)

* analysis of variance test for linear trend, p = 0.12

Table 6.1 gives the 24-hour voided volumes for the different age groups. These volumes were independent of age (analysis of variances test for linear trend, p = 0.177). Table 6.1 also gives the average volume per void and FBC for the men in different age groups.
Table 6.2 presents the results of the linear regression analyses on FBC. Parameters post void residual greater than 50 ml, smoking habits, diabetes mellitus, cardiac symptoms, hypertension, and body mass index had no significant influence in the univariate analyses (all p > 0.35). The FBC decreased significantly with advancing age, reduced flow rate and prostate enlargement, and was higher in men with COPD and those who drink over 2 units of alcohol per day. Drugs for COPD (corticosteroids, parasympaticolytics and sympaticomimetics) had no influence on FBC in our data. The significant effect of prostate volume disappeared in the multivariate analyses.

Table 6.2. *Determinants of functional bladder capacity (linear regression analyses)*

	univariate		multivariate		
	mean FBC (ml)	p-value	mean FBC (ml) and difference to constant value	($CI_{95\%}$)	p-value
Constant*			518	(482, 554)	
Age groups (years)					
50 to 4 (ref, constant)	438				
55 to 9	434	0.742	-2	(-26, 23)	0.880
60 to 4	414	0.060	-18	(-43, 7)	0.160
65 to 9	402	0.006	-28	(-9, -1)	0.042
70 to 8	379	0.000	-43	(-75, -11)	0.009
prostate enlargement (> 30 ml)					
no (ref, constant)	428				
yes	408	0.028	not significant		0.811
Reduced flow rate (< 15 ml/sec)					
no (ref, constant)	483				
yes	398	0.000	-73	(-93, -53)	< 0.001
Drinking habits					
no alcohol (ref, constant)	416				
1 to 2 units/day	406	0.342	-16	(-37, 5)	0.124
>2 units/day	463	0.000	+32	(6, 59)	0.017
COPD					
men without (ref, constant)	417				
men with	465	0.018	+54	(14, 95)	0.009

FBC = functional bladder capacity; CI = confidence interval; COPD = chronic obstructive pulmonary disease; * constant refers to men aged 50-54 years without prostate enlargement, reduced flow rate or COPD who don't drink alcohol (multivariate analyses)

The difference in FBC between the younger age groups (55 to 59 and 60 to 64) was not statistically significant from the reference group (men aged 50 to 54 years), in contrast to the older age groups (65 to 69 and 70 to 78).

The regression analyses on average volume per void demonstrated similar results, except for the parameters COPD (not significant in univariate analyses, p = 0.457) and drinking habits (not significant in multivariate analyses).

Table 6.3. *Functional Bladder Capacity and lower urinary tract symptoms*

	Functional Bladder Capacity, ml				
	1st quartile (< 300)	2nd quartile (300 to 400)	3rd quartile (400 to 500)	4th quartile (> 500)	p*
Age (years: mean ± SD)	62.4 ± 6.8	61.6 ± 6.7	60.2 ± 6.3	60.4 ± 6.1	<0.001†
Total IPSS score (mean)	6.4	5.5	4.8	3.9	<0.001†
IPSS > 7 (%)	30.5	26.8	22.0	16.0	<0.001
Single LUTS (%)‡					
1. feeling of incomplete bladder emptying	14.9	11.1	12.7	8.8	0.023
2. urinary frequency	25.8	22.7	19.9	16.0	<0.001
3. interruption	16.1	12.7	12.7	7.2	0.001
4. difficulty to postpone urination	20.4	14.3	11.0	6.6	<0.001
5. weak urinary stream	31.2	26.8	19.9	13.8	<0.001
6. straining	5.7	5.7	6.2	2.8	0.14
Nocturnal urinary frequency (%) (derived from frequency-volume chart)					
> 2 times	49.7	45.0	34.3	35.7	<0.001
> 3 times	14.5	9.6	8.1	5.8	<0.001

IPSS: International prostate symptom score; * p-value, chi-square test for linearity, † analysis of variance test for trend, ‡ presence of significant voiding symptoms (IPSS question 1 to 6): response "not at all" and "less than 1 time in 5" considered insignificant, other responses considered significant

Table 6.3 gives the relation between FBC and LUTS. The prevalence of LUTS decreased significantly with an increase of FBC. For the individual urinary symptoms, the same pattern was revealed, except from the symptom of straining (chi-square test for linear trend, p = 0.14). The statistical correction for nonresponse bias based on the differences in IPSS greater than 7 (using weighted analyses) resulted in a minor change in the mean FBC; for the total study population the mean FBC increased from 419 to 422 ml; the median and 25th to 75th percentiles remained unchanged.

The results of the logistic regression analyses on the presence of moderate to severe symptoms (IPSS greater than 7) are shown in Table 6.4. The multivariate analyses revealed that prostate enlargement had no influence (p = 0.453). The odds ratio for LUTS increased with advancing age, reduced flow rate and post void residual volume and decreased with increasing FBC.

In the analyses, prostate volume greater than 30 ml was chosen as the cut-off value for prostate 'enlargement'. Including prostate volume as a continuous variable in the analyses, or choosing other cut-off values (greater or less than 20 ml, or 40 ml) did not result in a significant influence of this parameter (all p > 0.05) in the multivariate analyses (Table 6.2 and 6.4), whereas the influence of other parameters remained unchanged. The same holds true for entering the parameter post void residual volume as a continuous variable in the analyses on FBC (Table 6.2).

Table 6.4. *Urological determinants of presence of moderate to severe voiding symptoms in older men*

	univariate analyses			multivariate analyses		
	OR	($CI_{95\%}$)	p-value	OR	($CI_{95\%}$)	p-value
Age groups (years)			<0.001			0.004
50 to 54 (ref)	1			1		
55 to 59	0.9	(0.6-1.3)		0.9	(0.6-1.3)	
60 to 64	1.2	(0.8-1.8)		1.1	(0.7-1.7)	
65 to 69	1.7	(1.2-2.6)		1.6	(1.1-2.4)	
70 to 78	2.2	(1.4-3.4)		1.8	(1.1-2.9)	
Prostate enlargement*			0.018	not significant		0.453
no (ref)	1					
yes	1.3	(1.1-1.7)				
Reduced flow rate†			<0.001			0.001
no (ref)	1			1		
yes	2.2	(1.6-3.2)		1.8	(1.3-2.6)	
Post void residual‡			<0.001			0.006
no (ref)	1			1		
yes	1.9	(1.3-2.7)		1.7	(1.2-2.5)	
Functional bladder capacity			<0.001			0.032
< 300 ml (ref)	1			1		
300 to 400 ml	0.8	(0.6-1.1)		0.8	(0.6-1.2)	
400 to 500 ml	0.6	(0.5-0.9)		0.8	(0.6-1.2)	
> 500 ml	0.4	(0.3-0.6)		0.5	(0.4-0.8)	

OR = Odds Ratio; CI = confidence interval; * prostate enlargement: volume greater than 30 cc; † reduced flow rate: maximum urinary flow rate (Qmax) less than 15 ml/sec; ‡ post void residual: residual volume more than 50 ml

Discussion

To our knowledge, this study is the first to determine the normal values for voided volume in an open population of older men using a frequency-volume chart. Moreover, this study is the first to suggest that FBC is an important correlate of LUTS in the population of older men, independent of age and reduced flow rate.

Considering the effort required from the responders and the number of invasive tests, the response rate (50%) was remarkably high. The results of the nonresponse study showed that the participants had a higher incidence of LUTS.[12] This nonresponse bias did not influence the estimation of FBC values significantly.

Only few studies on voided volumes have been reported. In a study of 50 male patients hospitalised for treatment or examination of urologic disease, Nakamura *et al* performed 24-hour uroflowmetry recordings.[7] The subjects in that study represented a highly selected, diseased population: 25 with benign prostatic hyperplasia (not defined), 8 with advanced prostate carcinoma, 17 with other diseases not related to urination difficulty. In our opinion, the results can not be generalised to men in the open population. The men were classified into middle-aged (younger than 65 years) and elderly (older than 65 years). The investigators analysed the circadian changes in bladder capacity but gave no values of FBC and average volume per void.[7]

In a well-described survey on healthy female subjects, Larsson and Victor have determined micturition patterns with a frequency-volume chart.[10] The 24-hour voided volume, average volume per void, and FBC in their study were similar to our findings. In contrast, these investigators did not find a relation between the voided volume and age and did not test the relation between bladder capacity and LUTS, as the subjects under study claimed to be symptom free.

Golomb *et al* determined the variability and circadian changes of home uroflowmetry in 32 men referred for benign prostatic hyperplasia (not defined) and young healthy controls.[14] They reported average voided volumes in healthy younger men comparable to those of our total population. In men with benign prostatic hyperplasia, these volumes were much lower (mean 151 ml).

In our study, the average volume per void was significantly lower than the functional (maximal) bladder capacity, indicating that people often void before the maximum bladder capacity has been reached. It also emphasises the fact that the voiding cycle is a complex process depending on urine production and bladder storage function but also on sensory processing of the filling state of the bladder which can be influenced by many other poorly defined factors.[10] The average volume per void in our study was comparable to that found by Golomb *et al* in healthy younger men (mean 261 and 250 ml, respectively).[14]

The estimation of FBC provides information about bladder function, additional to the parameters urinary frequency and average volume per void. The results from our study demonstrated that FBC decreases with advancing age and is strongly related to reduced urinary flow rate, whereas it is independent of post void residual volume. No effect of prostate enlargement on FBC was found by multivariate analyses. Although the difference between the groups was not statistically significant in their study, Nakamura *et al* reported the same relation.[7] Golomb *et al* reported significantly lower (average) voided volumes in men with benign prostatic hyperplasia than in healthy controls. It is unclear whether the difference in the latter study occurred because of the differences in age or other factors, such as reduced peak flow rate in men with benign prostatic hyperplasia. In the current study, one observer completed 86% of all transrectal ultrasound and post void residual measurements and three other experienced observers performed the other 14%. Therefore, we do not think that interobserver variability is a reason for the lack of correlation between prostate volume and post void residual urine volume and FBC.

Although a reduced flow rate and FBC are clearly correlated (Table 6.2), both are strong independent determinants of moderate to severe LUTS (Table 6.4). It should be noted that reduced flow rate is not equivalent to outflow obstruction.

We cannot explain our finding that COPD influences FBC, but not the average volume per void. The higher FBC in men with COPD cannot be explained from the medication use in these men; separate analyses showed that the use of parasympaticolytics and sympaticomimetics have no influence on FBC (both $p > 0.25$).

Conclusions

This population-based study in older men provides reference values for voided volumes and correlates of FBC. Moreover, our data suggest that FBC is an important correlate of LUTS in older men, independent of age, reduced urinary flow rate (less than 15 ml/sec) and post void residual (greater than 50 ml), with prostate volume (greater than 30 ml) a nonsignificant factor. Therefore, we believe that the traditional model of explaining LUTS in older men (as "prostate-related" or "benign prostatic hyperplasia") should be reconsidered. In evaluating patients with LUTS, doctors could use frequency-volume charts to determine the FBC.

Future studies are needed to establish the clinical significance of our findings; that is, to determine the pathophysiologic basis. Moreover, studies should be designed to test the effect of medications with influence on bladder capacity (such as anti-cholinergics), especially in men with a low FBC (less than 400 ml). Studies on the efficacy of drugs for LUTS should include FBC as a parameter.

References

1. Ouslander JG: Aging and the lower urinary tract. *Am J Med Sci* 1997;314:214-8.
2. Garraway WM, Collins GN and Lee RJ: High prevalence of benign prostatic hypertrophy in the community. *Lancet* 1991;338:469-71.
3. Peters TJ, Donovan JL, Kay HE, *et al.*: The International Continence Society "Benign Prostatic Hyperplasia" Study: the bothersomeness of urinary symptoms. *J Urol* 1997;157:885-9.
4. Barry MJ, Cockett AT, Holtgrewe HL, *et al.*: Relationship of symptoms of prostatism to commonly used physiological and anatomical measures of the severity of benign prostatic hyperplasia. *J Urol* 1993;150:351-8.
5. de la Rosette JJ, Witjes WP, Schafer W, *et al.*: Relationships between lower urinary tract symptoms and bladder outlet obstruction: results from the ICS-"BPH" study. *Neurourol Urodyn* 1998;17:99-108.
6. Saito M, Kondo A, Kato T and Yamada Y: Frequency-volume charts: comparison of frequency between elderly and adult patients. *Br J Urol* 1993;72:38-41.
7. Nakamura S, Kobayashi Y, Tozuka K, *et al.*: Circadian changes in urine volume and frequency in elderly men. *J Urol* 1996;156:1275-9.
8. Asplund R and Aberg HE: Micturition habits of older people. Voiding frequency and urine volumes. *Scand J Urol Nephrol* 1992;26:345-9.
9. Palnaes Hansen C and Klarskov P: The accuracy of the frequency-volume chart: comparison of self-reported and measured volumes. *Br J Urol* 1998;81:709-11.
10. Larsson G and Victor A: Micturition patterns in a healthy female population, studied with a frequency/volume chart. *Scand J Urol Nephrol Suppl* 1988;114:53-7.
11. Blanker MH, Bohnen AM, Groeneveld FP, *et al.*: Normal voiding patterns and determinants of increased diurnal and nocturnal voiding frequency in elderly men. *J Urol* 2000;164:1201-5.
12. Blanker MH, Groeneveld FPMJ, Prins A, *et al.*: Strong effects of definition and nonresponse bias on prevalence rates of clinical benign prostatic hyperplasia: the Krimpen study of male urogenital tract problems and general health status. *BJU Int* 2000;85:665-71.
13. Barry MJ, Fowler Jr FJ, O'Leary MP, *et al.*: The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. *J Urol* 1992;148: 1549-57.
14. Golomb J, Lindner A, Siegel Y and Korczak D: Variability and circadian changes in home uroflowmetry in patients with benign prostatic hyperplasia compared to normal controls. *J Urol* 1992;147:1044-7.

Chapter 7

Normal values and determinants of circadian urine production in older men

Abstract

Objective. We determined circadian urine production and its determinants in a large population based sample of older men.

Subjects and Methods. We collected data on 1688 men 50 to 78 years old, without radical prostatectomy, prostate or bladder cancer, neurogenic bladder disease or negative advice from their general practitioner, recruited from the population of Krimpen, the Netherlands. Measurements consisted of self-administered questionnaires, including the International Prostate Symptom Score (IPSS), a 3-day frequency-volume chart, transrectal prostatic ultrasound, uroflowmetry and post-void residual volume measurement. Hourly urine production was determined and urine production day/night ratio calculated from the frequency-volume chart.

Results. Men younger than 65 years showed a clear circadian urine production pattern, whereas in older men this pattern was less clear. Smoking, use of diuretic drugs, post void residual and 24-hour polyuria reinforced the circadian pattern, all in favour of urine production during daytime. The urine production day/night ratio was not associated with prostate enlargement, reduced urinary flow rate, body weight, hypertension, cardiac symptoms, diabetes mellitus, use of antidepressants, cardiac or hypnotic drugs.

Conclusions. Urine production in men aged younger than 65 years showed a clear circadian pattern in contrast to men aged older than 65 years. These data can be used as reference data when describing urine production patterns in selected populations.

In daily practice, frequency-volume charts can be used to determine urine production. This method is low-cost, easy-to-use, and provides valid information on urine production in a patient's natural environment.

Introduction

Increased nocturnal voiding frequency, often referred to as 'nocturia', is common in the elderly.[1,2] Many physicians consider it to be a sign of increased nocturnal urine production, often referred to as 'nocturnal polyuria'. The relationship between (increased) nocturnal voiding frequency and (increased) nocturnal urine production, however, has not been well established.

In patients with heart failure, venous stasis or changed hormonal status it has been suggested that increased nocturnal urine production may result from a change in circadian pattern of urine production.[3-6] There is, however, a lack of normal values for circadian urine production in the elderly. Consequently, information on determinants of circadian urine production is scarce.

In this study, we describe normal circadian urine production patterns in older men, based on frequency-volume chart recordings from participants in a large population-based study. In addition, we determined which factors (such as age, chronic medical conditions, drug use and urological parameters) are associated with these patterns.

Subjects and Methods

The data presented here were obtained as part of the Krimpen study on male urogenital tract problems and general health status. The design of this large community-based cohort study has been described in detail.[7] Briefly, the Krimpen study was performed to gain information on male urogenital tract dysfunction and general well-being among all men aged 50 to 75 years living in a Dutch municipality near Rotterdam. Men without radical prostatectomy, prostate or bladder cancer, neurogenic bladder disease or negative advice from their general practitioner, who were able to complete questionnaires and attend the health centre, were invited for the study. All men entering the study provided written informed consent. The Medical Ethical Committee of the Erasmus Medical Centre Rotterdam, the Netherlands, approved the study.

Data of 1688 responders (response rate 50%) were collected via self-administered questionnaires, frequency-volume charts and during visits to the local health centre (first phase) and the outpatient clinic of a urology department (second phase).

The questionnaire included the International Prostate Symptom Score (IPSS)[8] and questions on history of chronic disease, smoking habits, alcohol consumption and current medication use, which was checked at the health centre.

Of the participants, 1597 (95%) completed a three-day frequency-volume chart on which each micturition was recorded in one-hour time units. On the third day, the voided volume of each voiding was recorded. 'Bedtime' and 'time of rising' were recorded on the charts.

Measurements at the health centre and urology outpatient clinic were (among others): blood pressure, serum prostate specific antigen (PSA), digital rectal examination (DRE), transrectal ultrasonography of the prostate (TRUS), uroflowmetry and post voiding residual measurement, using transabdominal ultrasonometry. To exclude men with prostate carcinoma, biopsies were taken according to a protocol based on PSA, DRE and TRUS.[7]

In order to describe circadian urine production, we computed urine production for each hour of the day (day three on the chart) for all individuals, according to the method described by Van Mastrigt & Eijskoot.[9] Urine production was assumed constant between two voidings. Hourly urine production was estimated as the volume of each micturition divided by the number of hours that passed since the previous micturition.[9]
In order to analyse the circadian pattern, we quantified this pattern into a day/night ratio. For this purpose, the time period 10 a.m. to 10 p.m. was designated as daytime and 1 a.m. to 6 a.m. as nighttime. These time periods were chosen because approximately 90% of the men were 'awake' and 'asleep', respectively, in these two periods. Thus, the urine production day/night ratio was determined as mean hourly urine production during daytime divided by the mean hourly urine production during nighttime.
The 24-hour voided volume was estimated by adding all voided volumes on day three. A 24-hour voided volume greater than 2,500 ml was defined as '24-hour polyuria'.
Analyses on nocturnal urine production and its determinants will be reported separately.

Statistical analyses

We excluded from analyses all 106 men with newly diagnosed prostate cancer or previous operation for benign prostatic hyperplasia, of which one without a frequency-volume chart. Of the remaining men, 61 completed the frequency-volume chart inadequately and were therefore excluded; thus, 1431 men constitute the basis for this report. The participant characteristics are presented in Table 7.1. We categorized these men into 5-year age strata. Fifty-three men were aged 75 to 78 years and were added to the 70 to 75 year stratum to form the 70 to 78 year stratum.
Circadian urine production patterns will be presented for men aged 50 to 64 years and men aged 65 to 78 years. Differences in urine production patterns between these two age groups were analysed using Analyses of Variance (ANOVA) on the urine production day/night ratio.
To explore possible effects of determinants on the circadian patterns, we performed linear regression analyses with urine production day/night ratio as the dependent variable. Independent variables in bivariate models were: age strata, body weight, smoking and drinking habits, diabetes mellitus, hypertension, cardiac symptoms, medication use, 24-hour polyuria, post void residual (> 50 ml), prostate enlargement (sonographic volume > 30 cc) and reduced maximum urinary flow rate (< 15 ml/sec). Variables with a p-value less than 0.25 were entered in multivariate analyses, using the backward method (model fit). A p-value less than 0.05 was considered statistically significant. Final analysis was performed using statistically significant variables only. The percentage of explained variance (R^2) of the final model was estimated.
The Statistical Package for the Social Sciences 10 (SPSS Inc. Chicago, IL, USA) was used for statistical computations.

Table 7.1. *Characteristics of the 1,431 participants*

Characteristic	value
Age (mean, [SD])	61.3 (6.6)
Lower urinary tract symptoms, IPSS score (%)	
mild (1-7)	65.6
moderate (8-19)	21.8
severe (20 or more)	2.8
Prostate volume (mean, [SD])	34.1 (14.9)
percentage > 30 cc	51.7
Reduced urinary flow rate < 15 ml/sec (%)	75.9
Post void residual volume > 50 ml (%)	11.6
24-hour voided volume (mean, [SD])	1,622 (648)
percentage > 2,500 ml (%)	8.7
Nocturnal voiding frequency (%)	
two or more voiding episodes	42.5
three or more episodes	10.1
Bodyweight (mean, [SD])	81.7 (10.7)
Smoking (%)	23.4
Alcohol consumption (%)	
1 to 2 glasses per day	59.4
more than two glasses per day	18.8
Hypertension (%)	26.8
Diabetes mellitus (%)	3.6
Cardiac symptoms (%)	6.1
Diuretic users (%)	6.0
Cardiac drug users (%)	21.4
Antidepressant drug users (%)	1.0
Hypnotic drug users (%)	0.8

SD, standard deviation; IPSS, International prostate symptom score

Results

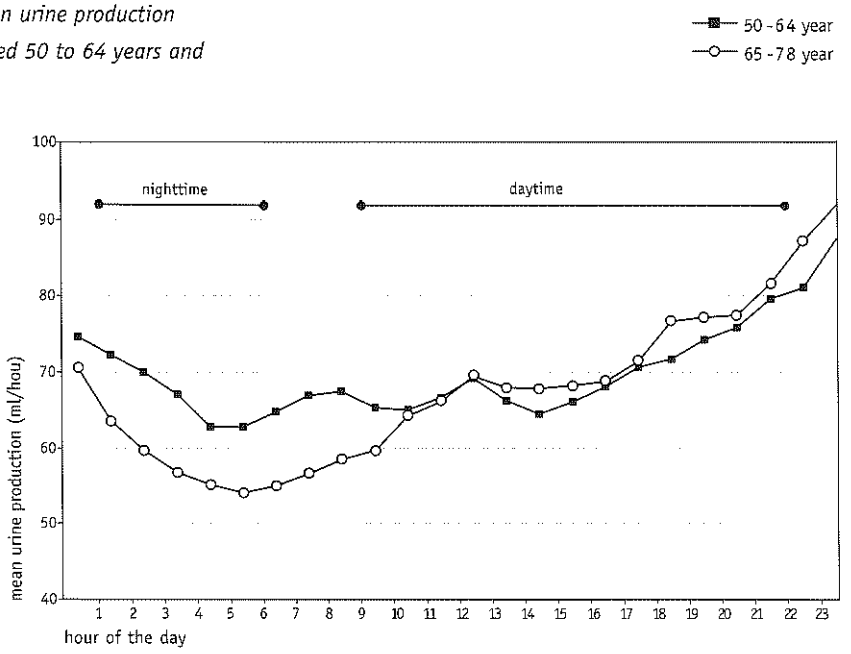
The circadian pattern of urine production is shown in Figure 7.1. Men younger than 65 years showed a clear circadian rhythm, with decreased production during nightly hours. The circadian pattern was less clear in men older than 65 years.

The quantitative figure of the circadian pattern was estimated as the urine production day/night ratio. For the total study population, the mean estimate was 1.40 (95% confidence interval [$CI_{95\%}$] 1.35-1.45), indicating that the urine production during daytime is higher than during nighttime. For men aged 50 to 64 years, the day/night ratio was 1.46 ($CI_{95\%}$ 1.40-1.52), as compared to 1.28 ($CI_{95\%}$ 1.20-1.36) for men aged 65 to 78 years (difference statistically significant; ANOVA, $p = 0.001$).

The results from the bivariate analyses on urine production day/night ratio are presented in Table 7.2. The variables hypertension, cardiac symptoms, diabetes mellitus, prostate enlargement, reduced urinary flow rate, cardiac drugs, antidepressants, and hypnotic drugs were non-significant ($p > 0.25$).

The independently associated variables that yielded from the multivariate analyses are presented in Table 7.3. With increasing age, the day/night ratio decreased (i.e. a shift towards nighttime). Men with 24-hour polyuria or post void residual and smokers and diuretic users had a higher day/night ratio (i.e. shift towards daytime). The percentage of explained variance (R^2) of the final regression model was 0.043.

Figure 7.1. *Circadian urine production pattern for men aged 50 to 64 years and 65 to 78 years*



gray blocks: time period in which 80-90% of the men are "getting up" and "going to bed"

Table 7.2. *Determinants for urine production day/night ratio*; bivariate linear regression analyses*

		number†	day/night ratio (mean)	p-value
Age strata (years)	50-54	296	1.50	< 0.01
	55-59	368	1.49	
	60-64	341	1.39	
	65-69	277	1.25	
	70-78	145	1.35	
Reduced urinary flow rate	no	307	1.40	0.667
(Qmax less than 15 ml/sec)	yes	963	1.38	
Prostate enlargement	no	679	1.39	0.938
(volume greater than 30 cc)	yes	727	1.40	
24-hour polyuria	no	1,306	1.37	< 0.001
(voided volume > 2,500 ml)	yes	125	1.73	
Post void residual	no	1,119	1.37	0.005
(>50 ml)	yes	148	1.59	
Smoking	no	1,070	1.37	0.005
	yes	337	1.53	
Alcohol consumption	no	306	1.37	0.096
(units (i.e. glasses) per day)	1-2	835	1.38	
	>2	266	1.51	
Body weight (linear variable)			1.61	0.236
increase per kg			- 0.003	
Hypertension	no	1,046	1.41	0.612
	yes	385	1.38	
Diabetes mellitus	no	1,357	1.40	0.947
	yes	50	1.40	
Cardiac symptoms	no	1,320	1.40	0.908
	yes	87	1.42	
Diuretic use	no	1,344	1.40	0.112
	yes	87	1.56	
Cardiac drug use	no	1,124	1.41	0.720
	yes	307	1.39	
Antidepressant drug use	no	1,416	1.40	0.888
	yes	15	1.43	
Hypnotic drug use	no	1,420	1.41	0.483
	yes	11	1.21	

* Urine production day/night ratio = mean hourly urine production during daytime (10 a.m.-10 p.m.) / mean hourly urine production during nighttime (1 a.m.-6 a.m.); † Number within category. Sum of numbers may differ due to missing data.

Table 7.3. *Independent determinants for urine production day/night ratio*; multivariate linear regression analyses*

		day/night ratio (mean)	p-value†
Constant‡		1.41‡	
Age strata (years)	50-54	Ref	
	55-59	-0.05	0.538
	60-64	-0.14	0.064
	65-69	-0.30	<0.001
	70-78	-0.28	0.004
Smoking	No	Ref	
	yes	0.14	0.017
24-hour polyuria	no	Ref	
(voided volume > 2,500 ml)	yes	0.33	<0.001
Post void residual	no	Ref	
(>50 ml)	yes	0.24	0.002
Diuretic use	no	Ref	
	yes	0.24	0.017
Bodyweight (linear variable)		NS	0.256
Alcohol consumption	No	NS	
(units (i.e. glasses) per day)	1-2		0.499
	>2		0.172

* Urine production day/night ratio = mean hourly urine production during daytime (10 a.m.-10 p.m.) / mean hourly urine production during nighttime (1 a.m.-6 a.m.); † p-value of final model, for nonsignificant variables p-value before exclusion; ‡ reference is day/night ratio for non-smoking men aged 50-54 years, without 24-hour polyuria, post void residual and diuretic use; NS, nonsignificant; Ref, Reference group

Discussion

The availability of frequency-volume charts from a large population-based sample of older men allowed to describe normal circadian patterns of urine production and to identify several factors associated with these patterns.

We have quantified the circadian pattern into a day/night ratio in order to analyse the pattern and to find significant determinants. The time periods used to define day and night are arbitrary. However, changing these periods to, for example, 1-7 a.m. (night) and 9 a.m. – 11 p.m. (day) did not change the conclusions (data not presented).

Previously, other urine production ratios have been used to define abnormal circadian urine production patterns.[10,11] In contrast to our day/night ratio, night/24-hour ratios were used in these definitions. A ratio exceeding 0.35 (i.e. nightly urine production exceeding 35% of the total urine production) was defined as abnormal.[10,11] This night/24-hour ratio corresponds to a day/night ratio of 1.86 (= 0.65/0.35); ratios smaller than this cut-off value would then be defined as abnormal. Accordingly, 77.4% and 82.7%, respectively, of the men aged 50 to 65 and 65 to 78 years would be categorized as having an abnormal circadian pattern, in the current study. This illustrates that the proposed definition (night/24-hour ratio > 0.35) is of little use in the general population of older men.

Our data indicate that in men aged 50 to 65 years there is a clear circadian pattern for urine production, whereas in older men (65 to 78 years) this pattern is attenuated, mainly due to an increased nocturnal urine production. This is consistent with findings by Nakamura *et al* who studied these patterns in a small number of patients from urologic clinics but, apart from age, did not report determinants for these patterns.[12]

With advancing age, the day/night ratio decreases (Table 7.2), meaning that in elderly men the urine production (ml/hr) during daytime is relatively low compared to nighttime production. Under the age of 65 years, the day/night ratio does not differ significantly between age groups, whereas this ratio in men aged 65 to 69 and 70 to 78 years differs significantly from men younger than 65 years (Table 7.3). This justifies the use of the two age categories shown in Figure 7.1.

The alterations of the day/night ratio with age might be due to more cases of subclinical heart failure among elderly men (65 years and over). However, as the absolute number of such patients will be low in this population-based study, this does not explain all of the difference.

The higher day/night ratio in men with 24-hour polyuria may be the result of a habitually high fluid intake in these men, which occurs mainly during daytime. Although this could not be proved, because volume intake was not registered in our study, the reasoning 'what comes out must have gone in' seems to be plausible. The higher day/night ratio as an effect of smoking is at variance with the previously assumed antidiuretic effect of nicotine during smoking.[13] We cannot explain the higher day/night ratio in men with post void residual volume.

In the bivariate analyses, alcohol consumption was associated to an increased day/night ratio. This may have resulted from our definition of daytime and nighttime. The time of dinner or after that, which most probably is the time at which alcohol intake especially takes place, is included in 'daytime'. The effect of alcohol consumption was lost in the multivariate analyses.

Our data do not confirm the relation between (a history of) cardiac symptoms and day/night ratio. This may be due to the fact that 'cardiac symptoms' include more than heart failure alone. Moreover, the men with 'cardiac symptoms' based on heart failure, may be adequately treated. The use of diuretic drugs did influence the day/night ratio in favour of daytime production, as patients normally take their drugs during daytime.

The total percentage of explained variance (R^2), of our linear regression model was low (4%), indicating that other factors contribute to the differences of the circadian urine pattern, but were not included in the model. For example, hormonal changes, such as atrial natriuretic peptide (ANP), were not measured in the current study. Recently, Carter *et al* aimed to describe the role of this and other hormones on nocturnal polyuria.[4] The authors, however, used a day/night ratio to define nocturnal polyuria. Although such a definition appears inadequate for determining nocturnal polyuria, a clear association between ANP and altered day/night ratio was shown.[4]

Kirkland *et al* showed that changes in nightly excreted sodium, potassium and solutes may result in increased nocturnal urine excretion in older men (age 60 to 80 years) compared to younger subjects (age 25 to 35 years).[14] In their study it is unclear whether these age-dependent differences also occurred in the age range of 60 to 80 years. Because we did not analyse the urine of our participants for the electrolyte composition, we cannot confirm the latter finding.

Conclusions

Our population-based study provides normal values for circadian urine production in older men. Men aged 50 to 65 years show a clear circadian pattern, in contrast to those 65 to 78 years old. Smoking, use of diuretic drugs, post void residual volume and 24-hour polyuria reinforce the circadian pattern, whereas other urological and non-urological variables show no influence.

Although the determinants found in our study explain only a small part of the total variance of the circadian urine production pattern, these determinants are clinically relevant and easy to assess in daily practice. Frequency-volume charts are low-cost and easy-to-use and provide valid information on urine production in a natural environment.[15,16] These charts may provide additional information in the diagnosis of heart failure and the underlying mechanisms of fluid redistribution; examples of such use have been reported.[9] When interpreting the charts, physicians should consider age, post void residual, 24-hour polyuria, diuretic use, and smoking as important determinants.

References

1. Chute CG, Panser LA, Girman CJ, *et al.*: The prevalence of prostatism: a population-based survey of urinary symptoms. *J Urol* 1993;150:85-9.
2. Blanker MH, Bohnen AM, Groeneveld FP, *et al.*: Normal voiding patterns and determinants of increased diurnal and nocturnal voiding frequency in elderly men. *J Urol* 2000;164:1201-5.
3. Bodo G, Gontero P, Casetta G, *et al.*: Circadian antidiuretic hormone variation in elderly men complaining of persistent nocturia after urinary flow obstruction removal. *Scand J Urol Nephrol* 1998;32:320-4.
4. Carter PG, Cannon A, McConnell AA and Abrams P: Role of atrial natriuretic peptide in nocturnal polyuria in elderly males. *Eur Urol* 1999;36:213-20.
5. Coe FL: *Alterations in urinary function and electrolytes*. 13th ed. New York: McGraw-Hill, Inc., 1994.
6. Brendler CB. Evaluation of the urologic patient. In: Walsh PC, Retik AB, Stamey TA and Vaughan ED, editors. *Campbell's Urology*. 7th ed. Philadelphia: Saunders, 1998:134.
7. Blanker MH, Groeneveld FPMJ, Prins A, *et al.*: Strong effects of definition and nonresponse bias on prevalence rates of clinical benign prostatic hyperplasia: the Krimpen study of male urogenital tract problems and general health status. *BJU Int* 2000;85:665-71.
8. Barry MJ, Fowler Jr FJ, O'Leary MP, *et al.*: The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. *J Urol* 1992;148: 1549-57.
9. van Mastrigt R and Eijskoot F: Analysis of voided urine volumes measured using a small electronic pocket balance. *Scand J Urol Nephrol* 1996;30:257-63.
10. Saito M, Kondo A, Kato T and Yamada Y: Frequency-volume charts: comparison of frequency between elderly and adult patients. *Br J Urol* 1993;72:38-41.
11. Weiss JP, Blaivas JG, Stember DS and Brooks MM: Nocturia in adults: etiology and classification. *Neurourol Urodyn* 1998;17:467-72.
12. Nakamura S, Kobayashi Y, Tozuka K, *et al.*: Circadian changes in urine volume and frequency in elderly men. *J Urol* 1996;156:1275-9.
13. Vapaatalo HI, Neuvonen PJ, Tissari A, Mansner R and Paasonen MK: Effect of cigarette smoking on diuresis induced by furosemide. *Ann Clin Res* 1971;3:159-62.
14. Kirkland JL, Lye M, Levy DW and Banerjee AK: Patterns of urine flow and electrolyte excretion in healthy elderly people. *Br Med J (Clin Res Ed)* 1983;287:1665-7.
15. Palnaes Hansen C and Klarskov P: The accuracy of the frequency-volume chart: comparison of self-reported and measured volumes. *Br J Urol* 1998;81:709-11.
16. Larsson G and Victor A: Micturition patterns in a healthy female population, studied with a frequency/volume chart. *Scand J Urol Nephrol Suppl* 1988;114:53-7.

part III

Genital tract (dys)function

Chapter 8

Erectile and ejaculatory dysfunction in a community-based sample of men 50 to 78 years old: Prevalence, concern and relation to sexual activity

Abstract

Objectives. To determine the prevalence rates of erectile and ejaculatory dysfunction, associated bother, and their relation to sexual activity in a population-based sample of older men.

Subjects and Methods. Data were collected from 1688 men by way of self-administered questionnaires (including the International Continence Society male sex questionnaire) and measurements at a health centre and urology outpatient department.

Results. The prevalence of significant erectile dysfunction (i.e. erections of severely reduced rigidity or no erections) increased from 3% in men 50 to 54 years old to 26% in men 70 to 78 years old. In the same age groups, the prevalence of significant ejaculatory dysfunction (i.e. ejaculations with significantly reduced volume or no ejaculations) increased from 3% to 35%. Pain or discomfort during ejaculation was rare (1%) and independent of age. In general, men were more concerned about erectile dysfunction than about ejaculatory dysfunction. However, most men had no or only little concern about their dysfunction. The percentage of men who reported being sexually active declined with increasing age and was lower in men with erectile and ejaculatory dysfunction and in men without a partner. In sexually active men, 17% to 28% had no normal erections, indicating that with advancing age normal erections are not an absolute prerequisite for a sexually active life.

Conclusions. Erectile and ejaculatory dysfunction are common in older men. The results of this study indicate that these conditions are much less of a problem for older men than previously suggested.

Introduction

The introduction of new classes of drugs and new modes of administration of existing drugs have increased the public demand for treatment of erectile dysfunction (ED).[1] Despite this, there are a paucity of detailed community-based data on ED and its impact on quality of life. Surveys conducted in the United States,[2-4] Japan,[5] and Europe[6] all show a high prevalence of ED and a clear increase of the problem with advancing age. The variation in the reported prevalence rates among these studies may be partly explained by differences in the definition of ED.

Ejaculatory dysfunction (EjD) has been studied only in a small group of community-based men in England.[7] A French survey investigated "ejaculatory difficulty,"[8] but it is unclear how the authors defined this concept. Thus, the epidemiologic database on EjD is very limited. Furthermore, it is unclear to what extent men are concerned about the ED and EjD and to what extent ED is associated with the cessation of sexual activity.

We have studied these aspects as part of a large, ongoing longitudinal study conducted in The Netherlands.[9] The purpose of the present study was to determine the prevalence of ED and EjD and associated bother and the proportion of men who are sexually active and the relation to ED.

Subjects and Methods

The data presented here were collected as part of a large, ongoing community-based study, the Krimpen study on male urogenital tract problems and general health status, described in detail elsewhere.[9] In brief, the Krimpen study investigated all men, 50 to 75 years old (n = 3924), in a Dutch municipality near Rotterdam, to gain information on male urogenital tract dysfunction. Men who had not undergone radical prostatectomy and had not had prostate or bladder cancer, neurogenic bladder disease or negative advice from their general practitioner, and who were able to complete the questionnaires and visit the health centre were eligible and were invited to participate in the study. Recruitment took place between August 1995 and January 1998. In this period, 152 men had become older than 75 years, but were nevertheless enrolled. All men entering the study provided written informed consent.

The study consisted of two phases. In the first phase, the data of 1688 responders (50% of all eligible men) were collected by way of a self-administered 113-item questionnaire which included the International Prostate Symptom Score[10] and the International Continence Society (ICS) *sex* questionnaire.[7] The ICS*sex* questionnaire covers four items, each with a bother score ranging from no problem to a serious problem on a four-point scale. In addition, the men were asked whether they were sexually active and, if not, how long ago their sexual activities ceased. The questionnaire also included a question on marital status. All men visited the local health centre for height, body weight, blood pressure measurement, and urinalysis.

In the second phase, 1661 men (98.4% of the participants) visited a urology outpatient clinic for the following tests: serum prostate-specific antigen, digital rectal examination and transrectal ultrasound

of the prostate, uroflowmetry, and post void residual urine volume. Prostate biopsies were taken according to a protocol described in detail previously.

Definitions

On the basis of the answers to the questions in the ICS*sex* questionnaire, the following definitions were made. Minor ED was defined as a report of erections with "reduced rigidity"; significant ED was defined as a report of erections with "severely reduced rigidity" or "no erections." Minor EjD refers to a report of ejaculations of "reduced quantity"; significant EjD refers to ejaculations of "significantly reduced quantity" or "no ejaculations." On the basis of this definition, we created mutually exclusive categories of sexual dysfunction: "no significant ED or EjD," "significant ED only," "significant EjD only" and "both significant ED and EjD."
A major concern about one of the topics in the ICS*sex* questionnaire was defined as a report of "quite a problem" or "a serious problem" on the associated questions.

Statistical analysis

A batch of 27 completed questionnaires was lost before the data were entered in the database. Men with newly diagnosed prostate cancer (n = 57, including one men with a lost questionnaire) were excluded from all analyses. The data of 1605 men constitute the basis for this report.
Men were categorised into 5-year age groups. Fifty-three men were aged 75 to 78 years and were included in the 70 to 75 year group to form the 70 to 78 year group. The prevalence of the sexual symptoms and associated concern from the ICS*sex* questionnaire was calculated for each of the 5-year age groups.
Spearman's correlation coefficient was used to characterise the relation between quality of erections and quantity of ejaculations and the relation between age and years that had passed since sexual activity ceased. To test the relationship between two variables that could be expressed in discrete categories, the chi-square test was used. If necessary, trend versions were used. Ninety-five percent confidence intervals ($CI_{95\%}$) were calculated for all percentages on the basis of the binomial distribution. A p-value of 0.05 was considered significant.

Results

In the total study population, 93.4% of the men were married or living together.

Sexual activity

Table 8.1 gives the percentage of sexually active men. For those who are no longer sexually active, Table 8.1 indicates the number of years that passed since sexual activity has ceased. The percentage of sexually active men decreased strongly with advancing age (chi-square test for trend $p < 0.001$). The percentage of sexually active was lower in men without a partner: for all ages, 72.5% ($CI_{95\%}$ 62.2% to 81.4%) compared with 89.0% ($CI_{95\%}$ 87.3% to 90.5%) for men with a partner (chi-square test $p < 0.001$).

Table 8.1. *Percentage of sexually active men and number of years that had passed since sexual activity ceased in men who were no longer sexually active*

Age groups, years (n)	Percentage sexually active % ($CI_{95\%}$)	Years since sexual activity ceased in those not sexually active median (Interquartile range)
50 to 54 (334)	96.4 (93.8-98.1)	2 (1-8)
55 to 59 (409)	96.3 (94.0-97.9)	2 (0-4)
60 to 64 (389)	87.4 (83.7-90.5)	3 (1-6)
65 to 69 (302)	79.1 (74.1-83.7)	4 (2-10)
70 to 78 (171)	69.0 (61.5-75.8)	6 (3-10)
total population (1605)	88.0 (86.3-89.6)	4 (2-10)
p-value	< 0.001*	< 0.001†

* Chi-square test for trend; † Spearman's correlation coefficient age vs. years since sexual activity ceased ($r_s = 0.27$).

Table 8.2. *Percentage of sexually active men and concern about sexual dysfunction for different sexual dysfunction categories**

	no significant erectile† or ejaculatory dysfunction‡ (n = 1,324) % ($CI_{95\%}$)	significant erectile dysfunction† only (n = 66) % ($CI_{95\%}$)	significant ejaculatory dysfunction‡ only (n = 108) % ($CI_{95\%}$)	both significant erectile† and ejaculatory dysfunction‡ (n = 107) % ($CI_{95\%}$)	p-value§
Sexually active men (%)	95 % (94-96)	68% (56-79)	69% (59-77)	33% (24-42)	
Concern‖ about:					
Significant erectile dysfunction	NA	38 % (26-51)	NA	37% (28-47)	0.9
Significant ejaculatory dysfunction	NA	NA	8% (4-15)	27% (19-37)	<0.001

NA not applicable; * Categories are mutually exclusive; † Significant erectile dysfunction: patients report of erections with severely reduced rigidity or no erections at all; ‡ Significant ejaculatory dysfunction: report of ejaculations with significantly reduced volumes or no ejaculations at all; § Chi-square test; || Report of "quite a problem" or "a serious problem" on dysfunction

Table 8.2 shows the relation between significant ED and EjD and sexual activity. Of the men with minor ED or minor EjD, 88% ($CI_{95\%}$ 84% to 91%) and 89% ($CI_{95\%}$ 86% to 92%), respectively, were sexually active.

Erectile dysfunction

Figure 8.1 shows the decrease in erectile function with age and that a complete absence of erections was rare before 65 years of age (1%; $CI_{95\%}$ 1% to 2%). In men 50 to 64 years old, 5% ($CI_{95\%}$ 4% to 7%) claimed to have erections with severely reduced rigidity. The prevalence of minor ED was relatively high across all age groups.

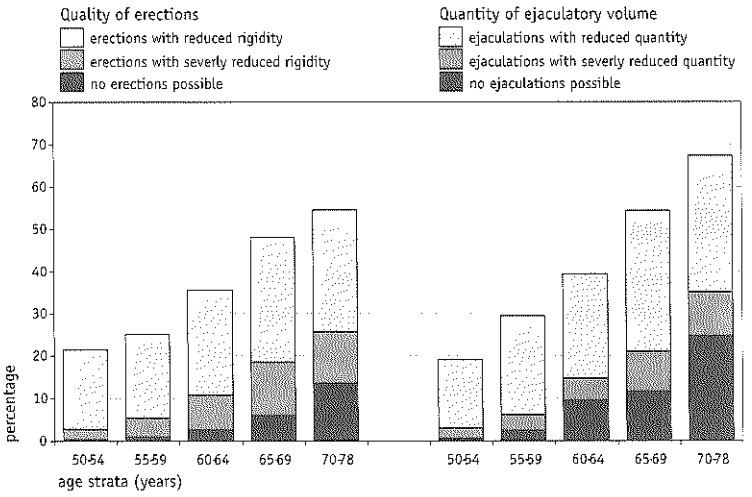


FIGURE 8.1. *Quality of penile erections and quantity of ejaculatory volume in men aged 50 to 78 years*

Ejaculatory dysfunction

Figure 8.1 also shows the decrease in ejaculatory function with age. Complete absence of ejaculations is rare before 65 years of age (4%; $CI_{95\%}$ 3% to 6%). Another 4% ($CI_{95\%}$ 3% to 5%) in this age group reported significantly reduced quantity. In men 65 years old and older, these percentages were 16% ($CI_{95\%}$ 13% to 20%) and 10% ($CI_{95\%}$ 7% to 13%).
The quality of erections and quantity of ejaculatory volume were positively related: i.e. men with a decreased quality of erection had a decreased quantity of ejaculatory volume ($r = 0.53$, $p < 0.001$).

Pain or discomfort during ejaculation

In this study population, pain or discomfort during ejaculation was rare. Of all men having ejaculations, regardless of the quantity of ejaculatory volume, only 1% ($CI_{95\%}$ 0% to 1%) experienced moderate to severe pain or discomfort, whereas 95% ($CI_{95\%}$ 94% to 96%) experienced no pain or discomfort at all. No differences were found between the age groups. Pain or discomfort during ejaculation occurred more often in men with significantly reduced quantity than in men with normal ejaculatory volumes: 19% ($CI_{95\%}$ 12% to 29%) and 2% ($CI_{95\%}$ 2% to 4%), respectively (chi-square test, $p < 0.001$).

Concern

Eight percent ($CI_{95\%}$ 5% to 11%) and 3% ($CI_{95\%}$ 2% to 5%), respectively, of men with minor ED or minor EjD had major concerns about their dysfunction. In this respect, no differences were found between age groups (both chi-square test for trend, $p > 0.2$) or between men with and without partner (both Chi-square test, $p > 0.2$). Table 8.2 gives the prevalence of concern about significant ED and EjD. Men were more concerned about ED than about EjD; concern about EjD was higher in men who also reported ED. Until the age of 70 years, no age-dependent differences were found. Men older than 70 years had much less concern about significant ED and EjD (20% [$CI_{95\%}$ 10% to 35%]

and 7% [$CI_{95\%}$ 2% to 16%], respectively) than younger men. No significant differences between men with and without a partner were found.
About two third of men with moderate or severe pain or discomfort during ejaculation had concerns about this, and about 12% ($CI_{95\%}$ 5% to 24%) of men with slight pain did.

Discussion

The results of this community-based survey indicate that ED and EjD are common in men 50 to 78 years old. However, most men have a low level of concern about their dysfunction.
The response rate of 50% in this study was remarkably high, considering the effort required from the participants and the number of invasive tests performed. Previous population-based studies on this subject achieved similar or lower response rates.[2,3,5] Higher rates were achieved only in questionnaire-based studies in which no invasive tests were performed.[7] Furthermore, a non-response study showed that the participants were comparable to nonresponders for age, educational and marital status, and for smoking and drinking habits; participants had more voiding symptoms and a slightly lower level of general wellbeing.[9] Moreover, we consider that the level of sexual functioning described in the current report is a good representation of the total population of men aged 50 to 78 years in The Netherlands, as the main subject of the study was not sexual functioning.
Comparing our study to others is hampered because different questions, response options and definitions were used and studies were performed in different cultures. Especially due to cultural differences, it is unlikely that one study in one country will establish epidemiologic baseline data that are valid throughout the world.

Erectile dysfunction

Between the age of 50 and 78 years, the prevalence of significant ED increased considerably, from 3% in men 50 to 54 years old up to 26% in men 70 to 78 years old. However, a complete inability to achieve an erection was relatively rare in men 50 to 65 years of age (only 1%). Our results suggest that minor ED is quite common (in about a quarter of the study population).
The prevalence rates found in our study were comparable to the findings in the Olmsted County study.[3] In the latter study, fewer than 1% of men 40 to 49 years old had "complete ED" as compared to more than one-quarter of men aged 70 to 79 years. Our results and those from the Olmsted County study have markedly lower prevalence rates than those reported in the Massachusetts Male Aging Study.[2] In the latter survey, 35% of men aged 40 to 70 years were suffering from "moderate to complete impotence." A calibration study was performed to determine "impotence." The responses of the Massachusetts Male Aging Study subjects to imprecise questions about erectile function were retrospectively transformed into more precise response categories. For this purpose, results from the urology clinic patients were used. These men had received the same questionnaire as the Massachusetts Male Aging Study subjects and additionally were asked to characterise themselves as "not," "minimally," "moderately" or "completely impotent." In this respect, no clear definition of "impotence" was used. The use of clinic patients for this calibration may have substantially increased

the prevalence of "impotence." Other surveys on ED also reported different results from the present study. This may be due to the different definitions used, varying from "erection difficulty"[8] to "erections seldomly sufficient for intercourse."[6]

Ejaculatory dysfunction

A reduction of ejaculatory volume was prevalent in our study population, closely associated with the quality of erections. Pain or discomfort during ejaculation was so uncommon in men 50 to 78 years old that this symptom probably represents an underlying disorder.

Information on ejaculatory function in published reports is scarce. In agreement with our results, a study in Great Britain (also using the ICS*sex* questionnaire) showed an association between reduced ejaculation and age.[7] In a community-based sample of 423 men, they also reported an absence of an association between age and pain or discomfort. "Ejaculatory difficulty" was studied in a French community-based sample of 1568 men[8]; 3% of those 50 to 59 years old reported "ejaculatory difficulty each time." This prevalence doubled in the subsequent age decades, reaching 12% in men 70 to 79 years old. It is unclear whether this figure included decreased volume and pain or discomfort, because a clear definition of "ejaculatory difficulty" was not given.

Concern

Most men in our study had no concern about their ED or EjD. The level of concern in men with significant ED or EjD was four to five-fold higher than in men with minor dysfunction. This justifies the use of these definitions. Still, only one third of the men with significant ED and only 13% of those with significant EjD regarded this as more than a bit of a problem. In contrast, most men with pain or discomfort during ejaculation were concerned about this.

Until 70 years of age, no age-dependent differences in level of concern were found. The percentage of men above 70 years with concerns about ED was roughly only half that of younger men.

The results of a Japanese survey are in line with our results, showing "little worry and concern about sexual functioning" in 80% of men aged 40 to 79 years.[5] In contrast to our study, the Olmsted County study yielded the counterintuitive result that older men aged 70 to 79 years were more worried about sexual functioning than younger men aged 40 to 49 years.[3]

No information was obtained on the impact of the sexual dysfunction on the partners. Future studies on sexual dysfunction should include this topic.

Sexual activity

Our results suggest that sexual activity decreases with advancing age and with the presence of ED and EjD. Sexual activity was not restricted to intercourse. In sexually active men, 50 to 70 years old, 17% to 28% did not have normal erections, indicating that with advancing age normal erections are not an absolute prerequisite for men to consider themselves sexually active. Sexual satisfaction was not a topic in this study.

In men no longer sexually active, the median number of years that had passed since sexual activity ceased increased from 2 to 6 in the youngest and oldest age group, respectively. This relatively low

increase might be explained by the fact that the number of men not sexually active cumulates after 60 years of age. Older men in the sexually inactive group stopped sexual activity relatively recently. Moreover, the state of sexual activity may alter within individuals over time. Men who stopped sexual activities may resume taking part in these after a certain period, for example in a new relationship. Furthermore, this low increase might indicate that men who stopped sexual activity tend to die before they reach the next 5-year age group. Smith and colleagues have described a protective effect of sexual activity on men's health, supporting the latter explanation.[11] Data from the longitudinal part of the Krimpen study may be of help in demystifying these findings.

Conclusions

The results of this study show that minor degrees of ED and EjD are common in Dutch men 50 to 78 years old. Significant ED and EjD are less common. However, the level of associated concern is rather low; this may indicate that most men consider this as part of the aging process. Men have more concern about ED than about ejaculatory dysfunction. Pain or discomfort during ejaculation is a rare but concern-provoking problem in these men.

Additional studies are needed to determine how these figures relate to doctors' consultation. Data on sexual functioning and associated concern using the same questions and definitions are needed from population-based studies in other countries, to determine whether these results are able to be generalised on an international level.

References

1. Wagner G and Saenz de Tejada I: Update on male erectile dysfunction. *BMJ* 1998;316:678-82.
2. Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ and McKinlay JB: Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. *J Urol* 1994;151:54-61.
3. Panser LA, Rhodes T, Girman CJ, *et al.*: Sexual function of men aged 40 to 79 years: the Olmsted County Study of Urinary Symptoms and Health Status Among Men. *J Am Ger Soc* 1995;43:1107-11.
4. Laumann EO, Paik A and Rosen RC: Sexual dysfunction in the United States: prevalence and predictors. *JAMA* 1999;281:537-44.
5. Masumori N, Tsukamoto T, Kumamoto Y, *et al.*: Decline of sexual function with age in Japanese men compared with American men-results of two community-based studies. *Urology* 1999;54:335-44.
6. Helgason AR, Adolfsson J, Dickman P, *et al.*: Sexual desire, erection, orgasm and ejaculatory functions and their importance to elderly Swedish men: a population-based study. *Age Ageing* 1996;25:285-91.
7. Frankel SJ, Donovan JL, Peters TI, *et al.*: Sexual dysfunction in men with lower urinary tract symptoms. *J Clin Epidemiol* 1998;51:677-85.
8. Macfarlane GJ, Botto H, Sagnier PP, *et al.*: The relationship between sexual life and urinary condition in the French community. *J Clin Epidemiol* 1996;49:1171-6.
9. Blanker MH, Groeneveld FPMJ, Prins A, *et al.*: Strong effects of definition and nonresponse bias on prevalence rates of clinical benign prostatic hyperplasia: the Krimpen study of male urogenital tract problems and general health status. *BJU Int* 2000;85:665-71.
10. Barry MJ, Fowler Jr FJ, O'Leary MP, *et al.*: The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. *J Urol* 1992;148: 1549-57.
11. Davey Smith G, Frankel S and Yarnell J: Sex and death: are they related? Findings from the Caerphilly Cohort Study. *BMJ* 1997;315:1641-4.

Chapter 9

Correlates for erectile and ejaculatory dysfunction in Dutch older men

Abstract

Objectives. We estimated correlates for erectile dysfunction (ED, defined as a report of erections of severely reduced rigidity or no erections) and ejaculatory dysfunction (EjD, defined as a report of ejaculations with significantly reduced volume or no ejaculations) in a large community sample of older men.

Subjects and Methods. Data were collected from 1688 Dutch men, 50 to 78 years old, by way of self-administered questionnaires (including the International Continence Society male sex questionnaire) and measurements at a health centre and urology outpatient department. Presence of ED and EjD (International Continence Society sex questionnaire), urinary tract symptoms (International Prostate Symptom Score), prostate enlargement (transrectal ultrasound), reduced urinary flow rate (uroflowmetry), obesity (body mass index), chronic obstructive pulmonary disease (COPD), diabetes mellitus, and cardiovascular problems. Determined marital status, educational level, and smoking and drinking habits. Population attributable risk (PAR) was estimated for correlates that yielded from multiple logistic regression models on ED and EjD.

Results. Multiple logistic regression analyses yielded the following correlates for significant ED: age, smoking, obesity, urinary tract symptoms, and treatment for cardiovascular problems and COPD. Age, erectile function, urinary symptoms and previous prostate operations proved to be correlates for significant EjD. Urinary symptoms and obesity had the highest PAR for ED, whereas decreased erectile function had the highest PAR for EjD.

Conclusions. Age, obesity and urinary tract symptoms were the most important correlates of significant ED in the population. Cardiac problems, COPD and smoking were other independent correlates. Significant EjD was largely related to age, decreased erectile function and previous prostatic surgery.

Introduction

Erectile dysfunction (ED) and ejaculatory dysfunction (EjD) are common in older men.[1] Prevalence rates of ED differ between studies, mainly due to the different methodologies and definitions used.[1-3] All studies show that ED has a strong age dependency. Additionally, various chronic medical conditions, medical and surgical treatments are reported to be related to ED.[1,2,4-6] Most reports on this topic, however, are based on information from clinical samples, which may have introduced a considerable bias, as these studies represent the most-severe cases of the disease under study. Only few studies describe related factors for ED in a population sample of older men[1,2,7]; in these latter studies, however, sample size was low due to low response rates,[1,2] a clear definition of ED was lacking,[1] or age of the responders was low.[7] Thus, a clear picture of the correlates for ED in community-dwelling older men is lacking. To our knowledge, even fewer data are available for EjD.[8] Moreover, it is unknown to what extent related factors attribute to the risk for having ED and EjD in the older population.

We studied these aspects in a large population survey among Dutch men. In this report, we describe correlates for ED and EjD and the attribution of these correlates to the risk of ED and EjD in the population.

Subjects and Methods

The data presented here were collected as part of a large ongoing, community-based study: the Krimpen study on male urogenital tract problems and general health status, described in detail elsewhere.[9] In brief, the Krimpen Study investigated all men 50 to 75 years old (age on reference date; n = 3924 of which 235 were excluded) in a Dutch municipality near Rotterdam, to gain information on male urogenital tract dysfunction. The study consisted of two phases. In the first phase, data were collected from 1688 responders (50% of all eligible men) by way of self-administered questionnaires and during a visit to a health centre. In the second phase, 1661 men (98.4% of all participants) visited a urology outpatient clinic. All men entering the study provided written informed consent.

First phase: The questionnaire included the International Prostate Symptom Score (IPSS)[10] and the International Continence Society (ICS) *sex* questionnaire.[11] The ICS*sex* questionnaire covers four items. In addition, the men were asked whether they were sexually active and, if not, how long ago their sexual activities had ceased. The questionnaire also included questions on treatment for chronic diseases such as cardiovascular problems, hypertension and chronic obstructive pulmonary disease (COPD), history of transurethral resection of the prostate (TURP) or diabetes mellitus, smoking habits and alcohol consumption. Moreover, the participants completed a 3-day frequency-volume chart. Two study physicians checked the questionnaires and completed these with data on the present use of medication using the Anatomical Therapeutical Chemical (ATC) classification.[12] Measurements at the health centre included height, body weight, blood pressure, and urinalysis.

Second phase: At the urology outpatient department the following measurements were obtained: serum prostate specific antigen, digital rectal examination and transrectal ultrasound of the prostate,

uroflowmetry, and post void residual urine volume. Prostate biopsies were taken according to a protocol described in detail previously.[9]

Nonresponders

A random sample (n = 500) stratified proportional to the number of nonresponders per general practice was taken from the list of nonresponders to evaluate whether the responders were representative. These nonresponders were invited to complete a short mailed questionnaire, which included the IPSS, a general health questionnaire and questions on treatment for chronic diseases, marital status, educational level, smoking and drinking habits, and current medication use. Of those not responding, 261 (55%) returned the short questionnaire. Participants were comparable to nonresponders for age, educational and marital status, and for smoking and drinking habits; participants reported a slightly lower level of general wellbeing and more voiding symptoms.[9]

Definitions

We defined significant ED as having reported "no erections" or "erections of severely reduced rigidity." Significant EjD was defined as having "no ejaculations" or "ejaculations of significantly reduced volume." Clinical benign prostatic hyperplasia (BPH) was defined as having moderate to severe voiding symptoms (IPSS greater than 7 points) with prostate enlargement (volume greater than 30 cc) and a reduced urinary peak flow rate (less than 15 ml/sec).[13]

Statistical analysis

A batch of 27 completed questionnaires was lost before the data were entered in the database. Men with newly diagnosed prostate cancer (n = 57, including one man with a lost questionnaire) were excluded from all analyses; the data from 1605 men constitute the basis for this report.
Spearman's correlation coefficient (r_s) was used to test the relation between IPSS scores and the extent that the participants felt their sex life was spoiled by urinary symptoms (first question ICS*sex* questionnaire).
To explore the possible effect of different variables on ED and EjD, we performed bivariate logistic regression analyses. For the following characteristics separate analyses were performed: age; smoking habits; alcohol consumption; body mass index; IPSS; prostate enlargement; reduced urinary peak flow rate; TURP; hypertension (diastolic blood pressure > 94 mm Hg, systolic blood pressure > 159 mm Hg, or use of antihypertensive drugs); treatment for diabetes mellitus, cardiovascular problems or COPD; current medication use (Table 9.1); marital status; and educational level. In the analyses on EjD, erectile function was also entered in the analyses. Variables with a p-value < 0.25 were entered into multiple models with ED and EjD as the dependent variables. Final analyses were performed using variables with a p-value < 0.05 in the multiple models.
The logistic regression approach produced adjusted odds ratios (ORs), which indicate the odds of having ED and EjD for men with a certain characteristic relative to a reference group, while controlling for other characteristics.

To estimate the proportion of ED and EjD that is related to the exposure to certain correlates, we calculated the "attributable proportion" (AP)[14] for the (dichotomous) variables with a significant influence in the multiple logistic regression models. To estimate the proportion of cases of ED and EjD in the total population that might be attributable to a certain correlate we calculated the "population attributable risk" (PAR)[15] for the same variables.
The AP was calculated by dividing the risk difference between exposed and unexposed cases through the risk in exposed cases.[14] The PAR was calculated by dividing the risk difference between the total population and unexposed cases through the risk in total population.[15] In these estimations a causality of the relations was assumed.
The Medical Ethical Committee of the Erasmus Medical Centre Rotterdam approved the study.

Results

In the total study population, 173 (11%) and 215 (13%) men reported significant ED and EjD, respectively. Half of all men with EjD reported concomitant ED. Men with higher IPSS scores more often felt that their sex life was spoiled ("somewhat or a lot") by voiding symptoms (r_s 0.23, $p < 0.001$).
Table 9.1 presents the results from the bivariate logistic regression analyses on significant ED and EjD. Table 9.2 gives the result of the multiple regression models on significant ED. There was a strong age dependency. Moreover, significant ED occurred more often in men with higher body mass index, higher IPSS scores, treatment for cardiac problems and COPD, and those who were current smokers.
Table 9.3 gives the result of the multiple logistic regression models on significant EjD. There was a strong age dependency. Furthermore, high ORs were seen in men with previous TURP, higher IPSS scores and men with erections of severely reduced rigidity or no erections. Significant EjD occurred less often in men with diabetes mellitus.
Table 9.4 shows the attributable risk percent and population attributable risk for ED and EjD.

Discussion

This community-based survey among older men gives a clear picture of factors related to significant ED and EjD. In addition to advancing age, correlates for ED were smoking, obesity, urinary tract symptoms, COPD and cardiac problems. EjD depended largely on age and erectile function. A history of prostate surgery is also an important correlate.
The response rate of 50% in the Krimpen Study is remarkably high, considering the effort required from the participants and the number of invasive tests performed. Previous population-based studies on ED achieved similar or lower response rates.[1-3,16] Higher rates were achieved only in those studies in which no invasive tests were performed.[11] Some of these studies report only on the prevalence of ED, without mentioning related factors.[3,16] In a nonresponse study, we showed that the participants in our study were comparable to nonresponders.[9] The fact that participants had slightly higher IPSS scores may have caused an overestimation of the prevalence of ED because these higher scores

Table 9.1. *Correlates for significant erectile (ED) and ejaculatory (EjD) dysfunction, yielded by bivariate logistic regression analyses*

	Unadjusted odds ratios (CI95%)			
	Significant ED	**p-value**	**Significant EjD**	**p-value**
Age (group vs. 50 to 54 years)		<0.001		<0.001
55 to 59	2.1 (0.9-4.5)		2.1 (1.0-4.5)	
60 to 64	4.4 (2.1-9.1)		5.6 (2.8-11.1)	
65 to 69	8.2 (4.0-16.9)		8.5 (4.3-17.0)	
70 to 78	12.5 (5.9-26.4)		17.5 (8.7-35.4)	
Smoking habits* (smokers vs. non-smokers)	1.3 (0.9-1.8)	0.166	0.9 (0.7-1.3)	0.602
Alcohol consumption (units/day)		0.125		0.042
1 to 2 vs. no alcohol	0.7 (0.5-1.0)		0.7 (0.5-0.9)	
> 2 vs. no alcohol	0.7 (0.4-1.1)		0.7 (0.5-1.1)	
Body mass index (kg/m^2)		0.007		0.448
25 to 30 vs. < 25	1.4 (1.0-2.0)		1.2 (0.9-1.6)	
> 30 vs. < 25	2.3 (1.4-3.8)		1.3 (0.8-2.2)	
Lower urinary tract symptoms†		<0.001		<0.001
mild vs. no symptoms	2.4 (1.0-5.6)		1.6 (0.9-3.1)	
moderate vs. no symptoms	6.0 (2.6-14.2)		3.8 (2.0-7.4)	
severe vs. no symptoms	9.9 (3.5-27.9)		7.8 (3.3-18.4)	
Prostate enlargement (yes vs. no)	1.5 (1.1-2.1)	0.016	1.3 (1.0-1.7)	0.102
Reduced urinary flow rate (yes vs. no)	1.3 (0.9-2.0)	0.198	1.2 (0.8-1.8)	0.277
Previous TURP (yes vs. no)	1.8 (0.9-3.7)	0.087	16.4 (9.1-29.3)	<0.001
Erectile function				<0.001
reduced vs. normal rigidity	NA		3.8 (2.5-5.6)	
severely reduced rigidity or no erections vs. normal rigidity	NA		33.2 (21.8-50.6)	
Hypertension (yes vs. no)	2.1 (1.5-2.9)	<0.001	2.0 (1.5-2.7)	<0.001
Under treatment for (yes vs. no)				
diabetes mellitus	2.4 (1.2-4.5)	0.011	0.5 (0.2-1.4)	0.171
COPD	3.1 (1.8-5.4)	<0.001	2.2 (1.3-3.9)	0.005
cardiac symptoms	3.1 (1.9-5.0)	<0.001	3.2 (2.1-5.1)	<0.001
Current medication use (ATC-codes)				
antidepressants (N06A)	1.6 (0.5-5.4)	0.482	3.0 (1.1-8.1)	0.026
benzodiazepines (N05BA and N05CD)	2.8 (1.3-5.8)	<0.001	2.1 (1.0-4.4)	0.041
cimetidine (A02BA)	1.1 (0.4-2.5)	0.897	2.2 (1.1-4.1)	0.018
beta-blocking agents (C07)	1.5 (1.0-2.3)	0.077	1.5 (1.0-2.3)	0.036
digoxin (C01AA)	5.1 (1.8-14.2)	0.002	5.2 (1.9-14.0)	0.001
thiazide diuretics (C03A C03EA C07B)	3.7 (1.1-12.3)	0.030	2.9 (0.9-9.5)	0.078
Marital status: widower/divorced vs. married/living together	1.3 (0.7-2.4)	0.447	1.8 (1.0-3.0)	0.033
Educational level: primary education only vs. more than primary education	2.5 (1.7-3.7)	<0.001	2.3 (1.6-3.3)	<0.001

Significant erectile dysfunction = patient report of erections with severely reduced rigidity or no erections.
Significant ejaculatory dysfunction = report of ejaculations of significantly reduced volume or no ejaculations
* Smoker: current smoker or stopped smoking less than five years ago. Non-smoker: never smoked or stopped more than five years ago; † Lower urinary tract symptoms: no symptoms (IPSS score 0), mild (1 to 7), moderate (8 to 19), severe (>19)

Table 9.2. *Correlates for significant erectile dysfunction, yielded by multiple logistic regression models*

Characteristic	adjusted odds ratio ($CI_{95\%}$)
Age (group vs. 50 to 54 years)	
55 to 59	2.3 (1.0-5.2)
60 to 64	4.6 (2.1-10.1)
65 to 69	8.9 (4.1-19.5)
70 to 78	14.3 (6.4-32.1)
Smoking habits* (smokers vs. non-smokers)	1.6 (1.1-2.3)
Body mass index (kg/m^2)	
25 to 30 vs. < 25	1.5 (1.0-2.3)
> 30 vs. < 25	3.0 (1.7-5.4)
Lower urinary tract symptoms†	
mild vs. no symptoms	1.8 (0.8-4.3)
moderate vs. no symptoms	3.4 (1.4-8.4)
severe vs. no symptoms	7.5 (2.5-22.5)
Under treatment for	
cardiac symptoms (yes vs. no)	2.5 (1.5-4.3)
COPD (yes vs. no)	1.9 (1.1-3.6)

Significant erectile dysfunction = patient report of erections with severely reduced rigidity or no erections; * Smoker = current smoker or stopped smoking less than five years ago. Non-smoker = never smoked or stopped more than five years ago; † Lower urinary tract symptoms: no symptoms (IPSS score 0), mild (1 to 7), moderate (8 to 19), severe (>19).

Table 9.3. *Correlates for significant ejaculatory dysfunction, yielded by multiple logistic regression models*

Characteristic	adjusted odds ratio ($CI_{95\%}$)
Age (group vs. 50 to 54 years)	
55 to 59	2.3 (1.0-5.2)
60 to 64	4.6 (2.1-10.1)
65 to 69	8.9 (4.1-19.5)
70 to 78	14.3 (6.4-32.1)
Erectile function	
reduced vs. normal rigidity	3.5 (2.1-5.1)
severely reduced rigidity or no erections vs. normal rigidity	29.5 (18.3-47.8)
Lower urinary tract symptoms*	
mild vs. no symptoms	1.0 (0.5-2.3)
moderate vs. no symptoms	1.9 (0.8-4.2)
severe vs. no symptoms	4.2 (1.4-12.9)
Previous TURP (yes vs. no)	26.7 (13.2-54.4)
Under treatment for	
diabetes mellitus (yes vs. no)	0.2 (0.1-0.7)

Significant ejaculatory dysfunction = report of ejaculations of significantly reduced volume or no ejaculations
*Lower urinary tract symptoms: no symptoms (IPSS score 0), mild (1 to 7), moderate (8 to 19), severe (>19).

Table 9.4. *Attributable proportion and population attributable risk for correlates of erectile and ejaculatory dysfunction*

	Attributable proportion (%)	Population attributable risk (%)
Significant erectile dysfunction		
moderate to severe urinary symptoms (IPSS > 7)	61	27
obesity (BMI > 25 kg/m^2)	30	21
treatment for cardiovascular problems	61	9
treatment for COPD	61	7
smoking habits	19	7
Significant ejaculatory dysfunction		
minor erectile dysfunction	85	65
significant erectile dysfunction	88	44
moderate to severe urinary symptoms (IPSS > 7)	57	24
previous TURP	83	15

Attributable proportion = (risk in exposed cases – risk in unexposed cases) / risk in exposed cases
Population attributable risk = (risk in total population – risk in nonexposed cases) / risk in total population

correlated with the occurrence of ED (Table 9.2). Alternatively, the exclusion of men with previous radical prostatectomy (n = 11) may have caused an underestimation of this prevalence, as ED is common following this type of operation.[17]

Erectile dysfunction

Only a few population studies on correlates for ED are available.[1,2,18] In an Australian survey among men aged over 40 years risk factors were determined for impotence, defined as "usual quality of erections not firm enough for intercourse."[2] Unfortunately, the overall response rate in this questionnaire survey was only 35%, and no nonresponse study was performed which limits the interpretation of the data from this study. In the Massachusetts Male Aging Study (MMAS), an overall response rate of 40% was achieved.[1] In that study, data were collected in male subjects 40 to 70 years old from 11 randomly selected cities and towns in the United States. A calibration study was performed to determine impotence; responses of the MMAS subjects to imprecise questions about erectile function were retrospectively transformed into more precise response categories. For this purpose, results from urology clinic patients were used; these men received the same questionnaire as the MMAS subjects and additionally were asked to characterise themselves as "not," "minimally," "moderately" or "completely impotent." In this respect, no clear definition of impotence is reported. The use of these clinical patients for this calibration may have substantially increased the prevalence of "impotence" and may have influenced the estimation of risk factors in the MMAS population. Although all comparisons in the MMAS data were controlled for age, no multivariate analyses including all related factors were presented. Therefore, it remains unclear which variables are independent risk factors for ED.[1] In a French community survey among 1734 men aged 50 to 80 years (response rate 44%), factors influencing "sexual life satisfaction" were assessed.[18] The differences in

definition of ED and methods used in the mentioned studies hamper making comparisons with our results. Therefore, we confine ourselves to comparing trends in results.

Age. The strong age-dependency of the prevalence of ED is in line with all previous reports on this topic.[1,2,18]

Life style. The present study underlines the previously described role of smoking in the occurrence of ED.[1,2,19,20] The higher risk in smokers may be explained by the fact that cigarette smoking induces arteriosclerosis in the hypogastric-cavernous arterial bed.[19] We found no influence of alcohol consumption on the prevalence of ED, whereas in the MMAS a slight correlation between excessive alcohol and impotence was found.[1]

Our results suggest that ED is related to obesity. Data from the Australian survey also indicated a higher prevalence of impotence in obese men,[2] but a cut-off value of body mass index was not mentioned. In the MMAS data, no correlation was found.[1] This may be explained by the fact that the mean body mass index in the latter study was higher than in our study (mean 27.5 [SD 4.4] compared to 26.0 [2.9]).

Urinary symptoms. The current study shows a clear relation between lower urinary tract symptoms (LUTS) and ED. Men with higher IPSS score more often reported ED and felt their sex life is spoiled by their urinary symptoms. Comparable results were obtained in a small survey in the United Kingdom constructed by the ICS.[11] The French survey indicated the same relation for LUTS and sexual life satisfaction.[18] Urinary flow rate and prostate enlargement (both included in the definition of clinical BPH) had no independent influence on ED.

Cardiovascular problems. Our finding that men reporting cardiovascular disease more often experienced ED is also in line with previous reports. The MMAS data showed a similar strong effect of treated "heart disease" on the impotence probability pattern.[1] A reported relation between hypertension and ED in male hypertensive outpatients is confirmed in our bivariate analyses on ED but not in the multivariate analyses.[5] This suggests that the relation between hypertension and ED may be explained by the sharing of several risk factors (age, smoking, and obesity).

Chronic obstructive pulmonary disease. Results from a small but elegant study on 20 male COPD patients suggested that ED can accompany COPD in the absence of other known causes of sexual dysfunction.[6] Our study confirms this finding.

Diabetes Mellitus. The role of diabetes in the occurrence of ED, described in the MMAS data,[1] is confirmed in our bivariate analyses (Table 9.1) but not in the multivariate analyses (Table 9.2, $p = 0.09$). This may be explained by the fact that in the MMAS only results from bivariate analyses on this subject are given.

Medications. Several medications seemed to be related to ED in the bivariate analyses (Table 9.1). These drug associations, however, were confounded by the underlying medical conditions; the relation between these medications and ED disappeared after adding the underlying diseases to the model. This was especially the case with the medication digoxin, beta-blocking agents, and thiazide diuretics and the variables hypertension and treatment for cardiac problems. Therefore, these medications were omitted from the multivariate models. The use of benzodiazepines did not significantly contribute to these models.

Educational level. Although significant in the bivariate analyses, educational level had no effect in the multivariate analyses (p = 0.12). In a U.S. study on men aged 18 to 59 years, ED also occurred more often in those with lower educational level.[7]

Ejaculatory dysfunction

To our knowledge, this survey is the first to address ejaculatory dysfunction in a community-derived sample of older men. It shows that the prevalence of EjD increases strongly with advancing age. Additionally, there are strong associations with the quality of erections and previous prostate operations. The influence of other factors on EjD in the bivariate analyses (Table 9.1) most probably should be explained by their effect on erectile function, because after adding the latter variable to the model, the effect of those variables diminished.

Although these findings are to be expected, to our knowledge, the first association (ED vs. EjD) has not yet been described. The second association (EjD vs. prostate surgery) has been well described in clinical patients: after TURP, the majority of the men have retrograde ejaculation.[21] In this study we did not distinguish retrograde ejaculation from anejaculation or low volumes of ejaculate, as it is difficult for participants to discriminate these sorts of ejaculation disorders by questionnaires.

We cannot explain the unexpected finding that men with diabetes mellitus have less EjD than those without diabetes. Among men with diabetes, the prevalence of EjD did not differ significantly between types of treatment (no medication, oral medication, and insulin).

Population attributed risk

Estimation of the PAR for certain correlates gives insight into the proportion of a disease in the population that is related to these factors. In these estimations, a causality of the relations is assumed. We calculated the PAR only for the correlates that yielded from multivariate analyses. There were no significant interactions between these variables. The PAR illustrated that cardiac problems were an important factor within men reporting ED, but that on a population level the contribution of this factor is relatively low. For ED it appears that LUTS and obesity (body mass index greater than 25 kg/m^2) have the highest PAR. If prevention of ED is desirable, these two correlates should be targeted. For significant EjD, it appears that the ED has the highest PAR.

We conclude that ED and EjD are common in this population-based sample of older men and strongly related to age. Obesity and urinary symptoms are significant contributors to the risk of having ED; cardiac problems, COPD and smoking are other independent correlates for ED. EjD is largely related to a decreased erectile function and previous prostate surgery.

Data from longitudinal surveys are needed to study which factors determine that a given man will develop ED or EjD. Moreover, future studies should be performed to determine causality of some of the relations between sexual disorders and medications and chronic diseases.

References

1. Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ and McKinlay JB: Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. *J Urol* 1994;151:54-61.
2. Pinnock CB, Stapleton AM and Marshall VR: Erectile dysfunction in the community: a prevalence study. *Med J Aust* 1999;171:353-7.
3. Panser LA, Rhodes T, Girman CJ, *et al.*: Sexual function of men aged 40 to 79 years: the Olmsted County Study of Urinary Symptoms and Health Status Among Men. *J Am Ger Soc* 1995;43:1107-11.
4. Wagner G and Saenz de Tejada I: Update on male erectile dysfunction. *BMJ* 1998;316:678-82.
5. Jensen J, Lendorf A, Stimpel H, *et al.*: The prevalence and etiology of impotence in 101 male hypertensive outpatients. *Am J Hypertens* 1999;12:271-5.
6. Fletcher EC and Martin RJ: Sexual dysfunction and erectile impotence in chronic obstructive pulmonary disease. *Chest* 1982;81:413-21.
7. Laumann EO, Paik A and Rosen RC: Sexual dysfunction in the United States: prevalence and predictors. *JAMA* 1999;281:537-44.
8. Vale J: Ejaculatory dysfunction. *BJU Int* 1999;83:557-63.
9. Blanker MH, Groeneveld FPMJ, Prins A, *et al.*: Strong effects of definition and nonresponse bias on prevalence rates of clinical benign prostatic hyperplasia: the Krimpen study of male urogenital tract problems and general health status. *BJU Int* 2000;85:665-71.
10. Barry MJ, Fowler Jr FJ, O'Leary MP, *et al.*: The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. *J Urol* 1992;148: 1549-57.
11. Frankel SJ, Donovan JL, Peters TI, *et al.*: Sexual dysfunction in men with lower urinary tract symptoms. *J Clin Epidemiol* 1998;51:677-85.
12. Miller GC and Britt H: A new drug classification for computer systems: the ATC extension code. *Int J Biomed Comput* 1995;40:121-4.
13. Bosch JL, Hop WC, Kirkels WJ and Schröder FH: Natural history of benign prostatic hyperplasia: appropriate case definition and estimation of its prevalence in the community. *Urology* 1995;46:34-40.
14. Rothman KJ: *Modern epidemiology*. Boston/Toronto: Little, Brown and Company, 1986.
15. MacMahon B and Pugh TF: *Epidemiology: principles and methods*. 2nd ed. Boston: Little, Brown & Co, 1970.
16. Masumori N, Tsukamoto T, Kumamoto Y, *et al.*: Decline of sexual function with age in Japanese men compared with American men-results of two community-based studies. *Urology* 1999;54:335-44.
17. Catalona WJ, Carvalhal GF, Mager DE and Smith DS: Potency, continence and complication rates in 1,870 consecutive radical retropubic prostatectomies. *J Urol* 1999;162:433-8.
18. Macfarlane GJ, Botto H, Sagnier PP, *et al.*: The relationship between sexual life and urinary condition in the French community. *J Clin Epidemiol* 1996;49:1171-6.
19. Rosen MP, Greenfield AJ, Walker TG, *et al.*: Cigarette smoking: an independent risk factor for atherosclerosis in the hypogastric-cavernous arterial bed of men with arteriogenic impotence. *J Urol* 1991;145:759-63.
20. Mannino DM, Klevens RM and Flanders WD: Cigarette smoking: an independent risk factor for impotence? *Am J Epidemiol* 1994;140:1003-8.
21. Kunelius P, Hakkinen J and Lukkarinen O: Sexual functions in patients with benign prostatic hyperplasia before and after transurethral resection of the prostate. *Urol Res* 1998;26:7-9.

Chapter 10

Prevalence of erectile dysfunction: a systematic review of population-based studies

Abstract

A systematic review was conducted on the prevalence of erectile dysfunction (ED) in the general population. Studies were retrieved which reported prevalence rates of ED in the general population. Using a specially developed criteria list, the methodological quality of these studies was assessed and data on prevalence rates were extracted.

We identified 23 studies from Europe (15), USA (5), Asia (2) and Australia (1). On our 12-item criteria list, the methodological quality ranged from 5 to 12. Prevalence of ED ranged from 2% in men younger than 40 years to 86% in men 80 years and older. Comparison between prevalence data is hampered by major methodological differences between studies, particularly in the use of various questionnaires and different definitions of ED.

We stress the importance of providing all necessary information when reporting on the prevalence of ED. Moreover, international studies should be conducted to establish the true prevalence of ED across countries.

Acknowledgements

The authors thank Mrs. Arianne Verhagen for her methodological comments and suggestions on the manuscript.

Introduction

Epidemiological research on erectile dysfunction (ED) is rapidly growing and studies on the prevalence of ED in the general population have recently been published. Subsequently, several unsystematic reviews have summarised selections from these studies.[1-5] Although most of these reviews conclude that the prevalence of ED differs between studies, the interpretation of these reviews is hampered by several problems. First, the methods used for the selection of articles are not presented in any of the reviews, second, no comment is made on the validity of the separate studies, and third, little attention is given to the used definitions of ED. These shortcomings are consistent with those found in epidemiological reviews in other research fields.[6]
To elucidate on the prevalence of ED in the general population, a systematic review study was conducted in which particular attention was paid to the methodological quality and value of the individual studies. For this purpose, a criteria list for the validity assessment of prevalence studies was developed.

Materials and methods

Search strategy

In December 2001, a search was made from 1966 to December 2001 in the Medline and Psychinfo database using the following keywords: [impotence OR erectile dysfunction OR sexual dysfunction] AND [general population OR community-based OR population-based OR epidemiology]. All items were searched using "All fields". Literature search was limited to the English and Dutch language.
Titles and abstracts of identified published articles were reviewed independently (by JP and MHB) to determine the relevance of the articles. Each citation was classified as 'inclusion', 'unsure' or 'exclusion'. In case of disagreement between the two reviewers, consensus was reached to solve the disagreement. After this, excluded citations were no longer considered. Reference lists of included articles were checked to identify additional studies not found in the Medline database.

Selection of studies

Included studies were assessed in detail (by JP and MHB) to make a final selection of studies for the review. Eligible were, studies with a cross-sectional study design or cohort studies that included men drawn from the general population and reported original data on prevalence rates of erectile dysfunction. Papers consisting of abstracts only were omitted.

Methodological quality assessment

In the judgement of methodological quality two aspects of validity are important: external validity relates to the applicability of study results to other populations, whereas internal validity implies accurate measurement apart from random error. As no criteria list for the quality assessment of prevalence studies was available, a list was designed (see Table 10.1) which includes 6 items on

Table 10.1. *Criteria for the methodological validity assessment of prevalence studies*

External validity
source population
a. does the method to select and invite participants result in a study population that covers the complete population or a random sample?
description of eligibility criteria
b. is the age range specified?
c. are inclusion and exclusion criteria specified?
participants and nonresponders
d. is the response rate > 70%, or is the information on nonresponders sufficient to make inference on the representativeness of the study population?
description of study period
e. is the study period specified?
description of study population
f. are important population characteristics* specified?
Internal validity
data collection
g. are the data prospectively collected?
measurement instrument (questionnaire, interview, additional)
h. is the measurement instrument validated?
i. is the period covered by the measurement instrument specified?
definition of disease†
j. is a definition of the disease stated?
reported prevalences
k. are age-specific and gender-specific prevalences reported?
l. are possible correlates of disease† reported?
Informativity
m. is the method of data collection properly described (interview, questionnaire, additional measurement)?
n. are the questions and answer possibilities stated?
o. are the reported prevalence rates reproducible?

* two or more of: (i) age distribution, (ii) relevant comorbidity, (iii) lifestyle factors (e.g. smoking and alcohol consumption), and (iv) socio-economic data (e.g. income, educational level, marital status); † disease equals erectile dysfunction in this review

internal validity, 6 items on external validity and 3 items on informativity. The latter items are not included in the methodological quality assessment but give an indication of the presentation of the reports. All items were scored positive or negative independently (by JP and MHB) and their importance was not weighed.

For feasibility reasons, the quality assessment was not performed under masked conditions. In case of disagreement, consensus was reached.

Data extraction

Using standardised forms, two reviewers (JP and MHB) independently extracted information and data from the individual studies. When no or insufficient information was provided in the article, we searched the Medline database for other papers on the same study to obtain additional information, using authors names or specific study groups. For feasibility reasons, no attempts were made to get in direct contact with authors of published papers.

Comparison of studies

The methodology of the individual studies was compared to establish whether comparison of the reported prevalence rates would be appropriate and meaningful.

Results

Selection of studies

The primary search yielded 581 citations, of which 63 were selected for full review, including 11 'unsure' citations for which no abstract was available. A check of the reference list of these papers yielded 39 additional citations, of which 30 were selected for full review. Thus, 93 citations were reviewed for eligibility. Of these, 47 papers were omitted for the following reasons: lack of original data (n = 25, of which 13 were review articles), study population not derived from general population (n = 8), paper consisted of abstract only (n = 2), paper contained no information on ED (n = 8), no additional information (n = 1), not available (n = 3). Ten papers originated from the Massachusetts Male Ageing Study (MMAS); of these, 4 papers were used to obtain all necessary information; the other 6 provided no additional information relevant for this review. One article was found with additional information about the selected studies. Finally, data from 40 papers provided information on 23 studies (references 7 to 46). Only two of these studies were selected by means of checking the reference lists.

Methodological quality assessment

Table 10.2 shows the results of the quality assessment. On average, 4.5 items (range 1-6) on external validity were scored positive as were 4.3 (range 2-6) on internal validity. Only two studies scored positive for all of the 12 validity criteria;[40,41,45] however, when considering the single question on ED, both these latter studies scored negatively on two items (*h* and *i*) of internal validity.

Description of selected study populations

A description of the populations included in the selected studies is given in Table 10.3. In 11 studies, the eligibility criteria were not specified. No information on nonresponders was available in 11 studies, whereas in 5 studies specific information was obtained from (a sample of) the nonresponders; 7 other studies compared participant characteristics to external databases, baseline population register or characteristics of baseline participants. In another study, due to the sampling method (stratified on continence state), the study population could not be generalised to the community from which the participants were selected.[7]

Data collection in selected studies

Table 10.4 lists the methods used to obtain data on erectile function and the definitions used for ED. In 17 studies self-administered questionnaires were used, 6 studies used an interview, and in 5 studies the methods used were not specified.

Table 10.2. *Year published and quality assessment of selected studies*

reference number	year*	external validity a	b	c	d	e	f	sum	internal validity g	h	i	j	k	l	sum	informativity m	n	o	sum	disagreement†
7	1990	-	+	-	-	-	-	1	+	-	-	+	+	+	4	+	+	-	2	
8,9	1993	+	+	-	+	+	+	5	+	-	+	+	+	-	4	+	+	+	3	*m*
10-13	1994	+	+	+	+	+	+	6	+	-	+	+	+	+	5	+	+	-	2	*d, h, i*
14-16	1995	+	+	+	+	+	+	6	+	-	+	+	+	-	4	+	+	-‡	2	*l*
17,18	1996	+	+	+	+	+	+	6	+	-	-	+	+	+	4	+	+	+	3	*h*
19,20	1996	+	+	+	-	+	+	5	+	-	+	+	+	-	4	+	+	+	3	*l*
21	1997	+	+	-	+	+	+	5	+	-	-	-	+	-	2	+	-	+	2	
22	1998	+	+	-	-	+	-	3	+	-	-	+	+	-	3	+	+	-	2	
23,24	1998	+	+	+	-	-	-	3	+	-	-	+	+	+	4	+	+	+	3	
25	1998	+	+	+	-	+	-	4	+	-	-	+	+	-	3	+	+	+	3	
26,27	1998	+	+	-	-	+	+	4	+	-	+	+	-	+	4	+	+	+	3	*h*
28	1999	+	+	+	-	+	+	5	+	-	+	+	+	+	5	+	-	+	2	
29,30	1999	+	+	+	+	+	-	5	+	-	+	+	+	+	5	+	+	+	3	*o*
16,31,32	1999	+	+	+	-	-	-	3	+	-	+	+	+	-	4	+	+	+	3	
33,34	1999	+	+	-	-	+	+	4	+	+	+	+	+	+	6	+	+	+	3	
35	2000	+	+	-	+	+	+	5	+	-	-	+	+	+	4	+	-	-	1	*o*
36,37	2000	+	+	-	-	+	+	4	+	-	+	+	+	+	5	+	-	+	2	
38	2000	+	+	-	-	-	+	3	+	-	+	+	+	+	5	+	-	+	2	*m*
39	2000	+	+	-	+	-	+	4	+	+	-	+	+	+	5	+	+	-	2	
40,41	2001	+	+	+	+	+	+	6	+	+	+	+	+	+	6§	+	+	+	3	
42-44	2001	+	+	+	+	+	+	6	+	-	-	+	+	+	4	+	+	+	3	
45	2001	+	+	+	+	+	+	6	+	+	+	+	+	+	6‖	+	+	+	3	
46	2001	+	+	-	+	-	+	4	+	-	-	+	+	+	4	+	+	-	2	*m*

items *a* to *o* refer to Table 10.1. * year published; † items on which the two reviewers disagreed; consensus reported; ‡ information not reproducible from original reports, data extracted from reference 31; § score on sexual function inventory (SFI), single question not validated and no period covered by questionnaire specified (i.e. negative score on item *h* and *i*; sum score 4); || score on international index for erectile function (IIEF), single question not validated and no period covered by questionnaire specified (i.e. negative score on item *h* and *i*; sum score 4)

Various questionnaires were used to assess ED in the population. These questionnaires contained either a single question on ED,[7-9,14-20,22-24,29-35,40-45] or a series of questions on ED from which a sum score was derived.[39-41,45]

In two studies, two methods were used to determine ED, i.e. a single question on ED and a larger questionnaire.[40,41,45] In the MMAS, a calibration study was used to determine impotence from answers to imprecise questions on sexual function.[10] In the first reports on ED, a urological clinic sample was used for this purpose ('clinical method'),[10] whereas in later reports on the longitudinal data, the study sample itself was used ('MMAS method').[12] These two methods resulted in different prevalence rates.[12]

Definition of erectile dysfunction

No definition of ED was specified in one report, whereas 4 studies defined 'impotence', and 3 studies defined 'erectile difficulty', 'erectile disability' or 'erection problems'. In the remaining 16 studies a definition of ED was given (see Table 10.4).

Table 10.3. *Description of the populations in the selected studies*

ref*	design†	source population & selection of participants	eligibility criteria: age (yr)	eligibility criteria: other	participants and nonresponders: N (%)‡	participants and nonresponders: representativeness
7	CS	Washetenaw County, MI, USA probability population sample; stratified (age, continence, gender) sample of participants	60+	NS	283 (29)	comparison with nonresponders second phase: participants poorer health, older, more often incontinent
8,9	CS	Copenhagen, Denmark all men in selected communes	51	NS	439 (81)	comparison with other Danish samples: different employment status; cohabitation, social groups similar
10-13	CS	Boston, MA, USA random population sample	40-70	men with sexual partner	1,290 (40)	interview 206 nonresponders (54%): participants more heart disease and cancer; diabetes, hypertension, arthritis or restricted activity attributed to health similar
14-16	survey	Olmsted County, MN, USA random population sample	40-79	no prostate/ bladder cancer/ surgery, low back surgery, CVA, neurogenic bladder, antiandrogen use	2,115 (55)	questionnaire 637 'partial participants' (36%) and medical record information: participants more urological diseases; chronic diseases similar
17,18	survey	Stockholm area, Sweden stratified (age) random population sample	50-80	born in Sweden, no prostate cancer§	315 (72)	comparison with Swedish statistics: participants more hypertension; prostate cancer, diabetes mellitus and myocardial infarction similar
19,20	survey	France stratified (region) random population sample	50-80	no previous urethral/ bladder disease, radiotherapy to prostate/ pelvic area or prostate cancer	1,734 (53)	NS
21	survey	Göteborg, Sweden stratified (birth cohort) random population sample	45+ 5- yr steps	NS	7,763 (74)	comparison with population register all 2,695 nonresponders: social factors similar
22	survey	Denmark stratified (birth cohort) random population sample	18-88 5-yr steps	NS	626 (51)	NS
23,24	CS	Leicestershire, UK all men registered at general practice	40+	ambulant, no prostate cancer or surgery, urinary problems caused by surgical treatment or neurological damage	423 (65)	NS

ref*	design†	source population & selection of participants	eligibility criteria: age (yr)	eligibility criteria: other	participants and nonresponders: N (%)‡	participants and nonresponders: representativeness
25	survey	Tampere, Finland stratified (birth cohort) random population sample	50, 60, 70	non-institutionalised	1,983 (63)	NS
26,27	survey	UK stratified (age, gender) random sample from general practice registers	18-75	NS	1,768 (39)	NS
28	survey	USA random population sample	18-59	not from barracks, college dormitories or prisons. English-speaking, at least one sexual partner in prior year	1,244 (70)	NS
29,30	survey	Sweden random population sample	18-74	domicile in Sweden, adequately mentally and physically able	1,288 (52)	comparison with all nonresponders: 'no sign of distortion of the material'; participants younger, more men
16,31, 32	CS	Shimamaki-mura, Japan all men	40-79	no prostate/ bladder cancer/ surgery, low back surgery, CVA, neurogenic bladder, antiandrogen use	289 (42)	NS
33,34	survey	South Australia probability population sample; all participants second phase	40+	NS	371 (35)	comparison with all 374 nonresponders second phase: age, marital status, blood pressure (medication), cholesterol and triglyceride levels, or visit to physician for LUTS similar
35	survey	Italy random sample from general practice registers	18+	NS	2,010 (79)	NS
36,37	survey	Thailand selection NS	40-70	NS	1,250 (?)	NS
38	survey	New York, NY, USA stratified (age) random population sample	50-76	NS	1,438 (28)	questionnaire 27 nonresponders (25%): prevalence of ED similar
39	survey	Cologne district, Germany stratified (age, marital status) random population sample	30-80	NS	4,489 (56)	comparison with German socio-economic data: marital status, family income similar
40,41	survey	Boxmeer, The Netherlands stratified (age) random population sample	40-79	Dutch-speaking	1,233 (70)	interview 45 nonresponders (8%): participants more symptoms, more often married

ref*	design†	source population & selection of participants	eligibility criteria age (yr)	eligibility criteria other	participants and nonresponders N (%)‡	participants and nonresponders representativeness
42-44	CS	Krimpen aan den IJssel, The Netherlands all men registered in all general practices	50-78	no prostate/ bladder cancer, radical prostatectomy, neurogenic bladder disease or negative advice by GP	1,605 (47)	questionnaire 261 nonresponders (55%): participants more LUTS and better health status; chronic diseases, medication use, social and lifestyle factors similar
45	survey	Spain stratified (age, community, population density) random population sample	25-70	non-institutionalised	2,476 (75)	NS
46	CS	Gwent, Wales, UK all men registered in 11 general practices	55-70	NS	2,027 (50)	comparison with Gwent Census: participants more often married; racial composition similar

* reference number; † design: survey (questionnaire only) or CS (cross-sectional study with additional measurements); ‡ response rate calculated as number of participants available for analyses divided by total of eligible men; § references present different eligibility criteria on same study population; NS not specified; LUTS lower urinary tract symptoms

Prevalence of erectile dysfunction

Prevalence rates varied considerably (Table 10.4). All studies showed a linear increase in prevalence with advancing age. In two studies no age-specific prevalences were given.[8,9,26] Prevalence rates for men younger than 40 years old (reported in 6 studies) ranged from approximately 2% to 9%. The prevalence rate for men older than 70 years (reported in 13 studies) ranged from 10% to 71%, whereas for men older than 80 years (reported in 3 studies) prevalence ranged from 18% to 86%. Direct comparison of prevalence was possible for only two pairs of studies. Reported prevalences in the Olmsted County Study (OCS)[14-16] and the Japanese survey[32] were roughly similar and showed a large increase in prevalence after the age of 70 years. The reported prevalences in Leicestershire (UK)[23] were considerably higher for the older age groups (60 to 69 and 70 to 79 years) than those from Krimpen aan den IJssel (The Netherlands);[43,44] in this comparison, in the Dutch study all ED severity categories were combined, because the UK study did not provide information on the separate ED severity categories.

Discussion

This is the first systematic review of the literature focussing on the prevalence of erectile dysfunction in the general population. Previously, available data in this rapidly growing epidemiological field of research were summarised nonsystematically,[1-5,47-54] or without a focus to the general population.[55] In particular, no information about the selection of included studies was provided,[1-5,47-54] and the validity of the included studies was not discussed by the authors.[1-5,47-55] In the current study, an overview

of the available literature is given and a validity assessment of individual studies is presented, according to proposed guidelines for reporting of systematic reviews.[56,57]

Selection of studies and data extraction

Only two studies were found via the reference lists, suggesting that the primary search strategy was sufficient. Studies reported in books were not included in the current review.
We decided not to contact authors of the selected studies as this could introduce a bias; authors of recent studies may be easier to contact, and information may be easier available than from older studies. Overall, we believe that information should be readily available to be used by readers of articles.

Methodological quality assessment

As no criteria list for the methodological quality assessment of prevalence studies was available, we developed such a list based on theoretical considerations and common sense (Table 10.1), which can also be used for a systematic review on the prevalence of other conditions in the general population. The distinction made between 'valid' and 'invalid' based on overall scores, and the use of cut-off points is arbitrary. It should be recognised however, that some of the selected studies have a high number of negative scores (Table 10.2). In itself, a study may be valid, but if the reporting is inaccurate, the comparability with other studies and its use in a systematic review will be restricted. Besides the overall validity assessment, several remarks can be made on separate validity criteria, such as the representativeness of the study population (item *d* in the validity assessment).
In 11 studies, the response rate was lower than 70% and insufficient data were available on the representativeness of the population. In two of these studies, the low response rate may be explained by the high effort required from the participants or the inclusion of additional measurements.[23,31,32]
Surprisingly, in 6 studies, no information was given on the study period.

Definitions of ED and questionnaires

Although various authors refer to the consensus definition of ED - 'inability to attain and maintain an erection sufficient for satisfactory sexual activity'[58] - in their reports, only two actually used it in the estimation of prevalence rates.[36-38]
The design of a questionnaire may influence the prevalence rates obtained from it; for example, the ED-rating scale in the Cologne ED Questionnaire consists of 5 closely related questions;[39] a positive score on one question will almost automatically mean a positive score on another question. Moreover, the ED-rating scale included a question on the ability to achieve orgasm;[39] this construction may cause a significant overestimation of the prevalence of ED.
The use of a urological clinic sample for the calibration study in the MMAS has led to an overestimation of the prevalence of ED, which was described in a later paper on this study.[12] In the longitudinal part of the MMAS, a single question on ED was added to the questionnaire, resulting in lower prevalences, especially for those of moderate to severe impotence.[12,13]

In 14 studies, a single question was used to obtain information on erectile function; however, none of these questions was formally validated. Recently, two studies showed that a single question on ED could be used in epidemiological surveys, but the precise formulation of such a question was not discussed.[13,45] Nevertheless, we assume that, when properly specified, the single questions used in other studies provide valid information.

TABLE 10.4. *Method used to obtain information on erectile dysfunction, definition and prevalence rates*

ref*	SAQ / interv†	definition of erectile dysfunction and severity when applicable	time period	prevalence rates (%) age (yr)	% ($CI_{95\%}$)‡
7	interv	'impotence': difficulty in getting or maintaining an erection	NS	60+	40 (35-46)
8,9	SAQ	ED: impaired erection making sexual intercourse impossible on more than a few occasions no ED: impaired erection making sexual intercourse impossible only occasionally or never	year	51	4 (2-6)
10-13	SAQ	moderate to complete impotent: sometimes able or never able to get and keep an erection good enough for sexual intercourse	6 months	40 45 50 55 60 65 70	23 (?)§ 27 32 36 40 45 49
14-16	SAQ	ED: ability to have an erection when sexually stimulated none of the time‖ no ED: ability to have an erection when sexually stimulated a little of the time – all of the time	month	40-49 50-59 60-69 70-79	1 (0-2) 6 (4-8) 22 (18-26) 44 (38-51)
17,18	SAQ	'psychological impotence': erectile stiffness seldom, hardly ever or never sufficient for intercourse or not relevant (no penis stiffness) no impotence: approximately as in youth – sufficient for intercourse most of the time or always	few months	50-59 60-69 70-80	3 (0-11) 24 (17-33) 49 (41-58)
19,20	SAQ	'erection difficulty': difficulty in having an erection each time or some time‖ no erection difficulty: rarely or never difficulty in having an erection	month	50-59 60-69 70-79	20 (17-23) 33 (29-37) 38 (33-44)
21	SAQ	NS	NS	50¶ 60 70 80 90+	2 (1-4) 8 (7-11) 10 (8-13) 18 (14-22) 6 (4-9)
22	SAQ	ED: sexual problem being decreased ability to achieve erection	NS	18, 23 31, 33 38, 43 48, 53 58-88#	2 (?)§ 2 1 5 18
23,24	SAQ	ED: erections of reduced rigidity, severely reduced rigidity or no erections possible no ED: erections of normal rigidity	NS	40-49 50-59 60-69 70-79 80+	9 (5-14) 29 (21-38) 57 (46-67) 79 (65-90) 86 (42-100)

ref*	SAQ / interv†	definition of erectile dysfunction and severity when applicable	time period	prevalence rates (%) age (yr)	% ($CI_{95\%}$)‡
25	SAQ	moderate/ complete ED: often experienced difficulties in getting and/or maintain an erection during intercourse or intercourse does not succeed‖ minimal/ no ED: no erectile difficulties disturbing intercourse or occasional trouble in getting and/or maintain an erection	NS	50 60 70	12 (10-15) 24 (21-28) 49 (44-53)
26,27	SAQ	ED: difficulty in getting or maintaining an erection	3 months lifetime	18-75 18-75	26 (23-30) 39 (35-42)
28	interv	ED: trouble maintaining or achieving an erection	year	18-29 30-39 40-49 50-59	7 (5-10) 9 (6-12) 11 (8-15) 18 (13-26)
29,30	interv	'erectile disability': penis does not become rigid or gets flaccid during intercourse quite often, nearly all the time, all the time no erectile disability: penis does not become rigid or gets flaccid during intercourse never, hardly ever, quite rarely	year	18-24 25-34 35-49 50-65 66-74	3 (1-6) 2 (1-4) 3 (1-4) 2 (1-4) 24 (17-33)
16,31,32	SAQ	ED: ability to have an erection when sexually stimulated none of the time / a little of the time‖ minimal/ no ED: ability to have an erection when sexually stimulated some of the time – all of the time	month	40-49 50-59 60-69 70-79	15 (6-28) 23 (14-35) 39 (30-49) 71 (59-82)
33,34	SAQ	ED: usual quality of erections firm enough for masturbation and foreplay only, not firm enough for any sexual activity, no erections at all no ED: usual quality of erections firm enough for intercourse	3 months	40-49 50-59 60-69 70-79 80+	6 (3-11) 12 (6-19) 41 (29-53) 63 (49-76) 81 (54-96)
35	interv	partial/ complete ED: some to all sexual performances considered unsatisfactory	NS	18-29 30-39 40-49 50-59 60-69 70+	2 (1-5)** 2 (1-4) 5 (3-7) 16 (12-20) 27 (22-32) 48 (41-56)
36,37	interv	moderate/ severe ED: sometimes or never able to achieve and keep an erection good enough for sexual intercourse mild/ no ED: usually or always able to achieve and keep an erection good enough for sexual intercourse	NS	40-49 50-59 60-70	7 (5-9) 22 (18-26) 49 (42-56)
38	SAQ	ED: recurrent inability to attain or maintain erections of sufficient rigidity for satisfactory sexual intercourse	6 months	50-54 55-59 60-64 65-69 70-76	26 (20-32)** 35 (29-41) 47 (40-53) 60 (54-66) 69 (62-75)
39	SAQ	impotence: more than 17 points on ED-rating scale (see text)	NS	30-39 40-49 50-59 60-69 70-80	2 (2-3)†† 10 (8-12) 16 (13-18) 34 (32-37) 53 (48-58)

ref*	SAQ / interv†	definition of erectile dysfunction and severity when applicable	time period	prevalence rates (%) age (yr)	% ($CI_{95\%}$)‡
40,41	SAQ	ED: problems in achieving an erection, or maintaining an erection hard enough for sexual intercourse‡‡	NS‡‡	40-49 50-59 60-69 70-79	6 (3-10) 9 (6-12) 22 (18-26) 38 (32-44)
42-44	SAQ	significant ED: erections of severely reduced rigidity or no erections minor/ no ED: erections of reduced/ normal rigidity	NS	50-54 55-59 60-64 65-69 70-78	3 (1-5) 5 (3-8) 11 (8-14) 19 (14-23) 26 (19-33)
45	SAQ	moderate/ severe/ complete ED: considered moderate or severe/ complete incapacity for erection‡‡ mild/ no ED: considered minimum incapacity for erection or no erection problem	NS‡‡	25-39 40-49 50-59 60-70	2 (1-3) 3 (2-5) 7 (5-10) 21 (18-25)
46	interv	complete ED: never able to attain a penile erection sufficient for satisfactory sexual activity	NS	55-60 61-65 66-70	7 (?)§ 13 22

* reference numbers; † SAQ: self-administered questionnaire, interv: interview; ‡ CI confidence interval, estimated in current review; § prevalence presented by authors without CI, not reproducible; || definition made in current review; ¶ only decades presented, information of five year cohorts omitted; # five year steps; ** reproduced figures inconsistent with original report; †† prevalence and CI presented by authors, not reproducible; ‡‡ single question on ED

Comparison of prevalence rates

The current review shows that the reported prevalences of ED vary considerably and that there are major methodological differences between studies. Therefore, it is unclear whether these varying prevalences reflect true differences between countries or methodological differences. In our opinion, the large methodological variations, especially the different definitions used, hamper the direct comparison of prevalence rates reported in most studies. Only a few studies can be meaningfully compared.

For example, the similar designs of the OCS and the Japanese study do allow comparisons to be made.[14-16,31,32] In the reports of the OCS,[14-16] however, no exact prevalence rates of ED are given, other than the cumulative distribution of the responses to the specific questions, in the combined report of both studies.[32] We derived the prevalences from this latter report: that 44% (109 out of 245) of these men reported to have *'erections none of the time'*.[32] Surprisingly, this prevalence is not in accordance with an earlier report from that study in which the authors state that *'the percentage of subjects who were able to have erections a little or none of the time increased.... to more than a quarter of men aged 70 or older'*.[14]

The studies from Leicestershire (UK) and Krimpen aan den IJssel (The Netherlands) used the same definition and questionnaire (International Continence Society *male sex* questionnaire).[23,44] Differences in risk profiles and different perceptions of the problem may both contribute to the dissimilarities in reported prevalence of ED between men aged 60 and over; further studies are needed to explain these differences.

Previously, it was concluded that the considerably lower prevalences in Spain (compared to the MMAS data) might be attributed to differences in perception of ED across different cultures.[45] In our opinion however, these differences are more likely caused by differences in the questions that were used (see Table 10.3).

Several conclusions can be drawn from this systematic review of the literature on the prevalence of erectile dysfunction in the general population. First, the information in many of the reports is insufficient to provide valid data on prevalence rates and can therefore not be generalised or used to draw conclusions from comparisons with other studies. Second, the methods used to obtain information on erectile function vary considerably. Differences in definitions (derived from various questionnaires) are the main hindrance to comparing reported prevalences. Third, in those studies that are similar, specific data on age-specific and severity-specific prevalences of ED are scarce, as is the information on comorbidity in these study populations.
When reporting on prevalences of ED, we stress the importance of describing all information relevant for the interpretation of the data. Future studies should aim to clarify whether reported differences in prevalences are due to methodological differences only, or may be attributed to cultural or other factors. Large international cohort studies appear to have the most appropriate design to address these questions, but re-analysing the raw data from available prevalence studies, as described in this review, may also be appropriate.

References

1. Wagner G and Saenz de Tejada I: Update on male erectile dysfunction. *BMJ* 1998;316:678-82.
2. Lewis RW: Epidemiology of erectile dysfunction. *Urol Clin North Am* 2001;28:209-16, vii.
3. Melman A and Gingell JC: The epidemiology and pathophysiology of erectile dysfunction. *J Urol* 1999;161: 5-11.
4. Lerner SE, Melman A and Christ GJ: A review of erectile dysfunction: new insights and more questions. *J Urol* 1993;149:1246-55.
5. Bortolotti A, Parazzini F, Colli E and Landoni M: The epidemiology of erectile dysfunction and its risk factors. *Int J Androl* 1997;20:323-34.
6. Breslow RA, Ross SA and Weed DL: Quality of reviews in epidemiology. *Am J Public Health* 1998;88:475-7.
7. Diokno AC, Brown MB and Herzog AR: Sexual function in the elderly. *Arch Intern Med* 1990;150:197-200.
8. Solstad K and Hertoft P: Frequency of sexual problems and sexual dysfunction in middle-aged Danish men. *Arch Sex Behav* 1993;22:51-8.
9. Solstad K and Davidsen M: Sexual behaviour and attitudes of Danish middle-aged men-methodological considerations. *Maturitas* 1993;17:139-49.
10. Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ and McKinlay JB: Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. *J Urol* 1994;151:54-61.
11. Araujo AB, Durante R, Feldman HA, Goldstein I and McKinlay JB: The relationship between depressive symptoms and male erectile dysfunction: cross-sectional results from the Massachusetts Male Aging Study. *Psychosom Med* 1998;60:458-65.
12. Kleinman KP, Feldman HA, Johannes CB, Derby CA and McKinlay JB: A new surrogate variable for erectile dysfunction status in the Massachusetts male aging study. *J Clin Epidemiol* 2000;53:71-8.
13. Derby CA, Araujo AB, Johannes CB, Feldman HA and McKinlay JB: Measurement of erectile dysfunction in population-based studies: the use of a single question self-assessment in the Massachusetts Male Aging Study. *Int J Impot Res* 2000;12:197-204.
14. Panser LA, Rhodes T, Girman CJ, *et al.*: Sexual function of men ages 40 to 79 years: the Olmsted County Study of Urinary Symptoms and Health Status Among Men. *J Am Geriatr Soc* 1995;43:1107-11.
15. Panser LA, Chute CG, Guess HA, *et al.*: The natural history of prostatism: the effects of non-response bias. *Int J Epidemiol* 1994;23:1198-205.
16. Epstein RS, Deverka PA, Chute CG, *et al.*: Validation of a new quality of life questionnaire for benign prostatic hyperplasia. *J Clin Epidemiol* 1992;45:1431-45.
17. Helgason AR, Adolfsson J, Dickman P, *et al.*: Sexual desire, erection, orgasm and ejaculatory functions and their importance to elderly Swedish men: a population-based study. *Age Ageing* 1996;25:285-91.
18. Helgason AR, Adolfsson J, Dickman P, *et al.*: Factors associated with waning sexual function among elderly men and prostate cancer patients. *J Urol* 1997;158:155-9.
19. Macfarlane GJ, Botto H, Sagnier PP, *et al.*: The relationship between sexual life and urinary condition in the French community. *J Clin Epidemiol* 1996;49:1171-6.
20. Sagnier PP, MacFarlane G, Richard F, *et al.*: Results of an epidemiological survey using a modified American Urological Association symptom index for benign prostatic hyperplasia in France. *J Urol* 1994;151:1266-70.
21. Malmsten UG, Milsom I, Molander U and Norlen LJ: Urinary incontinence and lower urinary tract symptoms: an epidemiological study of men aged 45 to 99 years. *J Urol* 1997;158:1733-7.
22. Ventegodt S: Sex and the quality of life in Denmark. *Arch Sex Behav* 1998;27:295-307.
23. Frankel SJ, Donovan JL, Peters TI, *et al.*: Sexual dysfunction in men with lower urinary tract symptoms. *J Clin Epidemiol* 1998;51:677-85.
24. Jolleys JV, Donovan JL, Nanchahal K, Peters TJ and Abrams P: Urinary symptoms in the community: how bothersome are they? *Br J Urol* 1994;74:551-5.

25. Koskimäki J, Hakama M, Huhtala H and Tammela TL: Effect of erectile dysfunction on frequency of intercourse: a population based prevalence study in Finland. *J Urol* 2000;164:367-70.
26. Dunn KM, Croft PR and Hackett GI: Sexual problems: a study of the prevalence and need for health care in the general population. *Fam Pract* 1998;15:519-24.
27. Dunn KM, Croft PR and Hackett GI: Association of sexual problems with social, psychological, and physical problems in men and women: A cross sectional population survey. *J Epidemiol Community Health* 1999;53: 144-148.
28. Laumann EO, Paik A and Rosen RC: Sexual dysfunction in the United States: prevalence and predictors. *JAMA* 1999;281:537-44.
29. Fugl-Meyer AR: Sexual disabilities, problems and satisfaction in 18-74 year old Swedes. *Scand J Sexol* 1999;2: 79-105.
30. Helmius G: The Swedish sex survey. An introduction and remarks on changes in early sexual experiences. *Scand J Sexol* 1998;1:63-70.
31. Tsukamoto T, Kumamoto Y, Masumori N, *et al.*: Prevalence of prostatism in Japanese men in a community-based study with comparison to a similar American study. *J Urol* 1995;154:391-5.
32. Masumori N, Tsukamoto T, Kumamoto Y, *et al.*: Decline of sexual function with age in Japanese men compared with American men-results of two community-based studies. *Urology* 1999;54:335-44.
33. Pinnock CB, Stapleton AM and Marshall VR: Erectile dysfunction in the community: a prevalence study. *Med J Aust* 1999;171:353-7.
34. Pinnock C and Marshall VR: Troublesome lower urinary tract symptoms in the community: a prevalence study. *Med J Aust* 1997;167:72-5.
35. Parazzini F, Menchini Fabris F, Bortolotti A, *et al.*: Frequency and determinants of erectile dysfunction in Italy. *Eur Urol* 2000;37:43-9.
36. Kongkanand A: Prevalence of erectile dysfunction in Thailand. Thai Erectile Dysfunction Epidemiological Study Group. *Int J Androl* 2000;23:77-80.
37. Group TEDES: An epidemiological study of erectile dysfunction in Thailand (Part 1: Prevalence). *J Med Assoc Thai* 2000;83:872-9.
38. Ansong KS, Lewis C, Jenkins P and Bell J: Epidemiology of erectile dysfunction: a community-based study in rural New York State. *Ann Epidemiol* 2000;10:293-6.
39. Braun M, Wassmer G, Klotz T, *et al.*: Epidemiology of erectile dysfunction: results of the 'Cologne Male Survey'. *Int J Impot Res* 2000;12:305-11.
40. Meuleman EJ, Donkers LH, Robertson C, *et al.*: [Erectile dysfunction: prevalence and effect on the quality of life; Boxmeer study] Erectiestoornis: prevalentie en invloed op de kwaliteit van leven; het Boxmeer-onderzoek [Dutch]. *Ned Tijdschr Geneeskd* 2001;145:576-81.
41. Boyle P, Keech M, Nonis A, *et al.*: The UrEpiK Study: a cross-sectional survey of benign prostatic hyperplasia, urinary incontinence and male erectile dysfunction, prostatitis and interstitial cystitis in the UK, France, the Netherlands and Korea. *J Epidemiol Biostat* 1998;3:179-87.
42. Blanker MH, Groeneveld FPMJ, Prins A, *et al.*: Strong effects of definition and nonresponse bias on prevalence rates of clinical benign prostatic hyperplasia: the Krimpen study of male urogenital tract problems and general health status. *BJU Int* 2000;85:665-71.
43. Blanker MH, Bohnen AM, Groeneveld FP, *et al.*: Correlates for erectile and ejaculatory dysfunction in older Dutch men: a community-based study. *J Am Geriatr Soc* 2001;49:436-42.
44. Blanker MH, Bosch JL, Groeneveld FP, *et al.*: Erectile and ejaculatory dysfunction in a community-based sample of men 50 to 78 years old: prevalence, concern, and relation to sexual activity. *Urology* 2001;57:763-8.
45. Martin-Morales A, Sanchez-Cruz JJ, Saenz de Tejada I, *et al.*: Prevalence and independent risk factors for erectile dysfunction in Spain: results of the Epidemiologia de la Disfuncion Erectil Masculina Study. *J Urol* 2001;166:569-74.
46. Green JS, Holden ST, Ingram P, *et al.*: An investigation of erectile dysfunction in Gwent, Wales. *BJU Int* 2001;88:551-3.

47. Gentili A and Mulligan T: Sexual dysfunction in older adults. *Clin Geriatr Med* 1998;14:383-93.
48. Korenman SG: Clinical review 71: Advances in the understanding and management of erectile dysfunction. *J Clin Endocrinol Metab* 1995;80:1985-8.
49. Monga M: The aging penis: erectile dysfunction. *Geriatr Nephrol Urol* 1999;9:27-37.
50. Morley JE: Impotence. *Am J Med* 1986;80:897-905.
51. Spector IP and Carey MP: Incidence and prevalence of the sexual dysfunctions: a critical review of the empirical literature. *Arch Sex Behav* 1990;19:389-408.
52. Avis NE: Sexual function and aging in men and women: community and population-based studies. *J Gend Specif Med* 2000;3:37-41.
53. Benet AE and Melman A: The epidemiology of erectile dysfunction. *Urol Clin North Am* 1995;22:699-709.
54. Cohan P and Korenman SG: Erectile dysfunction. *J Clin Endocrinol Metab* 2001;86:2391-4.
55. Simons JS and Carey MP: Prevalence of sexual dysfunctions: results from a decade of research. *Arch Sex Behav* 2001;30:177-219.
56. Oxman AD: Checklists for review articles. *BMJ* 1994;309:648-51.
57. Stroup DF, Berlin JA, Morton SC, *et al.*: Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000;283:2008-12.
58. NIH Consensus Development Panel on Impotence. NIH Consensus Conference. Impotence. *JAMA* 1993;270: 83-90.

Part IV

Health status

Chapter 11

Health status and its correlates among Dutch community-dwelling older men with and without lower urogenital tract dysfunction

Abstract

Objective. To study health status and its correlates in older men with and without lower urogenital tract dysfunction.

Subjects and Methods. Cross-sectional population-based study on 1688 men aged 50 to 78 years without bladder or prostate cancer, radical prostatectomy, neurogenic bladder dysfunction or a negative advice from their general practitioner. Data were collected through self-administered questionnaires, including Sickness Impact Profile (SIP, three domains), Inventory of Subjective Health (ISH), International Prostate Symptom Score (IPSS) and International Continence Society (ICS) Male Sex questionnaire, medication use, socio-economic and lifestyle factors. Additional information was collected by measurement of blood pressure, transrectal ultrasonography of the prostate and uroflowmetry.

Four health status domains were analyzed using the ISH and three domains of the SIP. Lower urinary tract symptoms (LUTS) were categorised using IPSS, erectile and ejaculatory dysfunction were defined using the ICS questionnaire.

Results. All urogenital characteristics and parameters were related to at least two of the health status domains. Multivariate regression analyses yielded that LUTS and cardiac symptoms were associated with suboptimal scores of all four domains. Chronic obstructive pulmonary disease and drugs for abdominal symptoms were related to three domains; erectile and ejaculatory dysfunction, muskuloskeletal or psycho(ana)leptic drugs and marital status to two domains.

Conclusions. The impact of LUTS on health status was equally important as the impact of cardiac symptoms. The impact of sexual dysfunction was smaller than expected. Longitudinal studies are needed to determine how health status and illnesses interact.

Introduction

Lower urogenital tract symptoms are common and bothersome symptoms in older men.[1-3] Nevertheless, only a few population studies considered the impact of lower urinary tract symptoms (LUTS) on general health,[4-6] or the relation between erectile dysfunction and (disease-specific) quality of life.[7-9]

When assessing health status in men with urogenital tract dysfunction, the impact on health status of comorbid conditions and other factors should also be considered, both in epidemiological studies and in daily practice.

To better understand the relation and interaction between health status and LUTS and erectile dysfunction there is a need for population-based data taking other important factors into account such as chronic diseases, medication use, demographic and lifestyle factors. In this report, we present the independent and simultaneous effect of such variables on generic health status measures in a large community-based study on Dutch men aged 50 to 78 years. The study was specifically designed to observe the relation between urogenital tract dysfunction and general health status.

Subjects and Methods

The data presented here were collected as part of a large ongoing community-based study: the Krimpen study on male urogenital tract problems and general health status.[3] This study investigated all men aged 50 to 75 years (age on reference date, n = 3924) in a Dutch municipality near Rotterdam. Men without radical prostatectomy, prostate or bladder cancer, neurogenic bladder disease or negative advice from their general practitioner, and who were able to complete questionnaires and visit the health center were found eligible and were invited for the study. At the time of enrollment, 152 men had passed the age of 75 years. All men entering the study provided written informed consent. The Medical Ethics Committee of the Erasmus Medical Center Rotterdam, the Netherlands, approved the study.

Data were collected from 1688 responders (50% response rate) via a self-administered 113-item questionnaire, which included the Sickness Impact Profile (SIP)[10,11], a short version of the Inventory of Subjective health (mini-ISH)[12], the International Prostate Symptom Score (IPSS)[13], and the International Continence Society male sex (ICSsex) questionnaire.[14]

The SIP and mini-ISH were used to assess health status.[10-12] The three categories of the SIP used in the current report were 'emotions, feelings and sensations' ('emotions', including 9 items), 'leisure pastimes and recreation' ('recreation', 8 items), and 'social interaction' ('social', 20 items). For each category, a score was computed based on weighing factors for each item, providing scores ranging from zero to 100. Higher scores indicate lower levels of health status.[10]

The mini-ISH is a 13-item questionnaire on subjective health with a score range from zero to 13 points; zero indicates optimal health status.[12] The SIP and mini-ISH are generic health status measures, meaning that they contain no disease-specific questions. Exception to this is one question on reduced sexual activities in the SIP category 'social interaction'.

The IPSS was used to rate LUTS severity: 0, no; 1-7, mild; 8-19, moderate; 20 or more, severe LUTS.[13] Based on the second and third item of the ICSsex questionnaire,[14] we defined 'no erections' and 'erections with severely reduced rigidity' as erectile dysfunction (ED), and 'no ejaculations' and 'ejaculations with severely reduced quantity' as ejaculatory dysfunction (EjD).
The questionnaire also included questions on comorbidity, smoking habits, alcohol consumption, educational level, and marital status. The current medication use was recorded.
Additional measurements at the local health center and urology outpatient department included blood pressure, height and bodyweight, urinalysis, serum prostate specific antigen, digital rectal examination and transrectal ultrasonometry of the prostate, uroflowmetry, and post void residual urine volume. Prostate biopsies (n = 171) were taken to detect prostate cancer, according to a previously described protocol.[3]
Clinical benign prostatic hyperplasia (BPH) was defined as moderate to severe LUTS with prostate enlargement and reduced urinary flow rate.[3]

Statistical analyses

A batch of 27 completed questionnaires was lost before the data were entered in the database. We categorized the men into age strata: 50-54, 55-59, 60-64, 65-70 and 70-78 years.
To analyze health status, we dichotomized the measures based on the observed distribution: for the SIP categories, we defined a zero score as 'optimal' and other scores as 'suboptimal'. For the mini-ISH, we grouped zero and one as 'optimal' and other scores as 'suboptimal'.
For various urological parameters, the percentage of men with a suboptimal health status score will be presented. Differences are tested with chi-square test (when appropriate for linear trend). Moreover, the median score will be presented for those with a suboptimal score.
Because health status has a multifactorial explanation that is not limited to urogenital factors we performed multivariate logistic regression analyses on the four health status measures. In these analyses we included urogenital characteristics (i.e. LUTS severity, prostate enlargement, reduced urinary flow rate, previous prostate operation, ED and EjD), age, other general health characteristics including comorbid conditions, used drugs and social factors. Only characteristics with a p-value of 0.25 or less in the univariate model were entered in the multivariate analysis.[15]
As erectile and ejaculatory dysfunction are closely related,[16] mutually exclusive categories were formed and used in the multivariate analyses: *neither* ED *nor* EjD, *either* ED *or* EjD only, *both* ED *and* EjD. Since LUTS severity, prostate enlargement (> 30 cm^3) and reduced flow rate (< 15 ml/sec) are used to define benign prostatic hyperplasia, "BPH" was not included in the multivariate analyses as a separate variable.
Variables with nonsignificant contribution (p-value less than 0.05) to the effect in the multivariate models were excluded. For the resulting variables, odds ratios are presented with 95% confidence intervals ($CI_{95\%}$). Moreover, the percentage of variance explained by the model ($R^2_{nagelkerke}$) was estimated for the resulting four models.[17]

Results

For the various urogenital parameters, the percentage of men with a suboptimal score on health status domains is given in Table 11.1. The percentage of men with suboptimal scores in all health status domains was about twice as high for men with severe LUTS as compared to men with no LUTS. All characteristics related to the urogenital tract, except for reduced urinary flow rate, were statistically significantly related to increased percentages of men with suboptimal health status scores in at least two domains. The variable "prostate enlargement" was statistically significantly related to decreased percentages of men with suboptimal scores in two domains (i.e. recreation and mini ISH).

The percentage of men with a suboptimal score on health status domains for various non-urogenital parameters is given in Table 11.2.

The median scores on the different domains of those with suboptimal scores were significantly higher in men with LUTS, previous prostate operation and sexual dysfunction.

Table 11.3 shows the results of the multivariate regression models on the health status domains

Table 11.1. *Percentage of men with suboptimal score and median score for those with suboptimal score on the four health status measures in relation to urological parameters*

			Sickness Impact Profile category						Mini-ISH	
			Emotional		Recreation		Social interaction			
		number	% (median)	p *	% (median)	p *	% (median)	p *	% (median)	p *
LUTS category†				<0.001		<0.001		<0.001		<0.001
no symptoms		169	17.8 (11)		31.0 (18)		43.2 (7)		37.9 (3)	
mild LUTS		1082	19.7 (10)		38.8 (19)		52.3 (6)		42.7 (3)	
moderate LUTS		357	33.6 (15)		54.9 (19)		68.3 (7)		59.2 (4)	
severe LUTS		49	46.9 (20)		63.3 (22)		75.5 (11)		77.6 (5)	
Prostate enlargement (volume > 30 cc)	no	790	24.2 (11)	0.213	45.3 (19)	0.010	56.5 (7)	0.365	49.9 (3)	0.008
	yes	816	21.6 (11)		38.9 (19)		54.3 (6)		43.3 (3)	
Reduced urinary flow rate (< 15 ml/sec)	no	359	21.4 (12)	0.507	43.3 (18)	0.684	52.1 (7)	0.139	45.0 (3)	0.414
	yes	1089	23.1 (10)		42.1 (19)		56.6 (6)		47.5 (3)	
Clinical benign prostatic hyperplasia	no	1258	20.9 (11)	<0.001	40.9 (19)	0.001	53.3 (6)	<0.001	45.0 (3)	0.001
	yes	171	33.9 (12)		53.8 (20)		70.2 (6)		57.9 (4)	
Previous prostate operation	no	1594	22.9 (11)	0.055	41.4 (19)	0.002	54.6 (6)	<0.001	46.6 (3)	0.434
	yes	63	33.3 (16)		60.9 (19)		78.1 (9)		51.6 (3)	
Erectile dysfunction (ED)	no	1478	21.7 (10)	<0.001	40.0 (19)	<0.001	51.2 (6)	<0.001	44.9 (3)	<0.001
	yes	179	36.9 (16)		60.1 (28)		91.1 (9)		62.0 (4)	
Ejaculatory dysfunction (EjD)	no	1431	21.5 (11)	<0.001	39.6 (19)	<0.001	51.0 (6)	<0.001	45.0 (3)	<0.001
	yes	226	34.5 (15)		58.4 (23)		83.6 (7)		58.0 (4)	
ED and EjD combined				<0.001		<0.001		<0.001		<0.001
neither ED *nor* EjD		1365	21.1 (10)		39.0 (19)		49.4 (6)		44.0 (3)	
either ED *or* EjD		179	29.1 (11)		53.4 (19)		77.1 (6)		59.2 (4)	
both ED *and* EjD		113	40.7 (17)		63.1 (28)		94.7 (10)		60.2 (4)	

* p-value χ^2 test, with exception of LUTS category (χ^2 for linear trend); † LUTS: lower urinary tract symptoms, according to International Prostate Symptom Score (IPSS); ‡ clinical benign prostatic hyperplasia: moderate to severe LUTS (IPSS score > 7) with enlarged prostate and reduced maximum urinary flow rate

Table 11.2. *Percentage of men with suboptimal score and median score for those with suboptimal score on the four health status measures in relation to non-urogenital parameters*

			Sickness Impact Profile category						Mini-ISH	
			Emotional		Recreation		Social interaction			
		number	% (median)	p*	% (median)	p*	% (median)	p*	% (median)	p*
Age & comorbidity										
Age strata (years)				0.176		<0.001		<0.001		0.724
50-54		340	24.1 (16)		37.1 (18)		46.8 (9)		47.4 (3)	
55-59		419	25.5 (10)		41.2 (19)		49.9 (7)		49.3 (3)	
60-64		400	23.5 (10)		39.0 (19)		56.0 (6)		45.3 (3)	
65-69		315	19.7 (11)		44.8 (19)		62.5 (6)		46.4 (3)	
70-78		183	22.4 (10)		56.6 (21)		71.2 (6)		44.0 (3)	
diabetes mellitus	no	1601	23.1 (11)	0.342	42.0 (19)	0.353	55.1 (6)	0.105	46.7 (3)	0.623
	yes	56	28.6 (14)		48.2 (18)		66.1 (9)		50.0 (3)	
cardiac symptoms	no	1554	21.7 (11)	<0.001	40.4 (19)	<0.001	53.6 (6)	<0.001	44.9 (3)	<0.001
	yes	103	47.6 (10)		69.6 (24)		83.5 (7)		74.8 (5)	
hypertension	no	1209	22.2 (15)	0.074	38.6 (19)	<0.001	51.1 (6)	<0.001	44.5 (3)	0.002
	yes	448	26.3 (10)		52.0 (20)		67.4 (7)		52.9 (3)	
COPD/asthma	no	1582	22.4 (11)	<0.001	40.7 (19)	<0.001	54.7 (6)	0.003	45.3 (3)	<0.001
	yes	75	42.7 (15)		73.3 (30)		72.0 (10)		77.3 (5)	
Current drug use (ATC-codes)										
abdominal complaints (A02 – A07)	no	1547	21.7 (10)	<0.001	41.0 (19)	<0.001	54.3 (6)	<0.001	44.7 (3)	<0.001
	yes	110	46.4 (18)		59.1 (27)		72.7 (10)		76.4 (4)	
muskuloskeletal disease (M01– M04, M09)	no	1593	22.8 (11)	0.032	41.1 (19)	<0.001	55.3 (6)	0.371	45.6 (3)	<0.001
	yes	64	34.4 (16)		68.8 (22)		60.9 (7)		76.6 (4)	
psycho(ana)leptic drugs (N05, N06)	no	1591	21.6 (10)	<0.001	41.6 (19)	0.020	54.8 (6)	0.004	45.5 (3)	<0.001
	yes	66	63.6 (18)		56.1 (27)		72.7 (9)		77.3 (4)	
Social and lifestyle factors										
Highest level of education				0.086		0.002		<0.001		0.167
> primary school		1442	22.6 (11)		40.8 (19)		53.4 (6)		46.1 (3)	
primary school only		215	27.9 (10)		51.9 (24)		69.3 (7)		51.2 (4)	
Marital status				0.015		0.011		0.053		0.524
married/living together		1565	22.7 (11)		41.5 (19)		54.9 (6)		46.6 (3)	
widowed/divorced/alone		92	33.7 (15)		54.9 (18)		65.2 (10)		50.0 (4)	
Smoking habits†				0.021		0.479		0.003		0.317
non-smoker		1131	21.7 (11)		41.6 (19)		53.1 (6)		45.9 (3)	
current smoker		526	26.8 (10)		43.5 (21)		60.7 (7)		48.6 (3)	
Alcohol consumption				0.012		0.339		0.367		0.175
no		375	24.8 (12)		44.2 (20)		54.4 (7)		47.1 (4)	
1-2 units/day		974	20.9 (10)		40.7 (19)		54.8 (6)		45.2 (3)	
> 2 units/day		308	28.9 (15)		44.5 (20)		59.1 (7)		51.3 (3)	

* p value χ^2 test, with exception of age groups (χ^2 test for linear trend); † smoker: current smoker or stopped smoking less than five years ago, non-smoker: never smoked or stopped smoking more than five years ago

Table 11.3. *Multivariate regression analyses on suboptimal score on four health status measures*

	Sickness Impact Profile category							
	Emotions		Recreation		Social interaction		Mini-ISH	
	OR ($CI_{95\%}$)	p	OR ($CI_{95\%}$)	p	OR ($CI_{95\%}$)	p	OR ($CI_{95\%}$)	p
Lower urogenital tract characteristics								
LUTS category*		<0.001		<0.001		0.002		<0.001
mild	1.2 (0.7-2.0)		1.4 (1.0-2.2)		1.3 (0.9-1.9)		1.1 (0.7-1.6)	
moderate	2.1 (1.2-3.6)		2.8 (1.8-4.4)		2.1 (1.3-3.2)		1.8 (1.2-2.7)	
severe	3.3 (1.5-7.5)		3.4 (1.5-7.4)		2.3 (1.0-5.6)		6.5 (2.5-16.9)	
Prostate enlargement†	NS	0.458	0.7 (0.6-0.9)	0.002	NS	0.140	0.7 (0.6-0.9)	0.001
Reduced flow rate†	NS	0.363	NS	0.426	NS	0.504	NS	0.365
Prostate operation†	NS	0.089	1.9 (1.1-3.2)	0.029	NS	0.442	NS	0.760
ED and EjD combined‡		0.006		0.240		<0.001		0.156
either ED *or* EjD	1.3 (0.9-2.0)		NS		2.9 (1.9-4.3)		NS	
both ED *and* EjD	2.2 (1.3-3.7)				14.0 (5.6-34.9)			
Other factors								
Age strata (years)		0.003	NS	0.092	NS	0.192	NS	0.061
55-59 vs. 50-54	1.0 (0.7-1.5)							
60-64 vs. 50-54	0.7 (0.5-1.1)							
65-69 vs. 50-54	0.5 (0.3-0.8)							
70-78 vs. 50-54	0.6 (0.3-0.9)							
diabetes mellitus†	not included		not included		NS	0.793	not included	
cardiac symptoms†	2.4 (1.5-3.8)	<0.001	2.1 (1.3-3.4)	0.004	2.7 (1.5-5.1)	0.002	2.7 (1.7-4.5)	<0.001
hypertension†	NS	0.803	1.4 (1.1-1.9)	0.004	1.6 (1.3-2.2)	<0.001	NS	0.430
COPD/asthma†	2.1 (1.2-3.8)	0.011	3.2 (1.8-5.9)	<0.001	NS	0.373	2.6 (1.4-4.7)	0.002
Current drug use§								
abdominal	2.6 (1.6-4.1)	<0.001	NS	0.275	1.7 (1.0-2.8)	0.034	2.9 (1.8-4.9)	<0.001
muskuloskeletal	NS	0.345	2.7 (1.5-4.9)	0.001	not included		3.2 (1.7-6.0)	<0.001
psycho(ana)leptic	4.5 (2.5-8.1)	<0.001	NS	0.924	NS	0.246	2.5 (1.3-4.6)	0.005
Level of education‖	NS	0.409	NS	0.566	NS	0.053	NS	0.367
Marital status#	2.2 (1.3-3.7)	0.004	2.2 (1.3-3.6)	0.002	NS	0.180	NS	0.206
Smoking habits**	NS	0.322	not included		1.4 (1.1-1.8)	0.003	not included	
Alcohol consumption	NS	0.085	not included		not included		NS	0.318
% explained variance of final model ($R^2_{nagelkerke}$)	0.143		0.115		0.166		0.127	

OR = odds ratio * LUTS: lower urinary tract symptoms, categories according to International Prostate Symptom Score (compared to no symptoms); † yes vs. no; ‡ mutually exclusive categories; category vs. no dysfunction; § users vs. non-users; ‖ primary school only vs. higher than primary school; # married/living together vs. widowed/divorced/alone; ** non-smoker or stopped smoking > 5 years ago vs. current smoker, stopped < 5 years ago; NS: not significant

considering urogenital tract characteristics as well as other general health characteristics. The percentage of explained variance ($R^2_{nagelkerke}$) was low in all models. LUTS had a statistically significant effect on all domains (chi-square for linear trend, all $p < 0.001$). The effect of previous prostate operation is lost in all but one domain ('recreation'), due to the characteristic LUTS. Men with

prostate enlargement less often report suboptimal health status. The combined characteristic ED/EjD showed a significant effect in SIP emotions and SIP social domains, but not in the other two domains. Analyses in which ED and EjD were entered as separate variables showed similar results.

Age and other characteristics

The strong effect of age on SIP recreation and SIP social was lost in the multivariate analyses. Although apparently not related in univariate analyses, the multivariate analyses yielded a clear relation between age and SIP emotions: increasing age was associated with lower OR for suboptimal scores. A comparable pattern was seen in the analyses on mini-ISH, but the results were not significant ($p = 0.061$).

Cardiac symptoms were significantly related to all four domains. Chronic obstructive pulmonary disease (COPD) and drug use for abdominal symptoms were related to three domains, and hypertension, muskuloskeletal or psycho(ana)leptic drug use and marital status to two.

Discussion

This study provides information on health status in a large population of Dutch older men with and without urogenital tract dysfunction, and the impact of age, various chronic diseases, drug use and social and lifestyle factors.

The response rate of the Krimpen study is remarkably high, considering the effort required from the participants and the number of invasive tests performed.[3] In a non-response study, we showed that the participants were similar to the non-responders with respect to age, educational level and marital status, and smoking and drinking habits.[3] Participants had slightly more voiding symptoms (IPSS > 7 in 25% versus 15% of the men). Moreover, general wellbeing, as measured by the ISH, in the total population was somewhat better than in our study population.[3] Inasmuch as a selection bias may affect "population point estimates" but not "associations", we assume that non-response bias will not affect the associations with other characteristics or parameters found in our study.

Several population-based studies on health status in older men have been published.[4-9,18-21] In some of these studies, urogenital tract dysfunction was not considered,[18-20] whereas in other studies the impact of possible confounding factors was not reported.[7,8] In the present study, effects of parameters of urogenital tract (dys)function on health status domains are put in relation to effects of co-morbid conditions, drug use, and demographic and lifestyle factors using multivariate analysis. Nearly all of the characteristics under study were associated with two or more health status domains, but the impact of most of these characteristics was lost in one or more of the multivariate analyses. The presence of LUTS increased the risk of suboptimal scores for all health status measures, independent of other determinants. The impact of LUTS was as large as the impact of cardiac symptoms.

LUTS

The negative impact of LUTS on health status has been demonstrated in previous studies.[4-6,21] In their report on the relation between symptom severity (LUTS) and health status, the researchers of the

Olmsted County Study gave no quantitative data on the role of other possible determinants of health status.[4] The authors only reported age-adjusted odds ratios for impaired health status and mentioned that 'adjustment for comorbidity did not change the results'; it is unclear what this means. In our study, the impact of LUTS on a person's health status decreased in the multivariate analyses, but the overall (negative) effect remained.

Recently, a comparable relation between LUTS and general wellbeing in a Dutch population was reported.[5] Although the authors presented other determinants of wellbeing in the study population, no multivariate analyses were applied. It therefore is unclear what the effect of LUTS is on health status, when considering other determinants. In contrast, Mozes *et al* reported multivariate analyses on impaired health status in Israeli men aged 45 to 75, without presenting the impact of separate factors.[6] In the latter study, the impact of the urinary symptom 'bothersomeness-severity' on quality of life was reported,[6] which one can expect to be related in advance. In the present study, use of the IPSS allowed to distinguish between men with different symptom severity levels. We prefer the use of this symptom severity to the use of 'bothersomeness-severity'.

In the definition of clinical BPH, the presence of LUTS is combined with prostate enlargement and reduced urinary flow rate.[22,23] Prostate enlargement was associated with better health status in the current study. It is difficult to explain this counterintuitive finding. From our analyses, we suggest that a negative impact of clinical BPH is mainly due to LUTS. Moreover, because only half of the men with moderate to severe LUTS also have clinical BPH,[3] we suggest to consider the effect of LUTS on health status in stead of clinical BPH, both in epidemiological studies and in daily practice.

Sexual dysfunction

Previously, a negative effect of ED on health status was reported.[7-9] In the recent report of Meuleman *et al,* the impact of ED on well being is presented next to other determinants.[9] No multivariate analyses were performed as the authors aimed at describing but not at explaining an association.[24] To our knowledge, we are the first to report the impact of ejaculatory dysfunction on health status in older men in the general population. It appears that the presence of EjD, especially in conjunction with ED, has a significant negative impact on health status; particularly, the SIP domains emotions and social interaction. For the latter domain, the item on reduced sexual activity may account for the size of the effect, but ignoring this item in the univariate analyses still yielded significant odds ratios (ORs) for the combined variable of ED and EjD (data not presented). It is unclear whether these conditions should be regarded as a cause of suboptimal health status or rather because of it. Results from longitudinal studies are needed to answer this question properly.

Other factors

The negative impact of cardiac symptoms on health status has previously been reported,[18,19] although in one study 'heart disease' was not associated with lowered wellbeing.[20] The negative effect of COPD is consistent with other studies.[6,18-20] Unlike previous studies,[6,19,25,26] the present study showed no independent relation between health status and diabetes mellitus or hypertension. This could be

because hypertension itself is not bothersome for most patients and the relatively low number of people with diabetes mellitus in this study (n = 56).
For several comorbidities, we used drug use as a proxy for the underlying disease. We assumed that people who use specific medication represent those with the most severe symptoms. The appropriateness of this could not be checked in the study data, but the consistency of our findings with studies on the impact of underlying diseases is supportive for our assumption.[18-20] We expect that the true relation between the underlying diseases may in fact be larger than estimated in our study, but whether the relation to health status is due to the underlying illness or to the medication itself (side effects) remains unclear.
In the univariate analyses, age was, as expected, strongly associated with health status domains social interactions and recreation. After adjustment for other correlates, this association remained positive in the SIP social interaction domain (i.e. higher OR for suboptimal scores with increasing age), but was no longer statistically significant (p = 0.192). In the SIP recreation domain, the association disappeared. In contrast, age had no effect on SIP emotional domain and ISH in univariate analyses (Table 11.2), but a rather strong effect after adjustment for other correlates: increasing age was associated with reduced OR for suboptimal scores, although statistically not significant for the ISH analyses (p = 0.061).
The negative effect of age on social interactions and recreational health status (both including a number of physical activities) may be explained by physical impairments, such as walking difficulties and visual and hearing impairment. These factors were not assessed in the current study. The positive effect of age on subjective wellbeing (ISH score) and emotional health status is consistent with findings in the Berlin Aging Study.[27] Authors from that study concluded that old age not only comprises risk factors such as poor functional health, but also factors that promote high subjective well-being.[27] The relation between age and health status needs further evaluation.

In conclusion, this population-based study among older men with and without urogenital tract dysfunction showed that the negative impact of LUTS on men's health status is as large as the negative impact of cardiac symptoms. The impact of ED is smaller than expected, whereas the effect of EjD is more important than expected, particularly if this dysfunction co-exists with ED. Although the associations described in this study seem clear, longitudinal studies are needed to determine how illnesses and health status interact. Next to the impact of lower urogenital tract dysfunction, physicians should consider the impact of comorbid conditions on patients' health status.

References

1. Jolleys JV, Donovan JL, Nanchahal K, Peters TJ and Abrams P: Urinary symptoms in the community: how bothersome are they? *Br J Urol* 1994;74:551-5.
2. Garraway WM, Collins GN and Lee RJ: High prevalence of benign prostatic hypertrophy in the community. *Lancet* 1991;338:469-71.
3. Blanker MH, Groeneveld FPMJ, Prins A, *et al.*: Strong effects of definition and nonresponse bias on prevalence rates of clinical benign prostatic hyperplasia: the Krimpen study of male urogenital tract problems and general health status. *BJU Int* 2000;85:665-71.
4. Roberts RO, Jacobsen SJ, Rhodes T, *et al.*: Natural history of prostatism: impaired health states in men with lower urinary tract symptoms. *J Urol* 1997;157:1711-7.
5. Sonke GS, Kolman D, de la Rosette JJ, *et al.*: [Prevalence of lower urinary tract symptoms in men and its influence on their quality of life: Boxmeer Study] Prevalentie van lagere-urinewegsymptomen bij mannen en de invloed op hun kwaliteit van leven: het Boxmeer-onderzoek [Dutch]. *Ned Tijdschr Geneeskd* 2000;144: 2558-63.
6. Mozes B, Maor Y and Shmueli A: The competing effects of disease states on quality of life of the elderly: the case of urinary symptoms in men. *Qual Life Res* 1999;8:93-9.
7. Masumori N, Tsukamoto T, Kumamoto Y, *et al.*: Decline of sexual function with age in Japanese men compared with American men-results of two community-based studies. *Urology* 1999;54:335-44.
8. Panser LA, Rhodes T, Girman CJ, *et al.*: Sexual function of men aged 40 to 79 years: the Olmsted County Study of Urinary Symptoms and Health Status Among Men. *J Am Ger Soc* 1995;43:1107-11.
9. Meuleman EJ, Donkers LH, Robertson C, *et al.*: [Erectile dysfunction: prevalence and effect on the quality of life; Boxmeer study] Erectiestoornis: prevalentie en invloed op de kwaliteit van leven; het Boxmeer-onderzoek [Dutch]. *Ned Tijdschr Geneeskd* 2001;145:576-81.
10. Pollard WE, Bobbitt RA, Bergner M, Martin DP and Gilson BS: The Sickness Impact Profile: reliability of a health status measure. *Med Care* 1976;14:146-55.
11. Jacobs HM, Luttik A, Touw-Otten FW and de Melker RA: [The sickness impact profile; results of an evaluation study of the Dutch version] De 'sickness impact profile'; resultaten van een valideringsonderzoek van de Nederlandse versie [Dutch]. *Ned Tijdschr Geneeskd* 1990;134:1950-4.
12. Jansen ME and Sikkel D: Verkorte versies van de VOEG-schaal [Dutch]. *Gezondheid en Samenleving* 1981;1: 78-82.
13. Barry MJ, Fowler Jr FJ, O'Leary MP, *et al.*: The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. *J Urol* 1992;148: 1549-57.
14. Frankel SJ, Donovan JL, Peters TJ, *et al.*: Sexual dysfunction in men with lower urinary tract symptoms. *J Clin Epidemiol* 1998;51:677-85.
15. Hosmer DW and Lemeshow S. Model building strategies and methods for logistic regression. In: Hosmer DW and Lemeshow S, editors. *Applied logistic regression*. New York: John Wiley & Sons, 1989:82-134.
16. Blanker MH, Bohnen AM, Groeneveld FP, *et al.*: Correlates for erectile and ejaculatory dysfunction in older Dutch men: a community-based study. *J Am Geriatr Soc* 2001;49:436-42.
17. Nagelkerke NJD: A note on a general definition of the coefficient of determination. *Biometrika* 1991;78:691-2.
18. Kempen GI, Ormel J, Brilman EI and Relyveld J: Adaptive responses among Dutch elderly: the impact of eight chronic medical conditions on health-related quality of life. *Am J Public Health* 1997;87:38-44.
19. Stewart AL, Greenfield S, Hays RD, *et al.*: Functional status and well-being of patients with chronic conditions. Results from the Medical Outcomes Study. *JAMA* 1989;262:907-13.
20. Lam CL and Lauder IJ: The impact of chronic diseases on the health-related quality of life (HRQOL) of Chinese patients in primary care. *Fam Pract* 2000;17:159-66.
21. Hunter DJ, McKee M, Black NA and Sanderson CF: Health status and quality of life of British men with lower urinary tract symptoms: results from the SF-36. *Urology* 1995;45:962-71.

22. Bosch JL, Hop WC, Kirkels WJ and Schröder FH: Natural history of benign prostatic hyperplasia: appropriate case definition and estimation of its prevalence in the community. *Urology* 1995;46:34-40.
23. Abrams P: New words for old: lower urinary tract symptoms for "prostatism" [editorial]. *BMJ* 1994;308:929-30.
24. Kiemeney LALM and Meuleman EJ: [Erectile dysfunction: prevalence and effect on quality of life; Boxmeer Study] Erectiestoornis: prevalentie en invloed op kwaliteit van leven; het Boxmeer-onderzoek [Letter; Dutch]. *Ned Tijdschr Geneeskd* 2001;145:1035.
25. Battersby C, Hartley K, Fletcher AF, *et al.*: Quality of life in treated hypertension: a case-control community based study. *J Hum Hypertens* 1995;9:981-6.
26. Lawrence WF, Fryback DG, Martin PA, Klein R and Klein BE: Health status and hypertension: a population-based study. *J Clin Epidemiol* 1996;49:1239-45.
27. Kunzmann U, Little TD and Smith J: Is age-related stability of subjective well-being a paradox? Cross-sectional and longitudinal evidence from the Berlin Aging Study. *Psychol Aging* 2000;15:511-26.

Part V

General discussion and summaries

Chapter 12

General discussion

The scope of this thesis is the epidemiologic aspects of lower urigenital tract dysfunction in older men by the analyses of the cross-sectional data derived from the Krimpen Study. The data from this study provide important information on lower urogenital tract dysfunction in older men. The results can be applied in daily practice and expand the epidemiological database on this topic.

Validity and clinical relevance

The Krimpen Study included 1688 men 50 to 78 years old, accounting for 50% of all eligible men. This 50% response rate can be considered high, taking into account the effort required from the participants and the number of invasive tests performed in a hospital setting. In the invitation letter, eligible men were asked to complete a 113-item questionnaire and a 3-day frequency-volume chart, and to attend both the health centre in Krimpen aan den IJssel and the urology outpatient clinic of the University Hospital Rotterdam for further measurements. All measurements, including blood sampling, digital rectal examination, transrectal ultrasonography, uroflowmetry and post-void residual volume, were performed in all men, irrespective of symptom status or other parameters. Higher response rates in studies on this topic were achieved only in those studies that did not include invasive tests.[1-8]

The 50% response rate does not impair the value of the study: in a survey among a representative sample of those not responding we showed that, based on various parameters, the participants were representative for the source population (chapter 3). Participants were similar to those not responding for age, educational level, marital status, chronic diseases, and smoking and drinking habits. Differences in lower urinary tract symptoms between participants and those not responding had clear effects on the point estimates of the prevalence of these symptoms and benign prostatic hyperplasia; therefore, we adjusted the prevalence rates for these differences. Besides this influence on point estimates, response bias generally does not affect other analyses,[9] such as the analyses on correlates for erectile and ejaculatory dysfunction or lower urinary tract symptoms in the current study.

In this cross-sectional part of the Krimpen study the relations described (e.g. erectile dysfunction and its correlates, chapter 9) cannot be interpreted as evidence of causality.[10] Most of the described

associations, however, seem physiologically plausible and are consistent with previous studies, suggesting that a true relation may be present.
The ongoing, longitudinal part of the Krimpen Study as well as other epidemiological and non-epidemiological studies are needed to analyse the true relation between the various associated parameters.
Epidemiological studies provide information on the distribution of symptoms and physiological and anatomical parameters in the community. Obtaining all measurements in all participants of the Krimpen Study allowed to describe such parameters for lower urogenital tract function in men aged 50 years and older, which can be used as reference values. It remains unclear, however, to what extent these data for the total population are representative for patients consulting general practice and specialised care. Identifying the participants of the Krimpen Study that seek medical attention for their lower urogenital tract symptoms during the follow-up period will clarify this. Moreover, it will give information on health care-seeking behaviour and its correlates. It is expected that the lower urogenital tract symptoms themselves will influence this behaviour more than physical parameters (e.g. prostate volume, maximum urinary flow rate, and post void residual volume), because most patients are unaware of the latter. Other medical and non-medical parameters (e.g. age, comorbidity, drug use, marital status, educational level, and smoking and drinking habits) and general health status may also be important.
Previous data on health care-seeking behaviour for lower urogenital tract symptoms were mainly collected retrospectively,[2,6,7,11-16] which may have introduced recall bias.[17] Moreover, no inference can be made on the predictive value of parameters on health care-seeking behaviour from these studies. Thus, prospectively collected data, such as gathered in the Krimpen Study, are needed to study this properly. During the follow-up of the Krimpen Study, the electronic medical records (and, if needed, letters from the specialists) of all participants will be reviewed for this purpose.

Lower urinary tract symptoms and benign prostatic hyperplasia

The Krimpen Study confirms the high prevalence of lower urinary tract symptoms in the general population.[2,6,18-21] Moreover, it confirms that the prevalence of clinical benign prostatic hyperplasia is strongly dependent on the definitions used (chapter 3), as previously reported by Bosch *et al.*[22] Differences in definition may also account for the variation in reported prevalences of clinical benign prostatic hyperplasia between countries, but differences in prevalence of lower urinary tract symptoms have also been reported.[23,24] We stress the importance of providing clear definitions and accurately describing the assessments in reports on this topic in order to draw valid conclusions from such reports.
Longitudinal data are needed to determine which definition of clinical benign prostatic hyperplasia is of best use in predicting medical outcomes, such as treatment effects and complications (e.g. acute urinary retention and urinary tract infections).[25,26]
The most widely used definition of clinical benign prostatic hyperplasia includes moderate to severe lower urinary tract symptoms, a prostate size larger than 30 cc, and a reduced maximum urinary flow rate (Q_{max} < 15 ml/sec).[22] In the current study it appeared that, according to this definition, only

half of the men with moderate to severe lower urinary tract symptoms have clinical benign prostatic hyperplasia, ranging from a quarter to one third in men aged 50 to 59 years to three quarters in men aged 70 to 78 years (Table 3.4). Previous population-based studies are in line with this finding.[21,22,27] Therefore, it seems inappropriate to classify lower urinary tract symptoms as 'prostate enlargement-related', especially in the younger age strata. In the older age strata, it is unclear whether prostate enlargement should be considered the cause of lower urinary tract symptoms, or just a (normal) finding correlated with age. Longitudinal data from men with and without lower urinary tract symptoms are needed to study these relations in more detail.

Besides these data on the prevalence of benign prostatic hyperplasia in men with lower urinary tract symptoms, results from treatment strategies for lower urinary tract symptoms may also be indicative for causes other than prostate enlargement. For example, the results of transurethral resection of the prostate (still considered the 'gold standard' treatment for clinical benign prostatic hyperplasia in the Netherlands) are disappointing for various lower urinary tract symptoms.[28,29] Many men with increased nocturnal voiding frequency retain this symptom after the operation.[29]

The main aim of drugs currently prescribed for lower urinary tract symptoms, is to reduce outflow resistance through selective alpha-adrenergic receptor blockade or to reduce prostate growth through 5-alpha reductase inhibition.[30] Although several physiological parameters show (statistically) significant improvement with these treatments,[31] the clinical relevance remains somewhat unclear. More importantly, the effect of these drugs on lower urinary tract symptoms is disappointing and the placebo effect is considerable:[31,32] Symptom score improvement in men taking alpha-blockers in all the trials included in a recent systematic review was 30-50%, whereas it was 10-30% in those taking placebo;[31] for finasteride (a 5-alpha reductase inhibitor), these figures were 15-30% (active treatment) and 0-20% (placebo).[31] Higher success rates were observed in men with prostate volumes greater than 40 cc.[31] In the present study, however, only the minority of men with moderate to severe lower urinary tract symptoms has a prostate of this size. Reduction of 'benign prostatic hyperplasia'-related complications with these medications requires large numbers needed to treat (NNT).[30] For example, in a four-year study on the use of finasteride (a 5-alpha-reductase inhibitor) 5 mg daily and placebo, the use of finasteride reduced the risk for acute urinary retention from 6.6% (placebo) to 2.8%, resulting in a NNT of 26. For the reduction of the risk for prostatectomy, NNT was 24.[33]

Thus, there are sufficient reasons to look at determinants other than prostate enlargement in the evaluation of older men with lower urinary tract symptoms.

Lower urinary tract symptoms and bladder dysfunction

In the current study, attention is given to bladder function and its relation with lower urinary tract symptoms (chapter 6). Bladder function was mainly assessed as functional bladder capacity, but it should be recognised that other frequently used urological parameters (e.g. reduced urinary flow rate and post void residual urine volume) are also related to bladder function.

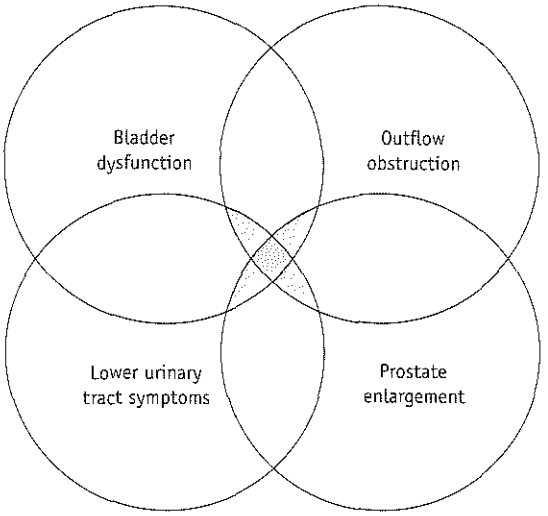
Reduced urinary flow rate is not equivalent to bladder outflow obstruction, but rather the combined result of bladder outflow obstruction and bladder function.[34] No pressure flow studies were performed in the current survey, so it remains unclear which part of the reduced flow rates should be attributed

to bladder dysfunction, outflow obstruction, or both. The functional bladder capacity reflects both the storage and the emptying function of the bladder; post-void residual reflects bladder-emptying function only.[35,36]

In our analyses, these three bladder function-related parameters were (besides age) clearly associated with lower urinary tract symptoms (Table 6.4). In these analyses, various cut-off values for prostate enlargement were used, as well as prostate volume as linear variable, but none resulted in a significant effect of prostate size.

Based on our analyses, we suggest that bladder dysfunction should be recognised as an associated factor for lower urinary tract symptoms in older men. In other words, lower urinary tract symptoms that are related to changes in the urinary bladder are not only important in women, but also in men. The role of bladder dysfunction is shown in Figure 12.1, together with the previously suggested parameters prostate enlargement and outflow obstruction.

Figure 12.1. *Schematic view of lower urinary tract symptoms and its determinants*



Longitudinal studies are needed to determine how these parameters interact, especially with respect to incidence of and changes in lower urinary tract symptoms. Such data may confirm results from previous studies in which bladder wall changes have been described in patients with chronically obstructed bladder outflow.[37] Alternatively, there is evidence that changes in the bladder wall may be a consequence of ageing, rather than a consequence of bladder outflow obstruction.[38] Therefore, age should also be considered in these longitudinal studies. Moreover, other characteristics that may influence bladder function (e.g. vascular factors, diabetes mellitus, neurological disease, drug use, and alcohol) should be studied.

Pressure flow studies in population-based surveys may also contribute important information. For this purpose, non-invasive procedures have been developed and are the preferred method to be used in large numbers of men.[39,40]

Future outcome studies on treatments for lower urinary tract symptoms should include parameters of bladder function. Treatment modalities with specific effects on bladder function may need more attention.

Normal values

The Krimpen Study provided normal values for various lower urinary tract parameters and information on possible determinants of these parameters. Normal values can be used in daily practice when evaluating older men with lower urinary tract symptoms.

Normal values for diurnal voiding frequency are 4.0 to 6.0 (interquartile range) and are independent from age (chapter 4). In these analyses, bladder capacity and 24-hour voided volume were not included. Additional analyses yielded that these two latter parameters are strongly related, which could be expected because bladder capacity, 24-hour voided volume and diurnal voiding frequency are mathematically related (i.e. derived from one another). Total voided volume approximates the total fluid intake. In daily practice, high fluid intake may therefore explain high voiding frequency. In such cases, low bladder capacity and signs or symptoms for urinary tract infection should be excluded.

Nocturnal voiding frequency increases strongly with advancing age (chapter 4). From the current study, it appears that the large majority of older men has at least one nocturnal voiding episode. Two of such episodes may even be considered normal in the older men, because this was reported by more than half of the men aged over 65 years. These figures may help in patient education in men presenting with nocturnal voiding frequency as main symptom. The use of frequency-volume charts and history taking in this respect are discussed below.

The role of increased nocturnal urine production in the occurrence of nocturnal voiding frequency was also considered (chapter 5). Our analyses suggested that nocturnal voiding frequency is indicative of nocturnal urine production, but that nocturnal urine production is not a good predictor of nocturnal voiding frequency. Previously suggested definitions for increased nocturnal urine production, especially those using a day/night ratio, should be omitted in future studies on nocturnal voiding frequency as these are based on an incorrect concept, were not properly validated, and were not based on normal distributions.

We also presented reference values for voided volumes (chapter 6). It appeared that the total voided volume did not differ between the age strata. The average volume per void and functional bladder capacity (maximum voided volume) decreased with advancing age, which may suggest changes in bladder function with age. These data are very similar to those found in healthy women.[41] Functional bladder capacity was significantly lower in men with reduced urinary flow rate and significantly higher in men treated for chronic obstructive pulmonary disease.

Urine production shows a clear circadian pattern in men younger than 65 years of age (chapter 7). In older men, this pattern is attenuated, mainly due to increased nocturnal urine production. Other correlates of circadian urine production pattern include 24-hour polyuria, post-void residual and diuretic use.

Use of frequency-volume charts

The normal values described above resulted from the analyses of frequency-volume charts of the participants. This is the first study to use a frequency-volume chart for this purpose in such a large number of men with and without lower urinary tract symptoms. Of the 1661 men participating in the second phase of the study, 1597 completed the 3-day frequency-volume chart; 1446 of these charts were sufficient for analyses. This high number of sufficiently completed charts (88%) confirms the previously described workable method for collecting data.[35,41-44] Participants were given written instructions about completing the charts. It is expected that the percentage of adequately completed charts will be higher when used in daily practice, as patients will be more motivated and additional instructions can be given.

It has been previously suggested to use frequency-volume charts in the assessment of male lower urinary tract symptoms.[41,42,44] In the Dutch guideline for general practitioners on the assessment of lower urinary tract symptoms and benign prostatic hyperplasia, however, these charts are not mentioned.[45] Frequency-volume charts can provide information on nocturnal and diurnal voiding frequency, bladder capacity and urine production. For these reasons, we feel that the use of such charts should be added to the guidelines.

In the assessment of increased nocturnal voiding frequency, it should be recognised that the information derived from frequency-volume charts is more valid than history taking (chapter 4). Detecting high fluid intake in men with increased voiding frequency (both diurnal and nocturnal) may be the key to resolving such a symptom.

The role of a frequency-volume chart in diagnosing heart failure has been described by Van Mastrigt *et al.*[46] In that particular case, the frequency-volume chart revealed a completely reversed day/night pattern in the circadian urine production of a 68-year old man which could be ascribed to heart failure. Future studies should reveal the value of frequency-volume charts in the assessment of patients with suspected heart failure, in addition to history taking and physical examination.

The need for patients presenting with lower urinary tract symptoms to play an active role in the assessment of this problem may be an additional value of the use of frequency-volume charts.[36] Moreover, the effect of medical treatments can be monitored analogously to, for example, the treatment of urge incontinence in women.[47]

Sexual function

In the current study, nearly 90% of the participants described themselves as sexually active (chapter 8). As expected, this percentage decreases with advancing age, but remains high in men age 70 to 78 years old; about 69% of the men in this age group report to be sexually active. Men without a partner were less often sexually active.

Although sexual activity was clearly related with erectile and ejaculatory dysfunction, the presence of normal erection or ejaculation appeared to be no absolute requisite for sexual activity. This may be explained by the fact that sexual activity was not restricted to intercourse. Longitudinal data are needed to determine whether sexual inactivity may relate to erectile or ejaculatory dysfunction or vice versa.

Erectile and ejaculatory dysfunction

In the Krimpen Study, a single question on erectile dysfunction was used to determine the prevalence of this condition, which is a valid method for this purpose (chapter 8 and 9).[48] Single questions are insufficient to diagnose erectile dysfunction in individual patients, but are accurate for large population studies.[48] No attempts were made to determine the origin of the erectile dysfunction (e.g. organic, psychogenic, or combined aetiology).[49] In daily practice, however, physicians should try to clarify the problem presented by the patient. Besides the distinction between organic and psychogenic (which is in itself difficult), physicians should distinguish erectile dysfunction from reduced libido, premature ejaculation and other sexual disorders, for which erectile dysfunction may be the presenting symptom.[50]

The prevalence of erectile dysfunction increased strongly with advancing age, which is in line with other reports on this topic. Further comparisons of prevalences reported in other countries are hampered by large differences in patient selection, study methods and presentation of results in other studies (chapter 10).

The prevalence of ejaculatory dysfunction in older men has not previously been described in such a large population. In our study, this prevalence was strongly related to age, erectile dysfunction, the presence of lower urinary tract symptoms, and a history of transurethral resection of the prostate (chapter 9).

Concern about erectile and ejaculatory dysfunction

In the total study population, the reported concern about sexual dysfunction was low and related to the severity of dysfunction (chapter 8). A similar result was reported in the Boxmeer Study, a study on lower urogenital tract dysfunction among 1771 Dutch men. Based on these results, Hengeveld and Gianotten suggested to redefine erectile dysfunction for prevalence estimations based on concern by the patient: 'erectile disorder', i.e. erectile dysfunction with distress.[51] Using this definition, the prevalences are much lower, but are more likely to represent the number of men that would probably seek medical attention.[51]

These epidemiological data give no information on individual patients that may attend the general practice or an outpatient clinic. Therefore, the low levels of concern about sexual dysfunction cannot be extrapolated to the consultation room; as with all symptoms and illnesses, the individual concern may result in a consultation with a general practitioner or another physician. Data from patients that consult the physician may reveal the role of associated concern in health care-seeking behaviour of men with erectile dysfunction.

Risk factors for erectile dysfunction

In the present study, several characteristics were shown to be clearly related to erectile dysfunction (chapter 9). Although these results are in line with other prevalence studies and are plausible from a physiological viewpoint, strictly speaking they should not be interpreted as risk factors.[10] To determine risk factors, data on incident cases of erectile dysfunction are needed. To date, only

incidence data from the Massachusetts Male Ageing Study are available.[52-54] The longitudinal data from the Krimpen Study will therefore contribute important information to the epidemiological database, which is at present still very small.

Erectile dysfunction and cardiovascular disease

Special attention will be given to the relation between erectile dysfunction and cardiovascular disease. It remains unclear whether erectile dysfunction should be defined as a part of cardiovascular disease or as a separate risk factor for the development of cardiovascular disease.[55-57] The prospective data collected for the Krimpen Study may answer this important question.

Erectile dysfunction and lower urinary tract symptoms

In the total study population, the presence of moderate to severe lower urinary tract symptoms contributed most to the prevalence of erectile dysfunction (Table 9.5). In these analyses on population attributed risk and attributable proportion, causality of the relation was assumed.[58,59] This assumption, however, was not based on pathophysiological grounds: no clear explanation for the relation between erectile dysfunction and lower urinary tract symptoms can be given, other than the shared associated factor of age.[60] Future studies are needed to reveal how these two concurrent conditions should be explained. In this respect, the role of hormonal changes, especially "androgen deficiency in ageing males, ADAM," must be explored.[61,62]

Health status

The cross-sectional part of the Krimpen Study provides information on health status in older men. Information on five domains of health status was collected and analyses on four of these domains are reported (chapter 11). It is difficult to evaluate health status of the total population because 'suboptimal' health status was defined by the study group itself. No clearly described definition of 'suboptimal' was available for the separate domains.[63,64] Nevertheless, the analyses of the determinants of this arbitrarily defined health status can be used. These analyses showed that lower urinary tract symptom severity had an impact on health status similar to that of cardiac symptoms. The impact of sexual dysfunction was much less, which is in line with the overall low level of concern about this condition (chapter 8).
Longitudinal data are needed to determine how associated factors and health status interact: are men with suboptimal health status at higher risk for developing diseases, especially lower urinary tract symptoms and sexual dysfunction, or should it be considered vice versa? In the future longitudinal analyses, special attention may be given to health status as a possible determinant of health care-seeking behaviour for lower urinary tract symptoms.

In older men, lower urinary tract symptoms are the result of the interaction between age-related changes in the bladder wall, bladder changes secondary to benign prostatic obstruction, prostate enlargement, and non-urinary tract related factors.

References

1. Malmsten UG, Milsom I, Molander U and Norlen LJ: Urinary incontinence and lower urinary tract symptoms: an epidemiological study of men aged 45 to 99 years. *J Urol* 1997;158:1733-7.
2. Sladden MJ, Hughes AM, Hirst GH and Ward JE: A community study of lower urinary tract symptoms in older men in Sydney, Australia. *Aust N Z J Surg* 2000;70:322-8.
3. Parazzini F, Menchini Fabris F, Bortolotti A, *et al.*: Frequency and determinants of erectile dysfunction in Italy. *Eur Urol* 2000;37:43-9.
4. Martin-Morales A, Sanchez-Cruz JJ, Saenz de Tejada I, *et al.*: Prevalence and independent risk factors for erectile dysfunction in Spain: results of the Epidemiologia de la Disfuncion Erectil Masculina Study. *J Urol* 2001;166:569-74.
5. Hunter DJ, McKee M, Black NA and Sanderson CF: Health status and quality of life of British men with lower urinary tract symptoms: results from the SF-36. *Urology* 1995;45:962-71.
6. Sonke GS, Kolman D, de la Rosette JJ, *et al.*: [Prevalence of lower urinary tract symptoms in men and its influence on their quality of life: Boxmeer Study] Prevalentie van lagere-urinewegsymptomen bij mannen en de invloed op hun kwaliteit van leven: het Boxmeer-onderzoek [Dutch]. *Ned Tijdschr Geneeskd* 2000;144: 2558-63.
7. Meuleman EJ, Donkers LH, Robertson C, *et al.*: [Erectile dysfunction: prevalence and effect on the quality of life; Boxmeer study] Erectiestoornis: prevalentie en invloed op de kwaliteit van leven; het Boxmeer-onderzoek [Dutch]. *Ned Tijdschr Geneeskd* 2001;145:576-81.
8. Sagnier PP, MacFarlane G, Teillac P, *et al.*: Impact of symptoms of prostatism on level of bother and quality of life of men in the French community. *J Urol* 1995;153:669-73.
9. MacMahon B and Trichopoulos D. Cohort Studies. In: MacMahon B and Trichopoulos D, editors. *Epidemiology: principles and methods*. 2nd ed. Boston: Little, Brown & Co, 1996:165-227.
10. Susser M: What is a cause and how do we know one? A grammar for pragmatic epidemiology. *Am J Epidemiol* 1991;133:635-648.
11. Berges RR, Pientka L, Hofner K, Senge T and Jonas U: Male lower urinary tract symptoms and related health care seeking in Germany. *Eur Urol* 2001;39:682-7.
12. Jacobsen SJ, Guess HA, Panser L, *et al.*: A population-based study of health care-seeking behavior for treatment of urinary symptoms. The Olmsted County Study of Urinary Symptoms and Health Status Among Men. *Arch Fam Med* 1993;2:729-35.
13. Roberts RO, Rhodes T, Panser LA, *et al.*: Natural history of prostatism: worry and embarrassment from urinary symptoms and health care-seeking behavior. *Urology* 1994;43:621-8.
14. Jacobsen SJ, Girman CJ, Guess HA, *et al.*: Do prostate size and urinary flow rates predict health care-seeking behavior for urinary symptoms in men? *Urology* 1995;45:64-9.
15. Wolfs GG, Knottnerus JA, Van der Horst FG, Visser AP and Janknegt RA: Determinants of doctor consultation for micturition problems in an elderly male population. *Eur Urol* 1998;33:1-10.
16. Simpson RJ, Lee RJ, Garraway WM, King D and McIntosh I: Consultation patterns in a community survey of men with benign prostatic hyperplasia. *Br J Gen Pract* 1994;44:499-502.
17. Coughlin SS: Recall bias in epidemiologic studies. *J Clin Epidemiol* 1990;43:87-91.
18. Britton JP, Dowell AC and Whelan P: Prevalence of urinary symptoms in men aged over 60. *Br J Urol* 1990;66: 175-6.
19. Norman RW, Nickel JC, Fish D and Pickett SN: 'Prostate-related symptoms' in Canadian men 50 years of age or older: prevalence and relationships among symptoms. *Br J Urol* 1994;74:542-50.
20. Chute CG, Panser LA, Girman CJ, *et al.*: The prevalence of prostatism: a population-based survey of urinary symptoms. *J Urol* 1993;150:85-9.
21. Garraway WM, Collins GN and Lee RJ: High prevalence of benign prostatic hypertrophy in the community. *Lancet* 1991;338:469-71.

22. Bosch JL, Hop WC, Kirkels WJ and Schröder FH: Natural history of benign prostatic hyperplasia: appropriate case definition and estimation of its prevalence in the community. *Urology* 1995;46:34-40.
23. Sagnier PP, Girman CJ, Garraway M, *et al.*: International comparison of the community prevalence of symptoms of prostatism in four countries. *Eur Urol* 1996;29:15-20.
24. Guess HA, Chute CG, Garraway WM, *et al.*: Similar levels of urological symptoms have similar impact on Scottish and American men–although Scots report less symptoms. *J Urol* 1993;150:1701-5.
25. Christensen MM and Bruskewitz RC: Clinical manifestations of benign prostatic hyperplasia and indications for therapeutic intervention. *Urol Clin North Am* 1990;17:509-16.
26. Guess HA, Jacobsen SJ, Girman CJ, *et al.*: The role of community-based longitudinal studies in evaluating treatment effects. Example: benign prostatic hyperplasia. *Med Care* 1995;33:AS26-35.
27. Girman CJ, Jacobsen SJ, Guess HA, *et al.*: Natural history of prostatism: relationship among symptoms, prostate volume and peak urinary flow rate. *J Urol* 1995;153:1510-5.
28. Doll HA, Black NA, McPherson K, *et al.*: Mortality, morbidity and complications following transurethral resection of the prostate for benign prostatic hypertrophy. *J Urol* 1992;147:1566-73.
29. Bruskewitz RC, Larsen EH, Madsen PO and Dorflinger T: 3-year followup of urinary symptoms after transurethral resection of the prostate. *J Urol* 1986;136:613-5.
30. Barry M and Roehrborn C. Men's health: Benign prostatic hyperplasia. In: Barton S, editor. *Clinical Evidence*. London: BMJ Publishing Group, 2001:649-659.
31. Clifford GM and Farmer RD: Medical therapy for benign prostatic hyperplasia: a review of the literature. *Eur Urol* 2000;38:2-19.
32. Hansen BJ, Meyhoff HH, Nordling J, *et al.*: Placebo effects in the pharmacological treatment of uncomplicated benign prostatic hyperplasia. The ALFECH Study Group. *Scand J Urol Nephrol* 1996;30:373-7.
33. McConnell JD, Bruskewitz R, Walsh P, *et al.*: The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia. Finasteride Long-Term Efficacy and Safety Study Group. *N Engl J Med* 1998;338:557-63.
34. Abrams P: Objective evaluation of bladder outlet obstruction. *Br J Urol* 1995;76:11-5.
35. Nordling J: Functional assessment of the bladder. *Ciba Found Symp* 1990;151:139-47.
36. Diokno AC, Wells TJ and Brink CA: Comparison of self-reported voided volume with cystometric bladder capacity. *J Urol* 1987;137:698-700.
37. Gilpin SA, Gosling JA and Barnard RJ: Morphological and morphometric studies of the human obstructed, trabeculated urinary bladder. *Br J Urol* 1985;57:525-9.
38. Lepor H, Sunaryadi I, Hartanto V and Shapiro E: Quantitative morphometry of the adult human bladder. *J Urol* 1992;148:414-7.
39. Pel JJ and van Mastrigt R: The variable outflow resistance catheter: a new method to measure bladder pressure noninvasively. *J Urol* 2001;165:647-52.
40. Pel JJ and van Mastrigt R: Non-invasive measurement of bladder pressure using an external catheter. *Neurourol Urodyn* 1999;18:455-75.
41. Larsson G and Victor A: Micturition patterns in a healthy female population, studied with a frequency/volume chart. *Scand J Urol Nephrol Suppl* 1988;114:53-7.
42. Abrams P and Klevmark B: Frequency volume charts: an indispensable part of lower urinary tract assessment. *Scand J Urol Nephrol Suppl* 1996;179:47-53.
43. Palnaes Hansen C and Klarskov P: The accuracy of the frequency-volume chart: comparison of self-reported and measured volumes. *Br J Urol* 1998;81:709-11.
44. Siltberg H, Larsson G and Victor A: Frequency/volume chart: the basic tool for investigating urinary symptoms. *Acta Obstet Gynecol Scand Suppl* 1997;166:24-7.
45. Klomp MLF, Gercama AJ, De Jonge-Wubben JGM, *et al.*: [Dutch College for General Practitioners Guideline for lower urinary tract symptoms in older men.] NHG-standaard Bemoeilijkte mictie bij oudere mannen (eerste herziening) [Dutch]. *Huisarts Wet* 1997;40:114-124.

46. van Mastrigt R and Eijskoot F: Analysis of voided urine volumes measured using a small electronic pocket balance. *Scand J Urol Nephrol* 1996;30:257-63.
47. Lagro-Janssen ALM, Breedveldt Boer HP, van Dongen JJAM, *et al.*: [Dutch College for General Practitioners Guideline for urinary incontinence.] NHG-standaard Incontinentie voor urine [Dutch]. *Huisarts Wet* 1995;38: 71-80.
48. Derby CA, Araujo AB, Johannes CB, Feldman HA and McKinlay JB: Measurement of erectile dysfunction in population-based studies: the use of a single question self-assessment in the Massachusetts Male Aging Study. *Int J Impot Res* 2000;12:197-204.
49. Ralph D and McNicholas T: UK management guidelines for erectile dysfunction. *BMJ* 2000;321:499-503.
50. Drenth JJ and van Lankveld JJDM. [Sexual disorders in males.] Seksuele stoornissen bij mannen [Dutch]. In: Slob AK, Vink CW and Moors JPC, editors. *[Textbook of Sexology] Leerboek seksuologie*. Houten: Bohn Stafleu Van Loghum, 1998:200-226.
51. Hengeveld MW and Gianotten WL: [Erectile disorders: the reality] Erectiestoornissen: de actuele situatie [Dutch]. *Ned Tijdschr Geneeskd* 2001;145:1381-4.
52. Johannes CB, Araujo AB, Feldman HA, *et al.*: Incidence of erectile dysfunction in men 40 to 69 years old: longitudinal results from the Massachusetts male aging study. *J Urol* 2000;163:460-3.
53. Aytac IA, Araujo AB, Johannes CB, Kleinman KP and McKinlay JB: Socioeconomic factors and incidence of erectile dysfunction: findings of the longitudinal Massachussetts Male Aging Study. *Soc Sci Med* 2000;51:771-8.
54. Araujo AB, Johannes CB, Feldman HA, Derby CA and McKinlay JB: Relation between psychosocial risk factors and incident erectile dysfunction: prospective results from the Massachusetts Male Aging Study. *Am J Epidemiol* 2000;152:533-41.
55. Eid JF, Nehra A, Andersson KE, *et al.*: First international conference on the management of erectile dysfunction. Overview consensus statement. *Int J Impot Res* 2000;12:S2-5.
56. Sullivan ME, Keoghane SR and Miller MA: Vascular risk factors and erectile dysfunction. *BJU Int* 2001;87:838-45.
57. Feldman HA, Johannes CB, Derby CA, *et al.*: Erectile dysfunction and coronary risk factors: prospective results from the Massachusetts male aging study. *Prev Med* 2000;30:328-38.
58. MacMahon B and Pugh TF: *Epidemiology: principles and methods*. 2nd ed. Boston: Little, Brown & Co, 1970.
59. Rothman KJ: *Modern epidemiology*. Boston/Toronto: Little, Brown and Company, 1986.
60. Vale J: Benign prostatic hyperplasia and erectile dysfunction–is there a link? *Curr Med Res Opin* 2000;16:s63-7.
61. Morley JE: Androgens and aging. *Maturitas* 2001;38:61-71.
62. Morley JE and Perry HM, 3rd: Androgen deficiency in aging men. *Med Clin North Am* 1999;83:1279-89.
63. de Bruin AF, Diederiks JP, de Witte LP, Stevens FC and Philipsen H: Assessing the responsiveness of a functional status measure: the Sickness Impact Profile versus the SIP68. *J Clin Epidemiol* 1997;50:529-40.
64. Jacobs HM, Luttik A, Touw-Otten FW and de Melker RA: [The sickness impact profile; results of an evaluation study of the Dutch version] De 'sickness impact profile'; resultaten van een valideringsonderzoek van de Nederlandse versie [Dutch]. *Ned Tijdschr Geneeskd* 1990;134:1950-4.

Chapter 13

Summary

Symptoms of the lower urogenital tract are common and bothersome in older men. With the ageing of the population, the number of men visiting their physician will increase significantly, with a related demand on health care resources. In the evaluation of lower urogenital tract symptoms, physicians are still hampered by a lack of commonly agreed definitions and normal values, by well founded insight in their natural history and, as a consequence, by the lack of unambiguous diagnostic and therapeutic tools. This thesis addresses some of these problems by applying basic epidemiological research methods around the following topics.

Lower urinary tract symptoms (LUTS). Medical doctors are traditionally educated to classify LUTS as "prostate related", but it was shown that there is only a weak association between symptoms and benign enlargement of the prostate and bladder outflow obstruction. In this study, the prevalence of LUTS and benign prostatic hyperplasia was estimated according to different definitions, as well as normal values of several components of lower urinary tract function.

Sexual dysfunction. Erectile dysfunction is common in older men, but the prevalence of this condition in the general population remains unclear, due to differences in definitions and methods used in the various reports on this topic. Moreover, only little is known about factors that are related to erectile dysfunction in the general population. Even less is known about the epidemiology of ejaculatory dysfunction in older men. In this thesis, both conditions and related factors are described.

Health status. Lower urogenital tract dysfunction has been reported as a determinant of reduced perceived health status. In this thesis, disease specific health status and general health status are described in relation to lower urogenital tract dysfunction and other concurrent factors.

To study the mentioned topics, the Krimpen study was conducted. In this study, all eligible men, 50 to 75 years old living in Krimpen aan den IJssel, were invited to complete a 113-item questionnaire, a three-day frequency-volume chart and to visit a health centre and a urology outpatient department of the University Hospital Rotterdam for additional measurements, including blood pressure, urinalyses, body height and weight, digital rectal examination, transrectal ultrasound of the prostate, uroflowmetry, post void residual urine volume, and serum prostate specific antigen. In total, 1688 men participated (response rate 50%). In a nonresponse study, the representativeness of the study population was assessed.

In chapter 3, we described that the participants were representative for the total population: they were similar to those not responding on marital status, educational level, smoking and drinking habits, treatment of chronic diseases, but had a slightly lower perceived general health status and more LUTS. The prevalence of LUTS (defined as an International Prostate Symptoms Score [IPSS] greater than 7) increased from 21% in men 50 to 54 years old to 37% in men 70 to 78 years old. Adjustment for nonresponse bias resulted in substantially lower prevalence rates; 12 and 24%, respectively. The prevalence of benign prostatic hyperplasia depended largely on the used definition. Adjustment for nonresponse bias resulted in lower prevalences for all definitions used.

In chapter 4, we described that diurnal voiding frequency was independent of age (median 5 voids, interquartile range 4 to 6), and was higher in men with clinical benign prostatic hyperplasia. Nocturnal voiding frequency increased with advancing age. Two nocturnal voids were reported in 30% of men 50 to 54 years old and in 60% of those aged 70 to 78 years. Three nocturnal voiding episodes were present in 4% and 20%, respectively. Nocturnal voiding frequency was related to benign prostatic hyperplasia and nocturnal polyuria. We noted poor agreement between the IPSS question on nocturia and the responses on the frequency-volume chart. The latter is preferred when estimating nocturnal voiding frequency.

In chapter 5, we re-analysed the role of increased nocturnal urine production in increased nocturnal voiding frequency. Nocturnal voiding frequency is an indicator of nocturnal urine production, as was expected. In contrast, however, increased nocturnal urine production is only a poor predictor of nocturnal voiding frequency. Therefore, the use of nocturnal urine production as an explanatory variable for nocturnal voiding frequency seems of little value.

In chapter 6, we described that 24-hour voided volumes were independent of age (median 1506 ml, interquartile range 1160 to 1950). The average volume per void and the functional bladder capacity (defined as the largest single voided volume) declined with advancing age. Functional bladder capacity was lower in men with reduced maximum urinary flow rate (less than 15 ml/sec) and independent of the post-void residual. Multivariate analyses showed no significant effect of prostate enlargement. Functional bladder capacity was strongly related with LUTS; a low capacity coincided with higher IPSS scores. The presence of moderate to severe LUTS (IPSS greater than 7) was independent of prostate volume, but dependent on age, a reduced flow rate, post void residual volume and functional bladder capacity. Frequency-volume charts are a valid, easy-to-use, and low-cost method to determine functional bladder capacity as an aspect of urinary tract (dys-)function in the evaluation of men with LUTS and to determine treatment options for LUTS.

In chapter 7, the circadian urine production pattern is shown to be clear in men aged 50 to 65 years in contrast to the pattern in 65 to 78 year old men. In the latter group, the pattern was attenuated, mainly due to increased nocturnal urine production. Smoking, use of diuretic drugs, post void residual, and a 24-hour voided volume greater than 2500 ml attenuated the circadian pattern in favour of daytime urine production.

In chapter 8, prevalence rates of erectile and ejaculatory dysfunction are presented for the study population, based on the participants responses to the International Continence Society (ICS) sex questionnaire. The prevalence of significant erectile dysfunction (i.e. erections of severely reduced

rigidity or no erections) increased from 3% in men 50 to 54 years old to 26% in men 70 to 78 years old. In the same age groups, the prevalence of significant ejaculatory dysfunction (i.e. ejaculations with significantly reduced volume or no ejaculations) increased from 3% to 35%. Pain or discomfort during ejaculation was rare (1%) and independent of age. In general, men were more concerned about erectile dysfunction than about ejaculatory dysfunction. However, most men had no or only little concern about their dysfunction. The percentage of men who reported being sexually active declined with increasing age and was lower in men with erectile and ejaculatory dysfunction and in men without a partner. In sexually active men, 17% to 28% had no normal erections, indicating that with advancing age normal erections are not an absolute prerequisite for a sexually active life.
In chapter 9, correlates for erectile and ejaculatory dysfunction are described. Age, obesity and urinary tract symptoms were the most important correlates of significant erectile dysfunction in the population. Cardiac problems, chronic obstructive pulmonary disease and smoking were other independent correlates. Significant ejaculatory dysfunction was largely related to age, decreased erectile function and previous prostatic surgery.
In chapter 10, a systematic review of the literature on the prevalence of erectile dysfunction is presented. Using a specially developed 12-item criteria list, the methodological quality of 23 included studies ranged from 6 to 12. The prevalence of ED ranged from 2% in men younger than 40 years to 86% in men 80 years and older. Comparison between prevalence data was hampered by major methodological differences between studies, particularly in the use of various questionnaires and different definitions of ED. We stress the importance of providing all necessary information when reporting on the prevalence of ED.
In chapter 11, correlates of health status in men with and without lower urogenital tract dysfunction are described. Health status was analysed using the Inventory of Subjective Health and three domains of the Sickness Impact Profile. All chosen characteristics were related to at least two of these domains. Multivariate regression analyses yielded that LUTS and cardiac symptoms were strongly associated with sub optimal scores of all four domains. Chronic obstructive pulmonary disease and drugs for abdominal symptoms were related to three domains; erectile and ejaculatory dysfunction, muskuloskeletal or psycho(ana)leptic drugs and marital status to two domains. LUTS and cardiac symptoms were the most important correlates for health status in the current study, when adjusted for various other correlates.

The data of this study provide important information on lower urogenital tract dysfunction in older men, which can be used in daily practice and are added to the growing epidemiological database on this topic. The relations described in this part of the Krimpen study cannot be interpreted as causally related factors, because the analyses were performed on cross-sectionally collected data. Most of the described associations, however, seem physiologically plausible and are consistent with previous studies, suggesting that a true relation may be present.
Frequency-volume charts have shown to be valid for collecting data on urinary tract function in a patient's natural environment. Especially data on voiding frequency, urine production and bladder capacity can be derived from these easy-to-use, low-cost, and valid charts.

Based on our analyses, we suggest that bladder dysfunction should be recognised as an associated factor for lower urinary tract symptoms in older men. In other words, LUTS that are related to changes in the urinary bladder are not only important in women, but also in men. In older men, LUTS are the results of the interaction between age related changes in the bladder wall, bladder changes secondary to benign prostatic obstruction, prostate enlargement, and non-urinary tract related factors.

Samenvatting

Plasklachten komen evenals genitale klachten veel voor bij oudere mannen. Met het ouder worden van de populatie wordt verwacht dat het aantal mannen dat voor deze problemen de huisarts bezoekt toe zal nemen. Bij de analysering van deze klachten worden artsen beperkt door een gebrek aan eenduidige definities, normaal waarden en gegevens over het natuurlijk beloop. Ten gevolge daarvan is er ook een gebrek aan eenvoudige diagnostische en therapeutische handvaten. In dit proefschrift wordt een aantal van deze zaken beschreven, waarbij basale epidemiologische methoden worden toegepast op de volgende onderwerpen.

Plasklachten. Artsen worden traditioneel opgeleid om plasklachten bij oudere mannen te verklaren als "prostaat-gerelateerd". Toch is eerder al aangetoond dat er slechts een zwak verband bestaat tussen plasklachten enerzijds en een goedaardige vergroting van de prostaat en urine uitstroom belemmering anderzijds. In deze studie wordt het voorkomen van plasklachten en goedaardige prostaatvergroting beschreven aan de hand van verschillende definities. Tevens worden normaalwaarden van verscheidene aspecten van het functioneren van de lage urinewegen gepresenteerd.

Seksuele disfunctie. Erectiestoornissen komen veel voor bij oudere mannen, maar de prevalentie en de gerelateerde factoren in de algehele populatie is onduidelijk. Dit wordt vooral veroorzaakt doordat verschillende methoden en definities zijn gebruikt in verschillende studies op dit onderwerp. Nog minder is bekend van de epidemiologie van ejaculatiestoornissen. In dit proefschrift wordt de prevalentie van beide aandoeningen beschreven, evenals de daarmee samenhangende ervaren hinder en de relatie met seksuele activiteit.

Welbevinden. Plasklachten en erectiestoornissen zijn beschreven als determinanten van afgenomen ervaren welbevinden. In dit proefschrift worden klachtenspecifiek en algemeen (on)welbevinden geanalyseerd in relatie tot andere bijkomende factoren.

Om de genoemde onderwerpen te bestuderen is de Krimpen-studie opgezet en uitgevoerd. In deze studie werden alle geschikte mannen (mannen zonder prostatectomie, prostaat- of blaaskanker of neurogeen blaaslijden die in staat waren vragenlijsten in te vullen en het gezondheidscentrum en de polikliniek te bezoeken) tussen 50 en 75 jaar oud woonachtig in Krimpen aan den IJssel uitgenodigd om een 113-item vragenlijst en een driedaags plasdagboek in te vullen en een gezondheidscentrum

en de polikliniek urologie te bezoeken voor aanvullende metingen. Bloeddruk, lengte en gewicht werden gemeten, urine geanalyseerd, een rectaal toucher, transrectale echografie van de prostaat, uroflowmetrie en residu bepaling uitgevoerd en het prostaat specifiek antigeen (PSA) gehalte bepaald. Zestienhonderdachtentachtig mannen namen deel aan de studie (respons percentage 50%). In een non-respons studie werd de representativiteit van de studie populatie geanalyseerd.

In hoofdstuk 3 beschrijven we dat de deelnemers representatief waren voor de gehele studiepopulatie: zij verschilden niet wat betreft burgerlijke status, opleidingsniveau, rook- en drinkgewoonten en chronische ziekten. Deelnemers hadden een lager ervaren algemeen welbevinden en meer plasklachten dan de nonresponders. De prevalentie van plasklachten (gedefinieerd als een score groter dan 7 op de Internationale Prostaat Symptoom Score, IPSS) steeg van 21% in mannen 50 tot 54 jaar tot 37% in mannen 70 tot 78 jaar oud. Correctie voor verschillen met nonresponders resulteerde in aanzienlijk lagere prevalenties, te weten 12% en 24%. De prevalentie van goedaardige prostaatvergroting hangt sterk af van de gebruikte definitie en de correctie voor verschillen met nonresponders.
In hoofdstuk 4 beschrijven we dat de plasfrequentie overdag onafhankelijk was van leeftijd (mediaan 5 episodes, interquartile range 4 tot 6) en hoger in mannen met goedaardige prostaatvergroting. Nachtelijke plasfrequentie nam toe met de leeftijd. Dertig procent van de mannen 50 tot 54 jaar oud en 60% van de 70 tot 78 jarigen rapporteerden twee nachtelijke plasbeurten; 4% en 20% van de mannen in deze leeftijdsgroepen rapporteerden drie nachtelijke micties. Nachtelijke plasfrequentie was gerelateerd aan goedaardige prostaatvergroting en toegenomen nachtelijke urineproductie. Er was een matige overeenkomst tussen de respons op de IPSS vraag naar nachtelijk plassen en de gegevens uit het plasdagboek. De laatste methode is het meest betrouwbaar voor het bepalen van de nachtelijke plasfrequentie.
In hoofdstuk 5 presenteren we de analyses van de relatie tussen urine productie en nachtelijke plasfrequentie. Nachtelijke plasfrequentie bleek, zoals verwacht, een indicator voor toegenomen nachtelijke urine productie. Nachtelijke urine productie was echter slechts een matige voorspeller voor nachtelijke plasfrequentie. Het gebruik van nachtelijke urine productie als een verklarende factor voor nachtelijke plasfrequentie lijkt daarom van weinig betekenis.
In hoofdstuk 6 beschrijven we dat het 24-uurs uitgeplast volume onafhankelijk was van de leeftijd (mediaan 1506 ml, interquartile range 1160 tot 1950). Het gemiddelde volume per mictie en de functionele blaascapaciteit (gedefinieerd als het grootste volume uit een enkele mictie) nam af met de leeftijd. Functionele blaascapaciteit was lager in mannen met afgenomen maximale urine stroomsnelheid (kleiner dan 15 ml/sec) en onafhankelijk van residu na mictie. Multivariate analyses toonden geen effect van prostaat vergroting. Functionele blaascapaciteit was sterk gerelateerd aan plasklachten; een lage blaascapaciteit ging samen met hogere IPSS scores (meer klachten). De aanwezigheid van matige tot ernstige plasklachten (IPSS groter dan 7) was onafhankelijk van prostaat vergroting, maar afhankelijk van leeftijd, afgenomen maximale urine stroomsnelheid, residu na mictie en functionele blaascapaciteit. Plasdagboeken vormen een goedkope, eenvoudige en valide

methode om functionele blaascapaciteit als een aspect van lage urinewegfunctie te bepalen bij de evaluatie van mannen met plasklachten en het bepalen van behandelopties voor plasklachten.
In hoofdstuk 7 tonen we dat het circadiane patroon van urine productie duidelijk was bij mannen tussen 50 en 65 jaar oud, terwijl bij mannen tussen 65 en 78 jaar dit patroon minder duidelijk was. In de laatste groep was het patroon vooral veranderd door een hogere nachtelijke urine productie. Roken, diuretica-gebruik, residu na mictie en een 24-uurs geplast volume groter dan 2,5 liter beïnvloeden het circadiane patroon ten gunste van de dagproductie.
In hoofdstuk 8 zijn de prevalenties van erectie- en ejaculatiestoornissen gepresenteerd voor de gehele studiepopulatie, gebaseerd op antwoorden op de International Continence Society (ICS) seks vragenlijst. De prevalentie van ernstige erectiestoornissen (gedefinieerd als afwezigheid van erecties of erecties met sterk verminderde hardheid) steeg van 3% in mannen tussen 50 en 54 jaar oud tot 26% in 70 tot 78 jarigen. In dezelfde leeftijdsgroepen nam de prevalentie van ernstige ejaculatiestoornissen (afwezigheid van ejaculaties of ejaculaties met sterk verminderd volume) toe van 3% tot 35%. Pijn of ongemak tijdens de ejaculatie was zeldzaam (1%) en onafhankelijk van de leeftijd. In het algemeen rapporteerden de deelnemers meer hinder van erectiestoornissen dan van ejaculatiestoornissen. Voor beide stoornissen was de ervaren hinder laag. Het percentage mannen dat aangaf seksueel actief te zijn nam af met de leeftijd en was aanzienlijk lager in mannen met erectie- of ejaculatiestoornissen en mannen zonder een partner. Van de seksueel actieve mannen had 17 tot 28% geen normale erecties wat aangeeft dat normale erecties geen absolute noodzaak zijn voor een seksueel actief leven. Gezien de sterke leeftijdsafhankelijkheid en de geringe ervaren hinder, lijkt het beter om 'erectiestoornis' aan te duiden met 'vermindering van erectiekwaliteit'.
In hoofdstuk 9 zijn aan erectie- en ejaculatiestoornissen gerelateerde factoren beschreven. Leeftijd, overgewicht en plasklachten waren de belangrijkste factoren voor ernstige erectiestoornissen in de populatie. Hartklachten, chronische obstructieve longziekte en roken waren andere gerelateerde factoren. Ernstige ejaculatiestoornissen waren voornamelijk gerelateerd aan leeftijd, afgenomen erectiekwaliteit en voorgaande prostaat operaties.
In hoofdstuk 10 is een systematisch overzicht van de beschikbare literatuur naar de prevalentie van erectiestoornissen in de open populatie gepresenteerd. Gebruik makend van een ontwikkelde 12-item scorelijst, bleek de methodologische kwaliteit van de 23 geïncludeerde studies te variëren van 6 tot 12. De meeste studies vertonen vele methodologische mankementen. De prevalentie van erectiestoornissen varieerde van 2% in mannen jonger dan 40 jaar tot 86% in mannen ouder dan 80 jaar. Vergelijking van prevalenties toonde grote verschillen tussen studies in dezelfde leeftijdscategorieën, maar werd ernstig beperkt door grote methodologische verschillen tussen de studies, vooral het gebruik van verschillende vragenlijsten en definities van erectiestoornissen. We benadrukken het belang van het leveren van alle noodzakelijke informatie bij het beschrijven van prevalenties van erectiestoornissen.
In hoofdstuk 11 zijn factoren welke gerelateerd zijn aan het algemeen welbevinden in mannen met en zonder plasklachten en genitaalklachten beschreven, zoals chronische ziekten, medicatie gebruik en sociale en leefstijl factoren. Welbevinden werd geanalyseerd met de Vragenlijst Onderzoek Ervaren Gezondheid en drie domeinen van de Sickness Impact Profile. Alle gekozen factoren waren gerelateerd

aan sub-optimale scores van één of meer welbevinden-domeinen. Multivariate regressie analyses toonden dat plasklachten en hartklachten aan alle vier domeinen sterk gerelateerd waren. Chronische obstructieve longziekte en medicatie voor abdominale klachten waren gerelateerd aan drie domeinen; erectie- en ejaculatiestoornissen, psycho(ana)leptica, medicatie voor aandoeningen van het bewegingsapparaat en burgerlijke staat aan twee domeinen. Plasklachten en hartklachten waren de belangrijkste factoren gerelateerd aan onwelbevinden, indien gecorrigeerd werd voor andere factoren. Plasklachten, alhoewel geassocieerd met minder mortaliteit dan andere chronische ziekte, hebben dus een grote impact op het welbevinden.

De gegevens van deze studie leveren belangrijke informatie over de functie van het urogenitaal stelsel bij oudere mannen, welke gebruikt kan worden in de dagelijkse praktijk en toegevoegd wordt aan de groeiende epidemiologische database van dit onderwerp. De beschreven relaties kunnen niet als causaal worden aangeduid omdat de data cross-sectioneel verzameld zijn. De meeste van de beschreven relaties komen echter overeen met eerdere studies en zijn fysiologisch plausibel. Dit suggereert dat een werkelijke relatie aanwezig kan zijn.
Plasdagboeken hebben aangetoond een valide methode te zijn om data van lage urinewegen-functie te verzamelen in een voor de patiënt natuurlijke omgeving. Vooral gegevens van plasfrequentie, urine productie en blaascapaciteit kunnen van het plasdagboek afgeleid worden.
Op basis van onze analyses suggereren wij dat blaasdisfunctie (h)erkend moet worden als een aan plasklachten gerelateerde factor in oudere mannen. Met andere woorden, plasklachten veroorzaakt door veranderingen in de urine blaas zijn niet alleen bij vrouwen van belang, maar ook bij mannen. Bij oudere mannen kunnen plasklachten veroorzaakt worden door de interactie van leeftijdsgerelateerde veranderingen van de blaaswand, blaas veranderingen door benigne prostaat obstructie, prostaatvergroting en niet aan de urinewegen gerelateerde factoren.

Part VI

Appendix

Publications related to the studies described in this thesis

Chapter 3:

M.H. Blanker, F.P.M.J. Groeneveld, A. Prins, R.M.D. Bernsen, A.M. Bohnen and J.L.H.R. Bosch: Strong effects of definition and nonresponse bias on prevalence rates of clinical benign prostatic hyperplasia: the Krimpen study of male urogenital tract problems and general health status. *British Journal of Urology International* 2000;85:665-71

Chapter 4:

M.H. Blanker, A.M. Bohnen, F.P.M.J. Groeneveld, R.M.D. Bernsen, A. Prins and J.L.H.R. Bosch: Normal voiding patterns and determinants of increased diurnal and nocturnal voiding frequency in elderly men. *Journal of Urology* 2000;164:1201-5

Chapter 5:

M.H. Blanker, R.M.D Bernsen, J.L.H.R. Bosch, S. Thomas, F.P.M.J. Groeneveld, A. Prins and A.M. Bohnen: Relation between nocturnal voiding frequency and nocturnal urine production in older men: a population-based study. *Urology (in press)*

Chapter 6:

M.H. Blanker, F.P.M.J. Groeneveld, A.M. Bohnen, R.M.D. Bernsen, A. Prins, S. Thomas and J.L.H.R. Bosch: Voided volumes: normal values and relation to lower urinary tract symptoms in elderly men, a community-based study. *Urology* 2001;57:1093-8

M.H. Blanker: Reply to editorial comment. *Urology* 2001;57:1098-1099

Chapter 7:

M.H. Blanker, R.M.D Bernsen, J.L.H.R. Bosch, S. Thomas, F.P.M.J. Groeneveld, A. Prins and A.M. Bohnen: Normal values and determinants of circadian urine production in older men: a population-based study. *Journal of Urology (in press)*

Chapter 8:

M.H. Blanker, J.L. Bosch, F.P. Groeneveld, A.M. Bohnen, A. Prins, S. Thomas and W.C. Hop: Erectile and ejaculatory dysfunction in a community-based sample of men 50 to 78 years old: prevalence, concern, and relation to sexual activity. *Urology* 2001;57:763-8.

Chapter 9:

M.H. Blanker, A.M. Bohnen, F.P.M.J. Groeneveld, R.M.D. Bernsen, A. Prins, S. Thomas and J.L.H.R. Bosch: Correlates for erectile and ejaculatory dysfunction in older Dutch men: a community-based study. *Journal of American Geriatrics Society* 2001;49:436-42

Chapter 8 and 9:

M.H. Blanker, A.M. Bohnen, F.P.M.J. Groeneveld, R.M.D. Bernsen, A. Prins, S. Thomas and J.L.H.R. Bosch: Erectiestoornissen bij mannen van 50 jaar en ouder: prevalentie, risicofactoren en ervaren hinder. *Nederlands Tijdschrift voor Geneeskunde* 2001;145:1404-9

Chapter 10:

J. Prins, M.H. Blanker, A.M. Bohnen, S. Thomas and J.L.H.R. Bosch: Prevalence of erectile dysfunction: a systematic review of population-based studies. *International Journal of Impotence Research (in press)*

Chapter 11:

M.H. Blanker, L.F.C. Driessen, J.L.H.R. Bosch, A.M. Bohnen, S. Thomas, A. Prins, R.M.D. Bernsen and F.P.M.J. Groeneveld: Health status and its correlates among Dutch community-dwelling older men with and without lower urogenital tract dysfunction. *European Urology* 2002;41(6):602-7

Chapter 12:

M.H. Blanker, J. Prins, A.M.Bohnen, S. Thomas, J.L.H.R. Bosch: De waarde van het plasdagboek bij oudere mannen met plasklachten. *(submitted)*

Dankwoord

Het mooie van een proefschrift is, dat het een gelegenheid biedt om mijn dank te verwoorden, waarbij de lengte van mijn dankwoord langer zal zijn dan mijn toespraakje op 11 juni 1999.

Het onderzoek zou niet kunnen zijn uitgevoerd zonder de betrokken medewerking van de deelnemers, hun huisartsen in Krimpen aan den IJssel en het team dat de dataverzameling heeft uitgevoerd (en nog steeds uitvoert). Door hen belandde ik in een gespreid bed.
Arthur Bohnen, mijn copromotor: jij hebt mij in 1995 op de afdeling welkom geheten en op het pad van het huisartsgeneeskundig onderzoek gezet. Ik had toen geen idee wat urologisch georiënteerd onderzoek mij ooit zou bieden. Sindsdien heb je me bij het onderzoek weten te inspireren om ermee door te gaan. Aan jouw veelzijdigheid, methodologische kunde, praktijkgerichtheid en vooral het vertrouwen dat ik van jou kreeg heb ik veel te danken.
Ruud Bosch, mijn eerste promotor: jouw enthousiasme voor het onderzoek, je wetenschappelijke kennis en natuurlijk de urologische kennis waren voor mij steeds een goede stimulans. Bijzonder dank ik je dat je altijd beschikbaar was, zolang je in Rotterdam was wel te verstaan.
Siep Thomas, mijn tweede promotor: dank voor de tekstuele commentaren en het slijpen van de manuscripten tot voor de (huisartsen-) praktijk relevante vraagstellingen en bewoordingen.
Frans Groeneveld, naast mijn promotoren en copromotor een van de motoren van het onderzoek: bedankt voor de humor die jij in het onderzoek hebt gebracht.
Ad Prins, ook sinds 1995 betrokken bij mijn gang in de wetenschap: ik dank je voor je altijd positieve en opbouwende commentaar en de link naar de praktijk.
Roos Bernsen, de statisticus van ons onderzoek: onze samenwerking lijkt ideaal: ik kom met onmogelijke (voor jou vaak onbegrijpelijke) klinische vraagstellingen; jij komt dan met mogelijke (voor mij vaak onbegrijpelijke) statistische oplossingen, of toch een gewone kruistabel. Dank voor jouw verhelderende bijdragen.

Jennie Prins, collega ceremoniemeester en nu collega onderzoeker: jij bracht de orde in onze review en op de kamer. Succes met jouw deel van de studie. Ook Boris Schouten wens ik succes bij zijn AIOTHO-traject binnen de Krimpen studie (of de Krimpen studie binnen zijn AIOTHO-traject). Laraine Isles-Visser poetste alle manuscripten op door de taalkundige missers met rood te omcirkelen; mijn dank daarvoor.

Hoewel ik mijn onderzoek vooral op mijn kamer heb uitgevoerd, was er buiten die kamer een afdeling met collega's. Na een jaar opleiding bleek het onderzoekersbestand fors uitgebreid en waren anderen vertrokken. Annet Lievense en Hanneke Otters (mijn collega AIOTHO's), Lya, Claudia, Christel, Vivian, Jaap, Bèr, Edith, Celinde, Anita, Sander, Herman, Mariet (de vrouw met de vieze tassen), Rebecca, Jacques, Max, Marjolein en Bart, dank ik voor de gezelligheid. Pim Witteman voor de geleverde streek en Ton van Os voor een bijzondere tijd in St. Petersburg. Petra Jellema weet al dat ik vind dat ze had moeten blijven, dus dat hoef ik haar niet te melden; toch succes in Amsterdam.
Hans Harmsen, mijn kamergenoot: jou dank ik eveneens voor de gezelligheid, maar ook voor een luisterend oor en de vaak lange gesprekken over 'ons vak'. Met jouw vertrek is een kleurrijk onderzoek helaas van de afdeling verdwenen. Succes met de afronding van je studie; je weet me te vinden.
Sita Bierma-Zeinstra, collega met een open deur en een Friese lach; veelvuldig liep ik bij je binnen voor weer eens een advies; dank dat je ook mijn geklaag hebt aangehoord.
Zonder Arianne Verhagen zou onze systematische review geen hole-in-one zijn geweest: dank voor je adviezen en collegialiteit.
Fits Bareman, plaatsvervangend hoofd van de huisartsenopleiding dank ik voor zijn vastberadenheid om de wereld te overtuigen dat AIOTHO's mensen zijn die ook in Rotterdam kunnen werken.

Zonder de combinatie van het onderzoek met mijn opleiding zou ik waarschijnlijk minder werkplezier hebben gehad. Om die reden ook een dankwoord voor enkelen die bij mijn opleiding een belangrijke rol speelden.
Sjors van Lieshout, arts in het Oosterscheldeziekenhuis in Goes, dank ik voor zijn bijdrage aan mijn dokter worden na mijn artsexamen.
Johan Tinke, mijn eerste huisartsopleider: voor de rust en gedrevenheid waarmee je mij hebt thuis gebracht in de huisartsenpraktijk uit ik mijn waardering. Guus en Antoinette waren een goed achtergrondkoor.
Mijn collega huisartsen in opleiding (Aziz, Daniëlle, Natalie, Marguérite, Ingrid, Deirdre, Janneke, Madja, Henry, Astrid, Dragan, Nienke en Caroline) en groepsbegeleiders (Frits, Karin, Simone en Anja) dank ik voor de terugkomdagen. In het bijzonder dank ik Astrid van Slobbe voor de verlevendiging en aanscherping van de opleiding: jouw snappertje heeft veel bijgedragen aan de eerste helft van mijn opleiding.
Ferdinand Thung en Monica Pop (psychiaters) en Frits Verpoort (unithoofd) begeleidden mij een half jaar tijdens mijn stage in het Deltaziekenhuis: jullie systematische en systeem benadering neem ik mee als bagage in de huisartsenpraktijk. Het verpleegteam dank ik voor de goede werksfeer.

Zonder vriendschap in mijn leven zou ik het werk niet hebben kunnen verrichten.
Papa en mama: Al ruim 30 jaar steunen jullie mij bij alles wat ik doe. Jullie onvoorwaardelijke liefde en vertrouwen waardeer ik meer dan ik op papier kwijt kan. Een toespraak heeft zoals jullie weten ook geen echte kans van slagen; dat heb ik al eens geprobeerd.
Mijn paranimfen Mischa en Michiel: Mischa, ik dank je dat je nu ook letterlijk naast mij wilt staan. Het figuurlijke mag ik al sinds het begin van onze studie meemaken. Ik hoop dat jij je net zo thuis zult voelen in de huisartsenpraktijk als ik; anders komt er niets terecht van onze oude afspraak.
Michiel (met Chantal natuurlijk): de vertrouwdheid van jullie aanwezigheid koester ik. Dat er nog maar lang M&M's verkocht zullen worden, en briketten natuurlijk. Vragen over mysterieus meteorisme laat ik door jou beantwoorden.
Utbus (Jacha, Paco en Lucas, Mireille en Bart, Thomas en Liesbeth, Martijn en Mariëlle): dank voor de mooie tijd van ons bestuursjaar en de jaren daarna.
Nabil, Leila en Ambra, voor de liefdevolle en levendige herinnering aan Kadri.
Richard en Els dank voor de rondjes 48.2. Eduard voor blijvende vriendschap (nu op afstand).
André en Mariëlle, Danny en Petra: dank voor jullie broeder- en schoonzusterschap. Ondanks onze verschillen en onze lage contactfrequentie voel ik me erg vertrouwd bij jullie.
Mijn schoonouders en Daniëlle en Arjan dank ik dat zij deze Rotterdammer in hun warme gezin hebben welkom geheten. Daniëlle: als je op de tiende jouw klus klaart ben ik trots op jouw afwezigheid.
Tot slot mijn vrouw: Lieve Simone, zonder jouw rust en gezelschap had ik mijn werk wellicht meer dan eens in de boom gehangen. Dank voor je liefde en trouw en voor het bedienen van de noodrem wanneer ik de wind in mijn rug niet meer onder controle had.

Curriculum vitae

Marcus Hendrikus (Marco) Blanker werd op 22 februari 1972 geboren te Rotterdam. Na het behalen van het VWO-diploma aan het Emmauscollege te Rotterdam in 1990 studeerde hij een jaar fysiotherapie aan de Hogeschool Rotterdam & Omstreken. In 1991 haalde hij het propedeutisch examen van die studie en maakte de overstap naar de studie geneeskunde aan de Erasmus Universiteit Rotterdam. Tijdens zijn afstudeeronderzoek onderzocht hij op het instituut huisartsgeneeskunde het beleid van Nederlandse huisartsen bij oudere mannen met mictieklachten (supervisor dr. A.M. Bohnen). In 1996 haalde hij het doctoraal examen. Aansluitend op het behalen van het artsexamen in 1998 werkte hij een jaar als poortarts op de spoedeisende hulp van het Oosterschelde Ziekenhuis te Goes en als parttime onderzoeker aan het instituut huisartsgeneeskunde van de Erasmus Universiteit Rotterdam. Sinds september 1999 werkt hij als arts in opleiding tot huisarts en onderzoeker (AIOTHO), waarbij de huisartsenopleiding en het onderzoek zoals beschreven in dit proefschrift worden gecombineerd.
In juni 2002 behaalde hij zijn *Master of Science* epidemiologie aan het Netherlands Institute for Health Sciences (NIHES, hoofd prof.dr. A. Hofman).
Op 11 juni 1999 huwde hij Simone Boks.