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Incidence, Etiology and Impact of Nocturia

Tampere Ageing Male Urologic Study

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ACADEMIC DISSERTATION
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Dedicated to
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Contents

List of original publications

This dissertation is based on the following original communications, and referred to in the text by Roman numerals.

I. Häkkinen J, Koskimäki J, Huhtala H, Tammela TLJ, Hakama M and Auvinen A (2004): Changes in prevalence of urinary symptoms in Finnish men: A population-based 5-year follow-up study. Scand J Urol Nephrol 38: 378-384

II. Häkkinen JT, Hakama M, Shiri R, Auvinen A, Tammela TLJ and Koskimäki J (2006): Incidence of nocturia in 50 to 80-year-old Finnish men. J Urol 176: 2541-2545

III. Häkkinen JT, Shiri R, Koskimäki J, Huhtala H, Tammela TLJ, Auvinen A and Hakama M (2007): Depression increases the incidence of nocturia – Tampere Ageing Male Urologic Study (TAMUS). Submitted for publication.

IV. Häkkinen JT, Hakama M, Huhtala H, Shiri R, Auvinen A, Tammela TLJ and Koskimäki J (2007): Impact of LUTS using bother index in DAN-PSS-1 questionnaire. Eur Urol 51: 473-478

Abbreviations

AVP	arginine vasopressin
AUA	American Urological Association
BI	bother index
BMI	body mass index
BPH	benign prostatic hyperplasia
CI	confidence interval
CNS	central nervous system
DAN-PSS-1	Danish Prostatic Symptom Score
DI	diabetes insipidus
DM	diabetes mellitus
FBC	functional bladder capacity
FVC	frequency volume chart
HUS	hours of undisturbed sleep
ICI	International Consultation on Incontinence
ICS	International Continence Society
IIEF	International Index of Erectile Function
IPSS	International Prostatic Symptom Score
LUTS	lower urinary tract symptoms
MHI-5	the 5-item version of the Mental Health Inventory
NBC	nocturnal bladder capacity
NP	nocturnal polyuria
NPS	nocturnal polyuria syndrome
N-QoL	Nocturia Specific Quality of Life
NUV	nocturnal urine volume
OAB	overactive bladder
OR	odds ratio
OSA	obstructive sleep apnea
QoL	quality of life
RP	radical retropubic prostatectomy
SPI	Symptom Problem Index
TAMUS	Tampere Ageing Male Urologic Study
TURP	transurethral resection of the prostate

Abstract

Objectives: To determine the prevalence and incidence of nocturia in 5 and 10-year follow-up studies in elderly male population. To describe deterioration and recovery of nocturia. To evaluate the effect of chronic diseases on the incidence of nocturia. To develop a new instrument for the evaluation of the bothersomeness of urinary symptoms.

Population and methods: A postal survey of a cohort of 3143 randomly selected men 50-70 years old at entry was conducted in Tampere and eleven neighbouring municipalities in 1994, 1999 and 2004. The questionnaire included questions related to sociodemographic status, medical conditions, urinary symptoms, sexual functioning, and the bother of the symptoms. Overall response rate was 70% in the 1994, 75% in 1999 and 76% in the 2004 survey. Nocturia data was attained from 1633 men in the first 5-year follow-up and from 1618 men in the second follow-up.

Results: The prevalence of nocturia (≥ 1 void per night) was 56% (95% CI 54-58) in 1994, 60% (95% CI 58-62) in 1999 and 74% (95% CI 72-76) in 2004. The prevalence increased with age, the lowest age-specific prevalence was 39% in 1994 in men 50 years old and highest 87% in 2004 in men 80 years old. 90% of the men with nocturia reported 1 or 2 voids per night. Three or more nightly voids were most common in the men 75 years old and over.

The incidence of nocturia was 75 (95% CI 66-85) cases per 1000 person-years in 1994-99 follow-up and 126/1000 (95% CI 113-149) in 1999-2004. Incidence also increased with age but not as linearly as prevalence.

Of the men with nocturia at baseline 7% deteriorated, 16% recovered and 77% had no change in the 1994-99 study. In the second follow-up the corresponding figures were 12%, 8% and 80%. The incidence of symptom deterioration increased and of recovery decreased with age.

Depressive symptoms, diabetes and arthritis were independent etiological factors of nocturia. Depressive symptoms significantly increased the incidence of moderate or severe nocturia (incidence rate ratio, RR 2.8, 95% CI 1.5-5.2). There was a 10% increase in risk by one point increment in the Mental Health Inventory (MHI-5) score. Nocturia did not increase the incidence of depressive

symptoms, thus the effect of depression was dose-respondent and unidirectional. Diabetes and arthritis increased the incidence of mild nocturia only.

Bother index (BI), a new measure of bothersomeness relative to symptom severity, was developed. BI ranged from 0.06 to 3.7 in lower urinary tract symptoms (LUTS) and showed much more variation than relative prevalence of symptoms (0.5 - 0.9).

Conclusions: The prevalence of nocturia is high in Finnish elderly men, and it increases with age. Nine out of ten men report mild symptoms. Although spontaneous recovery occurs in mild nocturia the overall trend is towards increasing prevalence and severity with increasing age.

Every year 10% of males over 50 years start to void during the night. The incidence of mild nocturia increases especially when men age from 50 to 60 years. In older men the incidence of severe nocturia increases markedly after the age of 75 years but the incidence of mild symptoms remains more stable. Recovery from nocturia is common in younger men, but happens seldom in men over 75 years.

Depressive symptoms are an independent risk factor for nocturia. Its effect is unidirectional; nocturia does not increase the incidence of depressive symptoms. The effect is also dose-related with an increase in depressive symptoms increasing the incidence of nocturia. Untreated depression has a stronger effect on the incidence of nocturia than symptoms during medical treatment. The effect of other chronic diseases on the incidence of nocturia is slight. Only diabetes and arthritis increased the risk of mild nocturia, but not that of moderate or severe nocturia.

The bothersomeness of a urinary symptom is an independent contribution to the assessment of LUTS. The BI may be a useful indicator of bothersomeness of urinary symptoms.

1. Introduction

Nocturia is a condition caused by nocturnal polyuria (NP), primary sleep disorders and lower urinary tract dysfunction (DuBeau 2006). It is one of the most common urinary symptoms but has only recently been recognised as a clinical entity (van Kerrebroeck et al. 2002). Although waking up for one nightly void is often considered part of normal ageing, frequent nocturia is bothersome and may markedly impair quality of life (QoL). Nocturia is one of the most common age-related alterations of the ageing lower urinary tract: frequency, nocturia and incontinence. Bothersome nocturia is a condition that can and should be evaluated and treated (Miller 2000, Wein and Abrams 2002).

The prevalence of nocturia is fairly well known worldwide due to recent intensive research of the epidemiology of lower urinary tract symptoms (LUTS). Nocturia studies have been numerous during the last ten years with a rapid increase in the knowledge of the etiology, pathophysiology and treatment of nocturia. Nocturia is a very common symptom affecting 56% to 73% of men 50 years old and older. Three or more nightly voids occur in 4% to 14% of the population (Beier-Holgersen and Bruun 1990, Norman et al. 1994, Sagnier et al. 1994, Koskimäki et al. 1998, Platz et al. 2002). Nocturia is more common with increasing age. The prevalence of nocturia is also well known in Scandinavia and Finland (Koskimäki et al. 1998, Andersson et al. 2004, Seim et al. 2005, Tikkinen et al. 2006b) but no follow-up studies have been conducted.

Overproduction of urine and over-activity of the bladder are the two pathophysiological mechanisms behind nocturia (Marschall-Kehrel 2004). Multiple conditions and diseases affect one or both of these and may lead to nocturia. Ageing independently, and also ageing with lower urinary tract symptoms (LUTS) indicative of benign prostatic hyperplasia (BPH) are the conditions most often related to nocturia (Marinkovic et al. 2004). Of the common chronic diseases diabetes, hypertension, heart failure, sleep apnea, Alzheimer's disease and depression have been associated with nocturia (Griffiths et al. 1994, Asplund 2002b, Umlauf et al. 2004, Yoshimura et al. 2004).

Recent knowledge of the etiology of nocturia is based on cross-sectional studies. In many studies the target populations consist of series of clinical patients or are otherwise not community-based. There is an abundance of follow-up studies of the etiology of nocturia. The temporal relation of the risk factor and the outcome is very important in estimating causality. In a cross-sectional study,

the detection of exposure and outcome is simultaneous and it is often unclear whether the exposure preceded the outcome in time or if it is actually the result of the effect of the outcome. Recall bias is also problematic in cross-sectional studies. Cohort studies do not have these problems while the incidence of the disease is detected in subjects originally free of it and data of the risk factors are collected at baseline before the follow-up period.

The Tampere Ageing Male Urologic Study (TAMUS) was initiated in 1994 to increase the knowledge of LUTS in Finnish male population. Our longitudinal study and population-based random target population was planned to overcome the problems and biases of cross-sectional prevalence studies and clinical materials.

2. Review of the literature

2.1. Terminology

Nocturia is the complaint when the individual has to wake at night one or more times to void (van Kerrebroeck et al. 2002). This International Continence Society's (ICS) definition applies to any number of voids at any time during the night. In a clinical setting nocturia is the number of voids recorded during a night's sleep: each episode is preceded and followed by sleep. Thus, the first void in the morning after waking up is not nocturnal. This stricter definition is useful and needed in the evaluation of nocturia episodes in shift workers who sleep during the day (Weiss 2006). When voiding occurs during sleep, it is called *nocturnal enuresis.* Those who wake with a need to void, but due to frail general condition are not able to reach the toilet before voiding, have a combination of nocturia and incontinence, not nocturnal enuresis. When waking is triggered by some other event than a desire to void, yet voiding is perceived to be necessary once awake, the person is considered to have nocturia (van Kerrebroeck et al. 2002).

According to the ICS terminology standardization report of 2002, *symptoms* are the subjective indicators of a disease or change in condition as perceived by the patient, caregiver or partner. *Signs* are observed by the physician, to verify and quantify them (Abrams et al. 2003). Lower urinary tract symptoms (LUTS) are always defined from the subjects' perspective.

LUTS are divided into three groups: storage, voiding and post-micturition symptoms. Storage symptoms include increased daytime frequency, nocturia, urgency and urge incontinence. Incontinence overall is described as stress, urge, mixed or continuous urinary incontinence. Voiding symptoms include slow stream, splitting or spraying, intermittent stream, hesitancy, straining and terminal dribble. Post micturition symptoms are experienced immediately after micturition and are classified as feeling of incomplete emptying and post micturition dribble (Abrams et al. 2003).

Nocturia, like other urinary symptoms, is evaluated with validated LUTS questionnaires and voiding lists. Voiding lists can be divided into three types, which provide different amounts of information: A micturition time chart records only the numbers and time-points of micturitions. A frequency volume chart

(FVC) also collects the voided volumes of each micturition. The most thorough way of recording micturition events is a bladder diary where the times of micturitions, voided volumes, incontinence episodes, pad usage, fluid intake and degree of urgency and incontinence are recorded. With a simple FVC all the important signs of nocturia can be evaluated: daytime frequency, nocturia, 24-hour frequency and 24-hour urine production. Additionally, polyuria, nocturnal urine volume (NUV), nocturnal polyuria (NP) and maximum voided volume can be derived from the FVC or bladder diary.

Polyuria is defined as measured production of more than 2.8 liters of urine in 24 hours in adults (70 kg person, voiding > 40 ml/kg).

NUV is defined as the total volume of urine passed between going to bed with the intention of sleeping and waking with the intention of rising. It excludes the last void before going to bed, but includes the first void after rising in the morning.

NP is present when an increased proportion of the 24-hour urine output occurs at night. In young adults this is more than 20% and in the elderly more than 33% (van Kerrebroeck et al. 2002). Nocturnal urine production is affected by age, but normal ranges have not yet been published.

Maximum voided volume is the largest volume of urine voided during a single micturition. According to the ICS recommendation maximum voided volume should replace the earlier term “functional bladder capacity” (FBC) (Abrams et al. 2003) but the latter is still widely used (Marinkovic et al. 2004, Weiss 2006). Nocturnal voided volume is respectively still often termed nocturnal bladder capacity (NBC).

2.2. Prevalence and incidence of nocturia

The prevalence of nocturia (≥ 1 void per night) varies from 31% to 82% in population based studies (Table 1). The prevalence of two or more and three or more nightly voids occurs from 9% to 41% and from 3% to 14% respectively. Mild nocturia is more common than severe nocturia and the prevalence increases markedly with age with up to 90% of individuals at the age of 80 years experiencing nocturia (Sagnier et al. 1996, Hunskaar 2005, DuBeau 2006). The prevalence of nocturia (≥ 2 voids per night) was 8% in 30-39 year-old men, 15-29% in 50-59 years old and 37-74% in 70-79 years old men (Garraway et al. 1991, Chute et al. 1993, Tsukamoto et al. 1995, Tan et al. 1997, Platz et al. 2002, Johnson et al. 2005, Yu et al. 2005). The great variation in the prevalence of nocturia between studies is obviously due to the different age ranges and age distributions of the study

Table 1. Prevalence of nocturia (%) in population-based studies.

Country	Sample size	Age range	Micturitions per night			Reference
			≥ 1	≥ 2	≥ 3	
Europe						
Denmark	955	60 – 70	-	-	14	Beier-Holgersen and Bruun 1990
England	578	60 – 85	82	25	-	Britton et al. 1990
Denmark	382	20 – 79	-	16	-	Sommer et al. 1990
Scotland	705	40 – 79	-	30	-	Garraway et al. 1991
Sweden	448	60 -	75	29	-	Asplund and Åberg 1992
Sweden	2,343	20 -	-	27	-	Hansen et al. 1994
England	423	40 -	-	14	-	Jolleys et al. 1994
France	1,815	50 – 80	69	24	7	Sagnier et al. 1994
Holland	1,692	55 -	58	26	8	Wolfs et al. 1994
Holland	502	55 – 74	75	29	-	Bosch et al. 1995
Sweden	7,763	45-	56	-	-	Malmsten et al. 1997
Finland	2,039	50 - 70	56	-	4	Koskimäki et al. 1998
Denmark	210	40 - 89	53	-	-	Kay et al. 1999
Austria	1,221	20 - 91	48	11	3	Schatzl et al. 2000
Holland	1,271	18 -	37	9		van Dijk et al. 2002
England	42,939	40-	55	18	3	McGrother et al. 2004
Sweden	387	41 - 81	50	-	10	Engström et al. 2004
Norway	23,220	20 -	53	19	8	Seim et al. 2003
Denmark	1,486	60-80	78	-	-	Bing et al. 2006
Finland	1,726	18-79	37	12	-	Tikkinen et al. 2006b
North America						
US	2,119	40 -	-	30	-	Chute et al. 1993
Canada	508	50 -	63	-	-	Norman et al. 1994
US	6,724	30 -	59	24	9	Platz et al. 2002
US	1,632	60 -	-	41	-	Johnson et al. 2005
Asia and Australia						
Japan	289	40 – 79	-	41	-	Tsukamoto et al. 1995
Australia	1,204	18-	-	13	-	Pinnock and Marshall 1997
Singapore	216	40 - 79	-	25	-	Tan et al. 1997
Korea	519	50 -	58	-	-	Lee E et al. 1998
Taiwan	844	30 -	-	16	-	Yu et al. 2005
Singapore	1,139	20-92	53	-	-	Liew et al. 2006
Qatar	545	20-63	31	11	3	Prasad et al. 2006

populations and in the absence of age-standardization of the reported prevalences in most studies. A crucial factor is the validity of the data collection method, i.e. how the individual interprets the as such simple question of the occurrence of

nocturia. Nocturia is not always troublesome and voiding less than 2 times per night is considered normal by many (Weiss 2006). Recall bias, i.e. difficulty in remembering events of the study period, easily affects the results, especially if mean values of nocturnal voids are elicited and if the time frame of the study is wide. A fluctuation in the nocturia frequency from one night to another has been reported (Lee et al. 1996, Yoshimura and Terai 2005) and this is not well controlled with the study questionnaires currently in use. One possibility to avoid recall bias and the effect of the symptom fluctuation is to consider the number of nocturic episodes as continuous variables and group them into categories e.g. 0; 1-2; 2-3 etc voids per night (Hunskaar 2005).

Nocturia is one of the most frequent LUTS, especially in elderly population. Other prevalent symptoms are weak stream, post-micturition dribble, daytime frequency and urgency (Chute et al. 1993, Norman et al. 1994, Tsukamoto et al. 1995). In addition to differences between individual studies, a clear international variation in prevalences can be seen in nocturia. In an international comparison of similar LUTS prevalence studies using the International Prostatic Symptom Score (IPSS) questionnaire, nocturia was most common in Japan and USA and clearly less common in France and Scotland (Sagnier et al. 1996). In most studies it is difficult to say what amount of differences in prevalence between populations is real and what is due to study design and cultural differences between countries. One study in Singapore found no differences between Chinese, Malayan, Indian and some ethnic minorities in the prevalence of nocturia (Liew et al. 2006). In overall LUTS and BPH, an early clinical impression has been that black men have the highest prevalence followed by Caucasians and Asians. Recently no difference between blacks and whites was found but Mexican-American men were slightly more likely to have LUTS (Platz et al. 2002). In a multicentre study the prevalences of LUTS in Asia and Australia were similar or greater than those in Europe and America (Homma et al. 1997).

Longitudinal nocturia studies are still rare. Numerous follow-up studies of LUTS and BPH have been published but nocturia is frequently not analysed separately but included in other urinary symptoms usually described by a symptom score such as IPSS. Change in the prevalence of nocturia has been estimated in studies in USA (Jacobsen et al. 1996), Scotland (Lee AJ et al. 1998) and Austria (Temml et al. 2003). These studies show an increase in cross-sectional prevalences and mean symptom scores during 3.5 to 5-year follow-up. Marked recovery was found in nocturia as well as other symptoms. However, deterioration was more common than recovery. Incidence rates for LUTS have been recently estimated in three studies (Verhamme et al. 2002, McGrother et al. 2004, Logie et al. 2005) but no separate incidence rates for nocturia have been published.

2.3. Natural course and effect on quality of life

Nocturia is infrequent in adolescence but its prevalence increases markedly with age (Barker and Mitteness 1988, Lundgren 2004). In longitudinal studies symptoms also tend to become more frequent (Jacobsen et al. 1996, Lee AJ et al. 1998). Despite this overall tendency to deterioration, marked recovery with up to 60% relief in nocturnal voiding frequency has been reported after two to five year follow-up (Lee AJ et al. 1996, Temml et al. 2003, Johnson et al. 2005). Fluctuation in number of voids during consecutive nights in the same individual has also been reported. Fluctuation was greatest in those with high nocturnal voiding frequency. The most prevalent reasons for the fluctuation reported by the patients were the amount of drinking, length of time in bed, feeling cold or warm while in bed and difficulties in falling in sleep (Yoshimura and Terai 2005).

Nocturia is one of the most bothersome symptoms in LUTS (Jolleys et al. 1994, DuBeau et al. 1995, Sagnier et al. 1995, Bertaccini et al. 2001, Eckhardt et al. 2001). The bothersomeness of nocturia stems from frequent awakening at night that is associated with sleep fragmentation and impairment in daytime functioning (Jennum 2002). Especially deleterious is waking soon after falling asleep because the restorative part of the sleep occurs during the first part of the night (Åkerstedt and Nilsson 2003, Stanley 2005). Sleep deprivation impairs cognitive and motor performance to a level similar to that produced by low levels of alcohol intoxication (Williamson and Feyer 2000). Various treatments have been shown to effectively diminish the number of nocturic episodes but little is known about the impact of these efforts on nocturia-related QoL (Homma et al. 2002, Johnson et al. 2003, Yoshimura et al. 2003) . Only recently the QoL aspect has attracted scientific and clinical interest with recommendations for investigations and treatment (Chapple et al. 2006). Because various bother scores in LUTS questionnaires are not symptom specific, a nocturia-specific Quality of Life questionnaire (N-QoL) have recently been developed and validated (Abraham et al. 2004).

Solitary nocturia is connected with ageing and not considered a very bothersome symptom. However, with validated questionnaires of health-related QoL Coyne et al. (2003) showed that even one nightly awakening to void is bothersome and affects health-related QoL and sleep. An increasing number of nightly voids significantly increased symptom bother, sleep disturbance and need for medical treatment (Coyne et al. 2003).

Persistent severe nocturia may lead to chronic sleep deprivation that causes daytime drowsiness and fatigue and may aggravate other diseases (Asplund and Åberg 1992, Hetta 1999). However, these consequences are associated with most

chronic diseases in the elderly (Asplund 1996, Koskimäki et al. 2001). In elderly patients with nocturia, impaired mental and physical health have been reported, but also in younger age a significant lowering in overall well-being, vitality and productivity in otherwise healthy and professionally active subjects has been observed (Kobelt et al. 2003). Nocturia may increase traffic accidents and falling injuries and even an elevated risk of death has been associated with voiding three or more times per night (Stewart et al. 1992, Asplund 1999, Jennum 2002).

Nightly waking for void also disturbs the partner's sleep. In a study by Boyle et al. (2003) 12% of the women who were woken at night because their partner got up to urinate reported that they were bothered quite a lot by this. If the partner was wakened to help the subject to the toilet 36% reported that this was quite bothering (Boyle et al. 2003). Nocturia may even increase the tendency to institutionalize elderly people because of the nocturnal disruption of other family members due to the repetitive awakenings of the elderly (Pollak and Perlick 1991).

2.4. Classification and pathophysiology of nocturia

The pathophysiological process of nocturia comprises three basic phenomena: polyuria, nocturnal polyuria (NP) and bladder storage problems (Marschall-Kehrel 2004). The classification of nocturia is based on voiding diaries and can be divided into four categories: nocturnal polyuria, low nocturnal bladder capacity (NBC), a combination of the two and polyuria (Weiss and Blaivas 2003, Homma 2005). The pathophysiology and underlying causes of nocturia are multifactorial affecting both nocturnal urine production and urinary bladder function. Further, all causes and conditions interact with each other as schematically illustrated in Figure 1 (Marschall-Kehrel 2004, Chang et al. 2006).

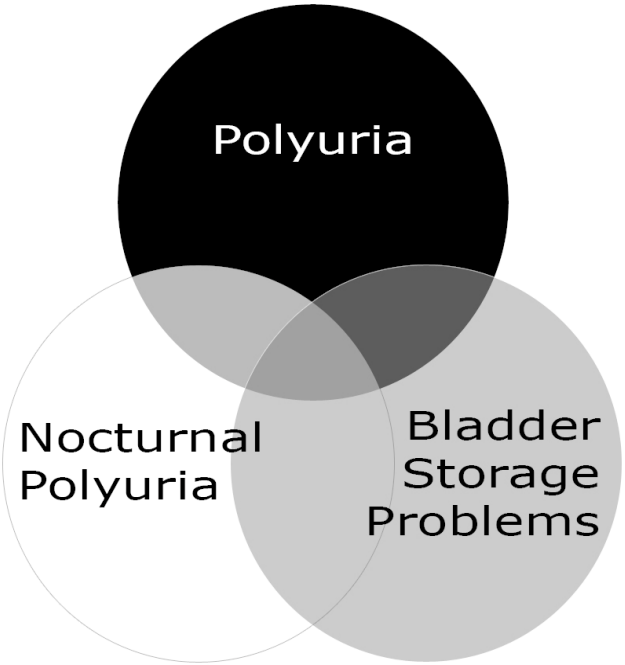

Figure 1. Pathophysiologic components of nocturia. (Reprinted from Urology 64(suppl 6A), Marschall-Kehrel D: Update on nocturia: the best of rest is sleep, page 22. Copyright (2006), with permission from Elsevier.)

Problems in the pathophysiology of nocturia can be condensed into two still unsolved questions: Why do some nocturic individuals produce abnormally large volumes of urine at night? And why do some nocturics void abnormally small volumes of urine at night and during the day? (Robertson and Nørgaard 2002).

2.4.1. Regulation of urine volume

The urine output is regulated by varying the amount of glomerular filtrate reabsorbed in nephron. Normally 90% of glomerural filtrate is reabsorbed in the proximal tubule and Henle's loop. Remaining filtrate passes to the distal tubule and collecting tubule where salt and water are removed. This mechanism is the basis for the salt and water homeostasis in the human body and it is controlled by aldosterone and antidiuretic hormone, arginine vasopressin (AVP) (Robertson and Berl 2000).

Vasopressin is synthesized in the hypothalamus, stored in and released from the posterior lobe of pituitary gland. Vasopressin decreases urine production and increases its concentration by promoting osmotic reabsorption of solute-free

water in the collecting tubules. The kidney is very sensitive to the antidiuretic effect of vasopressin and the level of antidiuresis varies directly with the plasma concentrations of AVP. The maximal effect results in very high osmolarity (1200 mOsmol/l) and low volume (0.5 l per day) of urine; and the minimal or absent effect in low osmolarity (≤ 100 mOsmol/l) and high volume (18 l per day), called *water diuresis*. Thus urine concentration is normally determined by the rate of AVP secretion that is regulated by osmoreceptors, which very sensitively detect the changes in plasma sodium concentration. (Robertson and Berl 2000).

Another mechanism in urine output regulation is *solute diuresis* that includes changes in solute excretion. An increase in the excretion of any solute (e.g. glucose, urea, sodium) increases urine production, irrespective of vasopressin activity. This is determined by diet and aldosterone, which is regulated in turn by the renin-angiotensin system, and hemodynamic variables (Robertson and Berl 2000). In conditions associated with altered urine production, some or all of these variables may have a role.

The newborn baby has no diurnal rhythm in diuresis. During the first years of life, nocturnal urine output gradually decreases with a parallel increase in daytime urine production (Asplund 2004). This is achieved by the maturation of the vasopressin system with the increase of night-time secretion of AVP. When the nocturnal urine volume decreases below bladder capacity, the child stop voiding during sleep, usually before the age of seven years (Rittig et al. 1989, Uygur et al. 1995). The diurnal voiding pattern, the decrease of nocturnal urine production, is largely due to a decrease in solute diuresis; the excretion of solutes such as urea, sodium and potassium, which are of dietary origin, are normally excreted promptly after meals. The other reason for the decrease in salt and water excretion is increase in urine concentration due to increase in AVP secretion or its action in kidney (Robertson and Nørgaard 2002). Secretion and release of vasopressin increases during the sleep (George et al. 1975) and this diurnal pattern of vasopressin secretion is linked to wake-sleep rhythm more than time of the day (Nadal 1996).

In a healthy adult, 25% or less of the 24-hour urine output occurs during the night and this circadian pattern is maintained until old age. After the age of 60 years, a gradual increase in the nightly urine production takes place (Kirkland et al. 1983). These changes are accompanied by diminution of diurnal rhythm of AVP secretion but the total 24-hour urine volume remains constant lifelong (Rittig et al. 1989, Matthiesen et al. 1996, Nakamura et al. 1996).

2.4.2. Nocturnal polyuria

Nocturnal polyuria is defined as the production of an abnormally large volume of urine during sleep (Saito et al. 1993, Weiss et al. 1998, van Kerrebroeck et al. 2002). On different occasions it has been specified as nocturnal urine production greater than 1.3 ml per minute (Asplund and Åberg 1992), NUV > 10 ml/kg (Homma et al. 2000), or more relatively as NUV > 20-33% of 24-hour urine production (van Kerrebroeck et al. 2002), or as nocturia index greater than 1.5; nocturia index being calculated as NUV divided by maximal voided volume (Weiss and Blaivas 2003). These different definitions have different sensitivity and lead to different identified prevalences in population (Rembratt et al. 2002). The ICS has adopted the relative definition and proposes it as a criterion for epidemiological and clinical studies. However, the ICS definition should be used only if 24-hour urine volume is within normal limits (≤ 40 ml/kg) (van Kerrebroeck et al. 2002).

In the presence of normal bladder capacity and absence of daytime frequency, the main explanation for nocturia is NP due to disturbance in the vasopressin system (Nakamura et al. 1996, Asplund 2004). The plasma concentration of AVP increases slowly with age, possibly because of a decrease in the sensitivity of vasopressin receptors in the kidney (Robertson and Nørgaard 2002). In NP, nocturnal urine production is increased associated with a lack of nocturnal increase in AVP secretion (Moon et al. 2004). A combination of deterioration of vasopressin circadian rhythm and very low or undetectable levels of vasopressin is called nocturnal polyuria syndrome (NPS). It is characterized by an increase in nocturnal urine output, in the most extreme cases reaching 85% of the 24-hour diuresis (Asplund 1995, Donahue and Lowenthal 1997). In NPS, the total 24-hour urine output is normal or only moderately increased (Asplund 2002a). A characteristic symptom in NPS is thirst that is most intense at night. NPS is estimated to occur in 3-4% of the population aged 65 years or over (Asplund 2004).

The regulation of thirst is closely related to NP. Nocturic elderly people need to get up to drink more often than non-nocturic individuals (Asplund 1999). In the absence of nocturnal AVP increase, nocturnal diuresis is not reduced and the person becomes thirsty and has to get up to drink to restore the fluid balance. Elderly persons often avoid drinking in the evening to reduce the number of nocturnal voids. In NPS, they do not benefit because due to increased diuresis they cannot resist the impulse to drink during the night. When nocturia is caused by low nocturnal bladder volume and no vasopressin deficiency is present the nocturnal urine excretion depends significantly on fluid intake of the previous evening (Griffiths et al. 1992) and the evening fluid restriction alleviates nocturia.

Other causes of NP include secondary defect of nocturnal vasopressin secretion or action due to sleep apnea; polydipsia in diabetes mellitus (DM), diabetes insipidus (DI) or psychiatric conditions; loss of third space due to congestive heart failure, venous insufficiency, excessive salt intake; hypoalbuminemia and nephrotic syndrome (van Kerrebroeck and Weiss 1999).

2.4.3. Low nocturnal bladder capacity

In nocturia caused by nocturnal bladder storage problems nocturnal urine volume exceeds the maximal voided volume and the patient feels an urge to void during sleep (Weiss and Blaivas 2002). In healthy adults 24-hour urinary volume varies from 1 to 1.5 litres and voided volumes from 400 ml to 750 ml with daytime voiding frequency of four to five in men. Ageing increases micturition frequency, the average of 4.3 voids during an 18-hour waking period in men in their third decade to 5.0 in men in their seventh decade and beyond (Burgio et al. 1991). With advancing age, there is also an increase in urgency most commonly due to detrusor overactivity. The prevalence of urgency increases from 40% to 49% in men respectively in their fifth and seventh decades (Sommer et al. 1990). Among elderly institutionalized persons with incontinence, 72% were found in urodynamic studies to have detrusor overactivity (Resnick et al. 1989). A consequence of OAB is diminished maximal voided volume. In a group of elderly men and women with average frequency of 8.6 voidings during the day and 1.8 during the night, the mean voided volume was 134 ml during the day and 181 ml in the night. 34% of the group had detrusor overactivity and their voided volume was only 89 ml during day and 98 ml during night (Saito et al. 1993).

Except for ageing itself, common causes of OAB and low nocturnal voided volumes include infravesical obstruction, acute or chronic cystitis with various etiologies, bladder tumors or stones, idiopathic detrusor overactivity, neurogenic voiding dysfunction, anxiety disorder, learned voiding dysfunction and the effects of some medications such as theophylline, caffeine and beta-blockers (Weiss and Blaivas 2003). The importance of detrusor overactivity in the symptoms of nocturic men was shown in a study of 114 men with LUTS. After 48-hour FVC and urodynamic evaluation, both NP and detrusor overactivity were independently associated with nocturia in multivariate analysis (Hirayama et al. 2005). Thus, through ageing, diminished nocturnal voided volumes due to OAB easily lead to nocturnal voiding. In simultaneous NP and low nocturnal voided volume, the increase in the number of nocturnal voids may become intolerable and also lead to urge incontinence.

2.4.4. Polyuria

In polyuria, the 24-hour urine production is abnormally high, according to the ICS definition more than 2.8 litres (van Kerrebroeck et al. 2002). Increased fluid intake causes increased day and night voiding frequency, which is due to urine overproduction in excess of bladder capacity (Weiss and Blaivas 2003). Causes of polyuria include DM, DI, primary thirst disorders and lithium induced polydipsia.

In diabetes, hyperglycaemia causes osmotic water diuresis and polyuria. Polyuria in diabetics may be an early sign of serious complications such as ketoacidosis or hyperglycaemic hyperosmolar nonketotic syndrome (Samos and Roos 1998). In DI, chronic water diuresis and polydipsia are caused by deficient antidiuretic function. It may be due to pituitary DI with a primary deficiency in AVP secretion, nephrogenic DI with resistance to AVP action, or primary polydipsia with a suppression of AVP by excessive fluid intake (Robertson and Nørgaard 2002).

2.5. Risk factors of nocturia

Nocturia is associated with many common diseases and chronic conditions. While most prevalent in elderly population, nocturia and chronic diseases may interfere in senescence. Pathophysiologic mechanisms of other diseases may alter urine excretion or bladder function. Also, many diseases in old age may have common underlying etiological factors (DuBeau 2006).

2.5.1. Sociodemographic factors

Age. Nocturia is highly correlated with age in cross-sectional and longitudinal studies (Sommer et al. 1990, Hansen et al. 1994, Pinnock and Marshall 1997, Platz et al. 2002, Tikkinen et al. 2006b). In a Norwegian study including all the men in one county any nocturia ($\geq$ 1 void per night) increased linearly throughout the lifespan. More severe nocturia was fairly stable in young men but increased rapidly after the age of 70 years. Prevalence and severity of nocturia increased significantly in any other decade-long age group compared to men 20-29 years old (Seim et al. 2003).

The level of education had no effect on nocturia in an Austrian study (Schatzl et al. 2000). Except age and gender, no other sociodemographic factor like marital status or education has been reported in other nocturia studies. In most earlier studies of BPH and LUTS, no association with marital status, education,

religion or living in urban versus non-urban area were found (Chyou et al. 1993, Platz et al. 2002).

2.5.2. Chronic conditions

Benign prostatic hyperplasia (BPH) is a risk factor for nocturia (Blanker et al. 2000, Seim et al. 2003, Yoshimura et al. 2004, Gourova et al. 2006). A common conception is that in these patients nocturia is mostly due to high post-void residual volume or OAB caused by infravesical obstruction. The fact that surgical treatment of BPH often fails to cure nocturia (Bruskewitz et al. 1986) and that after medical or surgical treatment of BPH the improvement in LUTS scores is low in nocturia (Yoshimura et al. 2003) suggests that other pathophysiological mechanisms are also involved. Matthiesen et al. (1996) studied 17 nocturic men referred for BPH treatment and 10 healthy controls. They found significant differences in NUV between the nocturic men and the controls. Patients with NP also had natriuresis and the authors assumed that one explanation for the defect in circadian sodium regulation may be pressure-induced lesions in the renal medullary and distal tubular system due to prolonged urinary tract obstruction (Matthiesen et al. 1996). The importance of NP in patients with LUTS was also supported in a recent study by Chang et al. (2006). They found NP in 83% of elderly LUTS patients; of these 59% had a small nocturnal voided volume and half of this group also had detrusor overactivity in a urodynamic study. A proportion of 44% had both NP and small nocturnal voided volume and a group of 44% had NP and infravesical obstruction (Chang et al. 2006). OAB alone without BPH, but due to irritating conditions like tumours, inflammation or stones has also been associated with small nocturnal voided volume and nocturia (Weiss 2006).

Diabetes mellitus (DM) and insipidus (DI). Diuresis is increased in unstable DM and DI, in most cases both in daytime and at night (Asplund 2004). Classically hyperglycaemia causes polyuria, which in turn may lead to nocturia (Samos and Roos 1998). Diabetes has been connected to nocturia in many population-based studies (Asplund 2002b, Yoshimura et al. 2004, Yu et al. 2005) but there are also contrary results and good glucose control in diabetes reduces nocturia (Blanker et al. 2000, Rembratt et al. 2003). Differences in study settings and target populations may explain some discrepancy in study results. For example, in a Swedish study, the effect of DM on the prevalence of nocturia in women was found only in patients treated with oral anti-diabetic medication, but not with those on insulin treatment or without medication (Asplund 2002b).

Hypertension. The hypothesis of the relation between NP and essential hypertension was published in 2000 (McKeigue and Reynard 2000). It postulates that NP and essential hypertension are manifestations of the same pathophysiological process, possibly defects in the nitric-oxide pathway. Patients

with NP are also probably at increased risk of developing heart failure. Epidemiological studies have reported contradictory results regarding the association between hypertension and nocturia. A large population-based study in Michigan, USA showed an increased risk in patients reporting a diagnosis of hypertension (Johnson et al. 2005). A Japanese study also found an increased risk, but the study sample was not truly population-based (Yoshimura et al. 2004). The Krimpen study (Blanker et al. 2000), which was the first population-based large study utilising FVC in data collection, found no significant correlation between nocturia and hypertension and a similar result was also reported in Tierp, Sweden (Rembratt et al. 2003). Another Dutch study from Maastricht showed a possible additive effect of parallel pathologic mechanisms causing nocturia. Individuals who had a combination of BPH, diabetes and hypertension had significantly increased risk, although none of the diseases alone was a significant predictor (Gourova et al. 2006).

Cardiac diseases. In a Swedish study with 6143 elderly men and women, nocturia ($\geq$ 3 voids per night) was associated with feeling irregular heartbeats, but not with spasmodic chest pain (Asplund 2002b). The relation between cardiac disease and nocturia is unclear, but it may be connected to disturbance in sodium homeostasis. Accordingly in subclinical heart failure, collection of fluid in the lower extremities and redistribution of the oedema fluid to the vascular compartment at night could cause nocturnal polyuria (McKeigue and Reynard 2000).

Respiratory diseases. Respiratory diseases increasing airway resistance, such as obstructive sleep apnea (OSA) and asthma are associated with increased renal sodium and water excretion by increased plasma ANP levels (Yalkut et al. 1996). Respiratory symptoms have not been evaluated in recent studies of nocturia epidemiology. In this paper OSA is discussed in the sleep disorders chapter.

Neurological diseases. Multiple system atrophy and Alzheimer's disease cause altered AVP secretion due to autonomic dysfunction in the central nervous system. The effect on diuresis is a DI like increase in urine output, which may cause nocturia, fluid loss and dehydration (Quinn 1989, Ouslander et al. 1998). In Alzheimer's disease, detrusor overactivity is also common. The combination of high nocturnal urine production, decreased nocturnal urine volume and cognitive impairment leads to incontinence in more than 80% of institutionalized Alzheimer's disease patients (Griffiths et al. 1994).

In epidemiological studies post-stroke symptoms and cerebrovascular diseases have been significantly associated with nocturia (Asplund 2002b, Gourova et al. 2006).

Depression. The first epidemiological evidence of the association between depression and nocturia was published by Asplund et al. in 2004. They found a 6.5 fold risk of nocturia ($\geq$ 2 voids per night) in men with major depression compared with men without depression (Asplund et al. 2004). Most AVP secretion takes place in the hypothalamus, in the neurons of the supraoptic and paraventricular nuclei (Lucassen et al. 1997). Zhou et al. (2001) found a markedly reduced synthesis and release of AVP in the suprachiasmatic nucleus of hypothalamus in depressed patients (Zhou et al. 2001). On the other hand, elevated AVP levels have been measured in seriously depressed individuals, but without normal nocturnal elevations in hormone plasma concentrations (van Londen et al. 1997). Circadian alterations in AVP secretion are crucial for reduced diuresis during the night (Asplund and Åberg 1991). Another finding, common for nocturia and depression, is a reduction of monoamines like serotonin and noradrenalin in the central nervous system (CNS) which cause both depression and overactive bladder in experimental animals (Steers and Lee 2001). Thus depression and nocturia may have a common etiology in disturbed vasopressin metabolism and depression may not only be the result of persistent nocturia and sleep deprivation but an individual with altered CNS monoamines could manifest both depression and OAB with nocturia.

Sleep disorders. Sleep has a dual role in nocturia. On the one hand nocturia impairs sleep quality (Tanaka et al. 1998) and is one of the most frequently reported reasons for disturbed sleep (Middelkoop et al. 1996, Kageyama et al. 2000). On the other hand, sleep-disordered breathing may lead to nocturia. Nocturia is common in OSA patients (Krieger et al. 1993, Umlauf et al. 2004). Additional evidence for an association between OSA and nocturia was found in a study where OSA patients were treated with a nasal continuous positive airway pressure device during sleep. After a one-year treatment period, the frequency of nocturnal voids was lowered significantly in the treatment group (Krieger et al. 1993).

The mechanism by which sleep-disturbed breathing causes nocturia has not been definitely identified. Increased atrial natriuretic hormone (ANP) levels and nocturnal urine volumes have been revealed in OSA patients (Umlauf et al. 2004). Airway obstruction during sleep cause decreases in the intra-thoracic pressure because of sustained ventilatory efforts. This, possibly together with hypoxia and acidosis, causes haemodynamic changes, which simulate central hypervolemia and give the heart a false signal to increase natriuresis and urine production to restore the homeostasis. Increased ANP secretion leads to decreased AVP secretion and polyuria (Lin et al. 1993, Umlauf et al. 2004, Oztura et al. 2006). In conclusion, the association between disturbed sleep and nocturia is multidirectional; poor sleep leads to nocturia, but waking from sleep may actually be triggered by sleep disturbance, not necessarily urge to void. In a sleep study, 76% of nocturnal micturitions were immediately preceded by an episode of obstructive apnoea or snoring (Pressman et al. 1996).

Surgical and medical treatments. Retropubic radical prostatectomy (RP) was associated with increased prevalence of nocturia in patients with no or only one nightly void preoperatively (Namiki et al. 2005). RP effectively reduces bladder outflow resistance and overall voiding symptoms improve, but incontinence, frequency and nocturia may affect some patients.

Diuretics have been used in the treatment of nocturia in patients with fluid accumulation. If taken six hours before going to bed, they result in a substantial reduction in nocturia (Reynard et al. 1998). Dosing time is crucial to induce polyuria only in the daytime. Increased risk of nocturia has been found for diuretics, antihypertensive drugs, cardiac medications other than drugs for angina pectoris and also for the overall use of medication (Blanker et al. 2000, van Dijk et al. 2002, Rembratt et al. 2003, Seim et al. 2003, Johnson et al. 2005).

2.5.3. Modifiable factors

Excessive drinking. Drinking large amounts of water to promote health has become popular. In older citizens, excessive fluid intake can be hazardous, for example increasing the risk of cardiac failure and inducing NP due to impaired rapid excretion of excess fluid (Miller 1997, Morley 2000). In normal ageing, the renal, hormonal and thirst regulatory systems controlling sodium and water balance changes and disbalancing events easily increase the risk of either retention or loss of sodium and water (Miller 1997). However, Johnson et al. found no association between nocturia and drinking or the amount of fluids at bedtime (Johnson et al. 2005).

Alcohol. Alcohol causes secondary water diuresis and may aggravate NP (van Kerrebroeck et al. 2002). On the other hand, alcohol also has quite complex effects on quality of sleep (Schneider 2002). Moderate alcohol consumption protected against nocturia in one study (Gourova et al. 2006) but four others failed to show a significant association between alcohol and nocturia (Blanker et al. 2000, Schatzl et al. 2000, Seim et al. 2003, Yoshimura et al. 2004).

Coffee. Like alcohol, caffeine acts as a diuretic causing rapid water diuresis. Drinking five cups or more of coffee in a day increased the risk of solitary nocturia (OR 1.10 CI 95% 1.04-1.17) but not of more frequent nocturia in a Norwegian study (Seim et al. 2003). No effect was found in the Michigan study, with the mean coffee consumption of only 2.7 cups per day (Johnson et al. 2005).

Smoking. Smoking had a protective effect against nocturia in three studies (Schatzl et al. 2000, Seim et al. 2003, Yoshimura et al. 2004). No effect was found in the Krimpen study (Blanker et al. 2000). The mechanism of the

negative association between smoking and nocturia is unclear. Because nicotine increases AVP secretion (Fuxe et al. 1989) the protective effect of smoking could be mediated by increase in nocturnal AVP leading to smaller nocturnal urine volumes. Compatible with this, smoking has been shown in a recent study to reinforce the diurnal rhythm of urine production (Blanker et al. 2002).

Obesity. Obesity (BMI $\geq$ 30), increases the risk of nocturia (Guilleminault et al. 2004, Tikkinen et al. 2006a). Waist/hip ratio also correlated positively with nocturia (Seim et al. 2003). Severe obesity is a multifactorial condition and associated with multiple diseases including diabetes, cardiac diseases and hypertension, which may result independently in nocturia.

2.6. The clinical role of nocturia

2.6.1. Diagnosis of nocturia

A diagnosis of nocturia is based on good history-taking, physical examination and laboratory testing. The aim is to differentiate polyuria, NP and OAB and reveal possible underlying reasons for them (Lundgren 2004). As the patients are likely to present symptoms that may be associated with nocturia, such as insomnia, daytime tiredness or related somatic disease, the clinician should be active in asking the patient about nocturia (Weiss and Blaivas 2003).

As nocturia often co-occurs with other LUTS, urinary symptom questionnaires are a useful help in history-taking. Both the DAN-PSS and the IPSS have been shown to be sensitive for detecting LUTS and although discrepancies between scores and objective measures have been found in other symptoms, nocturia is reliably reported by patients (Matzkin et al. 1996, Pannek et al. 1998). The DAN-PSS-1 does not discriminate between single void nocturia and two voids per night. However, the classification of nocturia into three severity grades probably describes the fluctuation of the actual number of nightly micturitions better than reporting the mean number of nightly voids only in other questionnaires. Additionally this may diminish the recall bias (Hunskaar 2005). Other important factors in focused history-taking are the amount and time of fluid intake, sleeping problems, medications and other diseases that may cause polyuria, NP or OAB (Weiss and Blaivas 2000).

The symptom assessment by history-taking and urinary questionnaires should be supplemented with the use of voiding diary or FVC (Jackson 1999, Weiss and Blaivas 2000). FVC data can provide three important parameters for the differential diagnosis of nocturia; voiding frequency, voided volume and volume distribution (Table 2). In polyuria both 24-hour urinary volume and voiding

frequency are elevated. In NP NUV is high, but total volume and frequency are normal. If the patient has OAB the frequency is elevated but other factors are normal.

Table 2. Relation of frequency, volume and distribution in the diagnosis of nocturia.

Parameter	Polyuria	Nocturnal polyuria	Bladder storage
24-h volume	Increased	Normal	Normal or decreased
Volume distribution	Day ≈ night	Day < night	Day ≈ night
No. of voids per 24 h	Increased	Normal	Increased

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After FVC or voiding diary evaluation and categorizing the patients as having polyuria, NP or OAB further examinations are planned (Weiss and Blaivas 2003). Congestive heart failure, renal insufficiency and DM should be identified among the patients with NP and appropriately examined. Polyuria should be further evaluated by an internist or nephrologist and sometimes by a psychiatrist. Because nocturia is very common in patients with OSA, sleep laboratory studies are indicated for nocturics, especially if they are obese, suffer from snoring or other sleep disturbances or have asthma (Krieger et al. 1993). Urodynamic studies have only a limited role in the diagnostics of nocturia. Pressure-flow study is needed to confirm suspected detrusor over or under-activity and bladder outlet obstruction, but have no role in other etiologies (Jackson 1999).

The evaluation of the impact of nocturia on quality of sleep and QoL is recommended as a part of diagnostic workshop (Chapple et al. 2006). In addition to general history, symptom specific tools for this are the N-QoL questionnaire and the measurement of hours of undisturbed sleep (HUS). HUS refers to the time from falling asleep to the first waking up to void and can be measured by sleep diaries or an actigraphy, a method that records body movements during sleep with a wrist-worn activity metre (Chartier-Kastler and Chapple 2006).

2.6.2. Treatment of nocturia

Behavioural therapy. Excess fluid intake results in nocturia even in healthy subjects. Nocturic patients should therefore during afternoon and evening drink only the amount of fluid that quenches their thirst (Asplund 2004).

Pharmacotherapy. In the pharmacotherapy of nocturia, the two main targets are detrusor overactivity and polyuria. Of the antimuscarinic agents, tolderodine, trospium, oxybutynin and propiverine are recommended for the treatment of detrusor overactivity by a committee of the 2nd International Consultation on Incontinence (ICI) (Andersson 2002). A novel antimuscarinic agent, solifenacine, also effectively improves the QoL of OAB patients (Kelleher et al. 2005).

The ICI committee could not find sufficient evidence in the recent literature to justify recommendations on the use of diuretics in nocturia (Andersson 2002). Morning dosing of diuretics can result in thirst and increased fluid intake during the afternoon leading to increased nocturnal urine production. If furosemide is taken six hours before going to bed, nocturnal diuresis and nocturia can be reduced (Reynard et al. 1998).

Desmopressin is a synthetic analogue of AVP used for years in diabetes insipidus and primary nocturnal enuresis (Abrams et al. 2002). It has been an effective and safe treatment in double-blind, placebo controlled, randomized studies with a low rate of adverse events (Asplund et al. 1999, Kuo 2002, Mattiasson et al. 2002). Desmopressin has been highly recommended for the treatment of NP by ICI (Andersson 2002). The effect of desmopressin on nocturia is dependent on the severity of the disorder in the vasopressin system. In individuals with severe symptoms, a substantial reduction in nocturia has been observed with the lowest dose of desmopressin (Asplund et al. 1999, Kuo 2002). Patients in desmopressin treatment are at elevated risk of hyponatremia and water retention. In a meta-analysis of seven studies 7.6% (95% CI 3.7-15.1) of the patients had hyponatremia (Weatherall 2004). The risk of hyponatremia is increased in elderly patients during the first weeks of treatment and the specific risk factors for hyponatremia are age, low serum sodium concentration at baseline, higher basal 24-hour urine volume and weight gain at the time of minimum serum sodium concentration (Callreus et al. 2005, Rembratt et al. 2006). Careful monitoring of sodium concentration should be organised when elderly patients with nocturia are treated with desmopressin. Those with serum sodium concentration below normal range should not be treated.

Alpha-adrenoceptor antagonist monotherapy with terazosin has been shown in a recent non-randomized clinical study to decrease nocturic episodes in men with LUTS (Paick et al. 2006). However, evidence from good quality clinical trials is not yet sufficient for recommendations (Andersson 2002). A pineal gland hormone, melatonin, can restore a normal circadian rhythm of micturition and improve sleep. A 10% reduction in nocturia has been reported in a pilot study of 20 nocturic men who had urodynamically proven bladder outlet obstruction (Drake et al. 2004).

Surgery. Surgical treatment of bladder outlet obstruction in BPH improves nocturia and restores the nocturia specific QoL of the patients (Cai et al. 2006). However, not all nocturics with BPH benefit from surgical treatment, which is most usually transurethral resection of the prostate (TURP). Overall, 15% of TURP patients did not improve within the first 3 months after the operation when evaluated with symptom scores and urinary flow rate measurements. Those patients, however, improved to the same level as other patients within 6 to 15 months. The preoperative factors associated with delayed symptom relief were low symptom score, less obstruction and more bladder overactivity than in those with fast recovery (Hakenberg et al. 1999). Nocturia has also been the least likely improving symptom within the seven symptoms in IPSS after TURP and medical treatment with α-blockers. Indications for the treatment of BPH should be carefully considered in patients whose chief symptom is nocturia (Yoshimura et al. 2003).

Other treatments: Nasal continuous positive airway pressure treatment improves nocturia significantly in patients with OSA (Krieger et al. 1993, Guilleminault et al. 2004). For patients in whom pharmacotherapy has failed and non-surgical or surgical interventions have proven unsuccessful, sacral neuromodulation can be effective in reducing the degree of urgency, urge incontinence and nocturia (Spinelli et al. 2003, Brazzelli et al. 2006).

3. Aims of the present study

In order to better understand the nature of LUTS the following specific aims of the present research were determined.

1. To determine the prevalence and incidence of nocturia in 5 and 10-year follow-up (I, II)

2. To describe deterioration and recovery of nocturia (I, II)

3. To evaluate depressive symptoms and chronic diseases as a risk factor of nocturia (III)

4. To develop a new instrument for the evaluation of the bothersomeness of LUTS with DAN-PSS-1 questionnaire (IV)

4. Populations and methods

4.1. Source population

The source population of the Tampere Ageing Male Urologic Study comprised the male population of twelve municipalities in the Tampere region in Finland (Koskimäki 1997). The study area included the city of Tampere and its neighbouring municipalities, (Hämeenkyrö, Kuhmalahti, Kuru, Kylmäkoski, Luopioinen, Pälkäne, Ruovesi, Sahalahti, Urjala, Viljakkala and Vilppula). At the beginning of 1994 the number of male inhabitants in the area was 105,272. During the second and third study rounds the numbers of men were 112,944 and 118,201 respectively. The age distribution of the source population is shown in Table 3 (Statistics Finland 2006).

Table 3. Age distribution of the source population during the study.

Age (years)	**1994 (%)**	**1998 (%)**	**2004 (%)**
0 – 9	12,925 (12.3)	13,612 (12.1)	12,618 (10.7)
10 – 19	12,177 (11.6)	12,595 (11.2)	13,164 (11.1)
20 – 29	15,828 (15.0)	17,882 (15.8)	20,998 (17.8)
30 – 39	17,482 (16.6)	18,291 (16.2)	17,167 (14.5)
40 – 49	17,900 (17.0)	17,067 (15.1)	16,768 (14.2)
50 – 59	11,807 (11.2)	14,912 (13.2)	17,128 (14.5)
60 – 69	9,805 (9.3)	10,099 (8.9)	10,611 (9.0)
70 – 79	5,291 (5.0)	6,330 (5.6)	7,174 (6.1)
80 – 89	1,894 (1.8)	1,940 (1.7)	2,330 (2.0)
90 -	163 (0.2)	216 (0.2)	243 (0.2)
Total	105,272 (100)	112,944 (100)	118,201 (100)

4.2. Target population

The original target population in 1994 was derived from the source population by the Population Register Centre and the individual address data of all the men born in 1924, 1934 or 1944 and residing in the study area at the beginning of 1994. Thus the men were 50, 60 or 70 years old at the end of 1994. The number of men was 3,152. Nine of them had died between the address search and the first survey, thus the eligible target population was 3,143. This cohort included 11% of the source population aged 50 years or over.

The same target population search was done at the beginning of 1999 and 2004 excluding those who had moved into the area subsequent to the first search. During the first 5-year follow-up, 262 men had died, six had emigrated and 36 were institutionalized or without an address for other reasons. The corresponding figures in the third study round in 2004 were 318 dead, 44 institutionalized and 9 living abroad. Thus, the final number of men in the target population was 2,837 in 1999 and 2,510 in 2004. The proportion of the youngest cohort was 44% at baseline, 46% in 1999 and 49% in 2004 and that of the middle cohort 32%, 33% and 33% and of the oldest cohort 24%, 21% and 17% respectively (Figure 2).

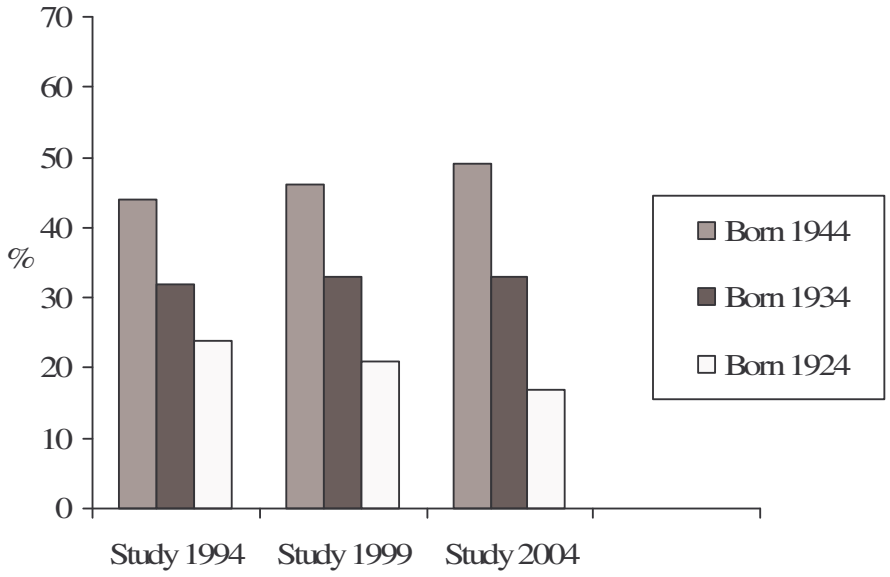

Figure 2. Age distribution of the target population of the study rounds.

In the first 5-year follow-up 1994-99, 1,683 men (54% of the baseline target population) responded to both the baseline and follow-up questionnaires. Due to missing data on nocturia, 50 were excluded, leaving 1633 men with information on nocturia at baseline and follow-up. They included 745 men free of nocturia, 835 with mild (1-2 voids per night), 49 with moderate (3-4 voids per night), and 4 with severe (≥ 5 voids per night) nocturia at baseline. The men free of nocturia (population at risk, n = 745) were included in the analysis of the risk factors and incidence of mild nocturia. Subjects free of nocturia or with mild nocturia at baseline (n = 1,580) were included in the analysis of the risk factors and incidence of moderate or severe nocturia (II, III).

In the second follow-up the number of responders was 1,679 (53%). After exclusions, the data of 1,618 men were found eligible, with adequate responses to the nocturia question in both the 1999 and 2004 survey. At baseline 667 were free of nocturia, 871 had mild, 78 moderate and 2 severe nocturia. Thus, the population for the estimation of incidence of mild nocturia was 667 men and of moderate or severe nocturia 1538 men (II). Men with moderate or severe nocturia at baseline were excluded from both analyses.

4.3. Questionnaire survey

Personal letters including a covering letter, study questionnaire and prepaid return envelope were mailed to 3,152 men in May 1994, 2,864 men in May 1999 and 2,516 men in April 2004. An identical communication was sent three months later to the 1,433, 1,162 and 844 men who did not respond to the initial mailing respectively. Two months after the reminder, the study was closed and data recorded. Thus, the total study period was five months during each study round. Overall 2,198 (70%) questionnaires were returned in 1994, 2,133 (75%) in 1999 and 1,905 (76%) in 2004. The study flow chart is seen in the Figure 3.

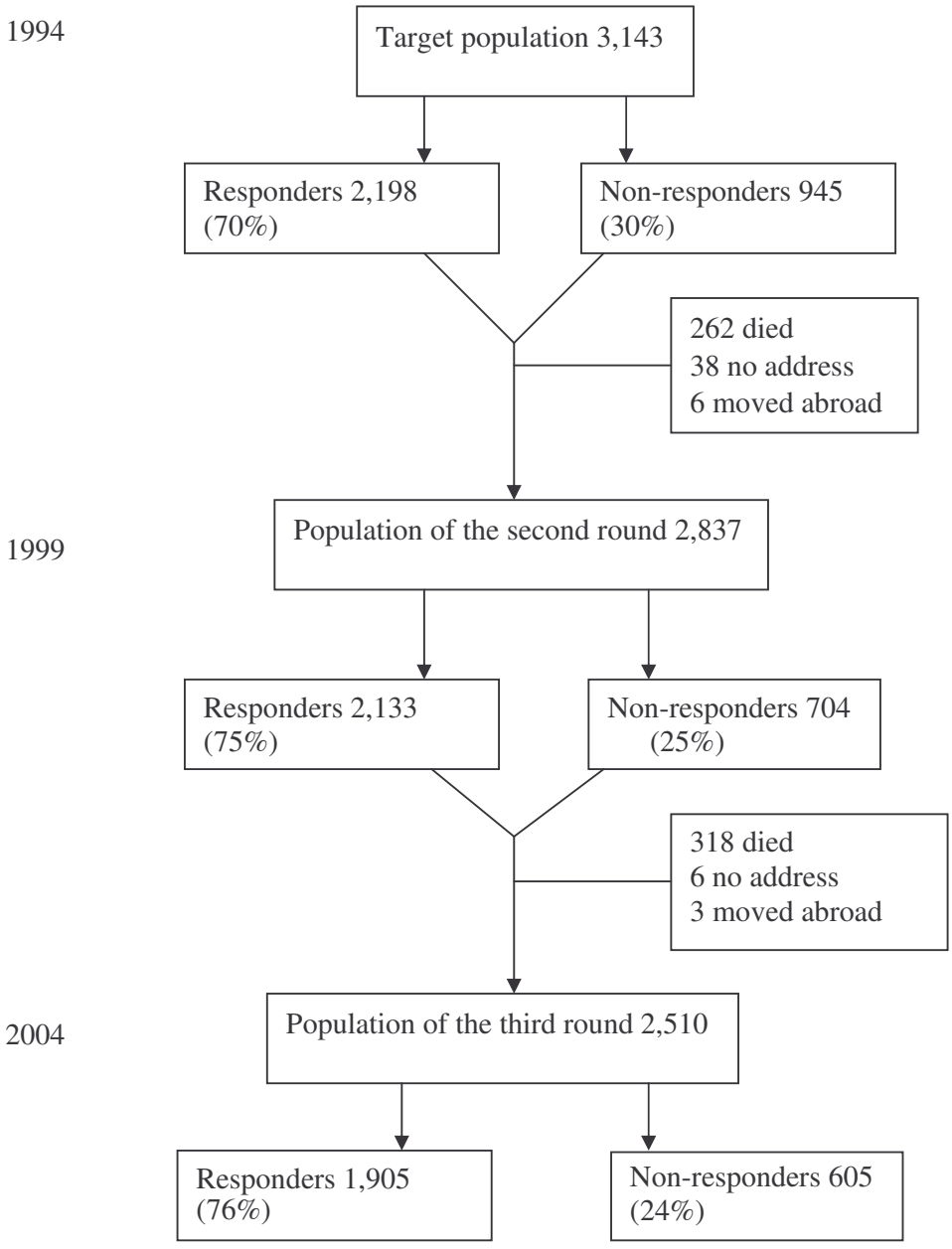

Figure 3. Flow chart of the target population at 5 and 10-year follow-up.

4.4. Assessment of urological and depressive symptoms

The study information in the TAMUS studies was collected by means of a mailed self-administered questionnaire (Appendix 1). In the 1994 survey the questionnaire included a variety of items on sociodemographic, medical and lifestyle factors in addition to questions on LUTS and ED and their impact on daily life and QoL (Koskimäki 1997). For the 1999 survey, the original questionnaire was condensed and the items of number of children, place and type of residence, familial predispositions to urinary disorders, diet and sauna bathing were omitted. The complete set of urinary questions in the DAN-PSS-1 questionnaire was added to the questionnaire (Hald et al. 1991). The 15D instrument for health-related QoL (Sintonen and Pekurinen 1989) and the 5-item version of the IIEF questionnaire (Rosen et al. 1999) were also included. The questionnaires used in the 1999 and 2004 surveys were identical.

Information about nocturia was collected using the DAN-PSS-1 question: "How many times do you have to urinate during the night?", which fulfills ICS definition for nocturia (van Kerrebroeck et al. 2002). The response alternatives were: "0 – none; 1 – one or two times; 2 – three to four times; and 3 – five times or more" (Hald et al. 1991). Nocturia was classified as mild if one or two nocturnal micturitions were reported, moderate if three to four and severe if five or more per night.

Depressive symptoms for Study III were assessed by the five-item version of the Mental Health Inventory (MHI-5), which was derived from the 38-item Mental Health Inventory (Berwick et al. 1991, Rumpf et al. 2001). The MHI-5 score ranges from 5 to 30, a higher score indicating increasing severity of depressive symptoms. Men with scores 5-15 were classified as free from depressive symptoms, those with scores 16-22 as having mild to moderate depressive symptoms and scores 23-30 as moderate to severe depressive symptoms.

For Study III the information on regular use of non-steroidal anti-inflammatory drugs and medication for psychiatric disorders (antidepressants and antipsychotics) was collected in the questionnaire. The question was "Do you take analgesics regularly?" with a similarly worded question for psychiatric medication. Subjects were also asked to provide the names and doses of the drugs they took daily.

In Study IV the complete DAN-PSS-1 questionnaire was used including the twelve questions of typical storage, voiding and post-micturition symptoms, incontinence and dysuria (Meyhoff et al. 1993). Each symptom was rated with A and B questions, the first one inquiring frequency or severity and the second one the bother of the symptom. Each question had four response options graded from

0 to 3 with increasing frequency or severity (symptom score) and bothersomeness (bother score). In bother scores, zero was considered as no bother, and other three grades small, moderate or severe perceived problem respectively.

To estimate bother relative to symptom, a bother index (BI), was produced for each urinary symptom. BI was calculated by dividing the number of men reporting bother score higher than symptom score by the number of men reporting bother score lower than symptom score. Each index was derived from cross-tabulation of the scores, symptom scores in rows and bother scores in columns, including all the men who responded to both A and B questions. In practice, the number of scores above the diagonal cells of the table was divided by that under the diagonal.

A low BI was considered to describe a symptom that was tolerable or innocuous, and by contrast a high BI a symptom inconvenient at any symptom score level. The responses in which symptom and bother scores were equal provided no information on BI. Thus it was insensitive to the prevalence of the symptom, but detected the symptoms which were frequently considered extremely inconvenient (high BI) and also those with a low bothersomeness (low BI) compared to the severity or frequency of the symptom.

4.5. Statistical analyses

Prevalence was estimated as the ratio of the men with a symptom to all the men with data on the symptom. The age-specific prevalences of nocturia with 95% confidence intervals (CI) were estimated.

The incidence of moderate or severe nocturia was calculated in those initially free of nocturia or with mild nocturia at entry, by dividing the number of new cases of moderate or severe nocturia occurring between baseline and follow-up by the number of person-years of follow-up. Person-years were calculated by multiplying the number of new cases by 5/2 years and the number of men who did not develop a symptom by 5 years, and summing up the products. The incidence of mild nocturia was estimated in a similar way in those free of any nocturia at entry. The numbers of new cases of mild to severe nocturia during follow-up were divided by the corresponding person-years. The incidence rates were expressed as number of new cases per 1,000 person-years and 95% CI were calculated assuming that the number of cases follows a Poisson distribution. Incidence rates were calculated for two consecutive 5-year study periods (II).

The incidence of depressive symptoms was estimated in a similar way in those with MHI-5 score less than 16 at entry. The numbers of new cases of

depressive symptoms (score 16 or higher) during follow-up were divided by the corresponding person-years.

Poisson regression modelling was used for the analysis of the incidence density ratio (IDR) of nocturia by age (II). Statistical significance (two-tailed p-value < 0.05) was assessed by chi-square test for categorical variables and by *t* test for continuous variables. Poisson regression model was used in the multivariate analyses. Subjects' age, diabetes, heart disease, arthritis, pulmonary disease, depressive symptoms, non-steroidal anti-inflammatory drugs and psychiatric medications were included as explanatory variables in the multivariate models (III). In Study I the statistical significance of non-parametric binomial data was established by McNemar's test and 95% CI presented.

5. Results

5.1. Participation

In the 1994 survey 2,198 (70%) men returned the questionnaire. In the second and third study rounds the participation rates were 75% and 76% with 2,133 and 1,905 returned questionnaires respectively. After the exclusion of the men without nocturia information, the participation rates were 65% in 1994, 73% in 1999 and 74% in 2004. Of those included in the baseline sample, 80% responded in 1999 and 78% in the 2004 follow-up.

The men with complete follow-up information in the 1994-99 study were on average three years younger than those with incomplete follow-up (Table 4). At baseline, they had a higher level of education, were more frequently married or cohabiting and had less arthritis, cerebrovascular diseases, diabetes, pulmonary diseases and depressive symptoms than those with incomplete follow-up. No differences were found regarding hypertension and heart diseases.

In the 1999-2004 study the men with complete follow-up information were on average four years younger than those with incomplete follow-up (Table 4). At baseline they had a clearly higher level of education, were more frequently married or cohabiting and had less hypertension, arthritis, heart diseases, pulmonary diseases, diabetes and cerebrovascular diseases than those with incomplete follow-up.

Table 4. Background characteristics of men with complete or incomplete follow-up at baseline.

Characteristic	Follow-up 1994-1999		Follow-up 1999-2004	
	Complete	Incomplete	Complete	Incomplete
	N=1633	N=406	N=1618	N=458
Demographic factors				
Age in years, mean (SD)	58.4 (7.8)	61.2 (8.6)	62.0 (7.4)	65.7 (8.3)
Education (%)				
Basic compulsory	49.5	58.2	46.3	62.3
Intermediate or secondary school	28.0	28.1	29.1	23.3
College or university	22.5	13.7	24.5	14.4
Marital status (%)				
Married or cohabiting	81.7	69.3	80.8	72.0
Bachelor, widower or divorced	18.3	30.7	19.2	28.0
Medical history (%)				
Hypertension	29.2	29.1	33.7	36.9
Arthritis	16.3	21.1	22.0	23.8
Heart disease	26.8	25.6	17.1	27.5
Pulmonary disease	9.7	12.3	12.2	15.3
Diabetes	7.2	10.1	7.7	12.9
Cerebrovascular disease	5.5	10.1	5.1	9.8
Depressive symptom score, mean (SD)	11.3 (3.8)	12.5 (4.5)	11.1 (3.7)	12.0 (4.2)

5.2. Prevalence of nocturia

The overall prevalence of nocturia (≥ 1 voids per night) was 56% (95% CI 54-58), 60% (95% CI 58-62) and 74% (95% CI 72-76) in the 1994, 1999 and 2004 surveys respectively (Table 5). Age-specific prevalence increased from 39% in 50-year-old men at baseline to 87% in men who were 80 years at the end of follow-up. Also, a small increase by calendar time was seen (Figure 4). The prevalence of mild nocturia increased rapidly in the two younger cohorts while no increase was seen in men 70 to 80 years old. Moderate or severe nocturia (≥ 3 voids per night) increased most rapidly in men 75 years old and over.

Table 5. Prevalence of nocturia by severity, age and follow-up round.

Age at baseline (years)	Study round	Number of micturitions per night							
		0		1 – 2		3 – 4		≥ 5	
		N	%	N	%	N	%	N	%
50	Baseline	474	61.2	289	37.3	10	1.3	1	0.1
	5y follow-up	484	53.6	402	44.5	17	1.9	-	-
	10y follow-up	321	35.4	547	60.2	39	4.3	1	0.1
60	Baseline	288	40.9	392	55.6	21	3.0	4	0.6
	5y follow-up	234	32.4	439	60.7	48	6.6	2	0.3
	10y follow-up	120	18.9	454	71.4	57	9.0	5	0.8
70	Baseline	142	25.4	377	67.3	37	6.6	4	0.7
	5y follow-up	107	23.8	296	65.8	46	10.2	1	0.2
	10y follow-up	41	13.4	201	65.7	57	18.6	7	2.3
Total	Baseline	904	44.3	1058	51.9	68	3.3	9	0.4
	5y follow-up	825	39.7	1137	54.8	111	5.3	3	0.1
	10y follow-up	482	26.1	1202	65.0	153	8.3	13	0.7

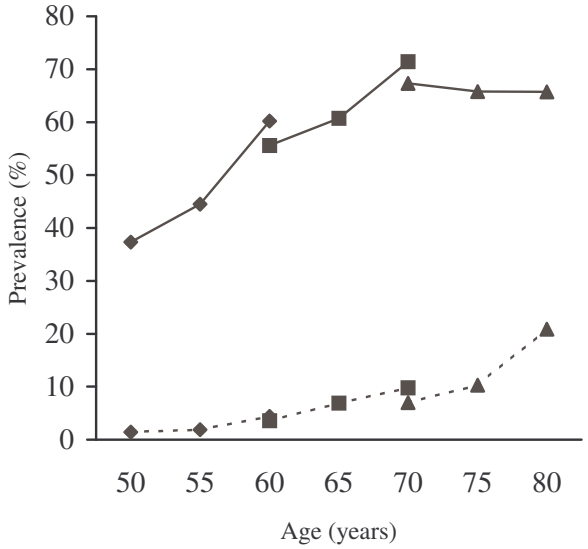

Figure 4. Prevalence of mild (continuous line) and moderate or severe nocturia (dotted line) by age in three study cohorts. The three age-groups are indicated by different figures.

5.3. Incidence of nocturia

The overall nocturia incidence rate was 75 (95% CI 66-85) cases per 1,000 person-years at the first 5-year follow-up and 126/1,000 (95% CI 113-140) at the second follow-up (II). The incidence of moderate or severe nocturia was 9/1000 (95% CI 7-11) and 14/1,000 (95% CI 12-17), respectively (Table 6). The incidence rate for any nocturia in the 50-year-old group at baseline was 61/1,000 (95% CI 50-73) during the first follow-up and 102/1,000 (95% CI 88-119) during the second. In 70-year old men the incidence increased from 93/1,000 (95% CI 67-127) to 167/1,000 (95% CI 122-225). The age-specific incidence of moderate or severe nocturia in men who were 50 and 70 years old at baseline increased from 3/1,000 (95% CI 1-5) and 7/1,000 (95% CI 5-11) to 16/1,000 (95% CI 11-24) and 42/1000 (95% CI 31-55) respectively. The incidence increased statistically significantly with age when older cohorts were compared to the youngest cohort (IDR 1.5 – 5.7 per five years). This increase was most prominent in men younger than 60 years for mild nocturia, but for severe symptoms it was most marked in men older than 75 years. A marked increase in the incidence of mild nocturia is also seen by calendar time in the extrapolated incidence curves (Figure 5) i.e. the incidence of consecutive cohorts at the same age was always higher in the previous cohort.

Table 6. Nocturia incidence and incidence density ratios (IDR) for age cohorts.

1994-1999 follow-up						
Age (years)	Baseline sample	Incident cases	Incidence / 1000	95% CI	IDR	95% CI
Any nocturia severity						
50-55	399	105	61	50-73	1	
60-65	245	91	91	74-112	1.5	1.1-2.0
70-75	101	38	93	67-127	1.5	1.1-2.0
Total	745	234	75	66-85		
Moderate or severe nocturia						
50-55	634	9	3	1-5	1	
60-65	588	33	12	8-16	4.0	1.9-8.4
70-75	358	28	16	11-24	5.7	2.7-12.1
Total	1580	70	9	7-11		
1999-2004 follow-up						
Age (years)	Baseline sample	Incident cases	Incidence / 1000	95% CI	IDR	95% CI
Any nocturia severity						
55-60	406	165	102	88-119	1	
65-70	191	113	168	140-202	1.6	1.3-2.1
75-80	70	41	167	122-225	1.6	1.2-2.3
Total	667	319	126	113-140		
Moderate or severe nocturia						
55-60	745	27	7	5-11	1	
65-70	538	32	12	9-17	1.7	1.0-2.8
75-80	255	48	42	31-55	5.6	3.5-9.0
Total	1538	107	14	12-17		

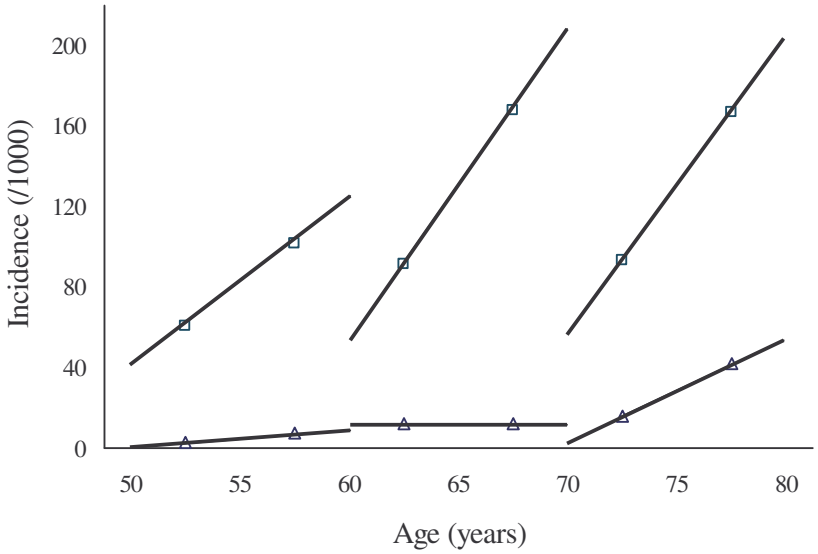

Figure 5. Extrapolated incidence rates of any (squares) and moderate or severe (triangles) nocturia by age.

5.4. Deterioration and recovery

After the first follow-up period increase of nocturia was reported by 7.4% of the men with mild or moderate symptoms at baseline. 15.5% had recovered and in 77.1% symptom score had not changed (I). In the second follow-up in 2004 the figures were 11.6%, 7.9% and 80.5%.

The overall incidence of recovery to at least one point lower symptom score in men with any nocturia at baseline was 35 cases per 1,000 person-years (95% CI 29-40) for the first follow-up period and 17/1,000 (95% CI 13-20) for the second (II). Accordingly, the incidence of deterioration was 15/1,000 (95% CI 12-19) in the first and 25/1,000 (95% CI 20-29) in the second follow-up. The age-specific incidence of recovery was 42/1,000 (95% CI 30-53) at the mean age of 52.5 years and 9/1000 (95% CI 3-14) at 77.5 years (Figure 6). The age-specific incidence of deterioration was 6/1,000 (95% CI 2-10) and 54/1,000 (95% CI 39-69) respectively. The incidence of surgical treatment of BPH was 9/1,000 (95% CI 7-11) during the first study round and 6/1,000 (95% CI 4-8) during the second round. The incidence of the use of medication affecting the prostate or bladder, such as alfuzosin, prazosin, tamsulosin, finasteride, Curbicin or antimuscarinic agents was 10/1,000 (95% CI 8-13) and 17/1,000 (95% CI 14-20) respectively.

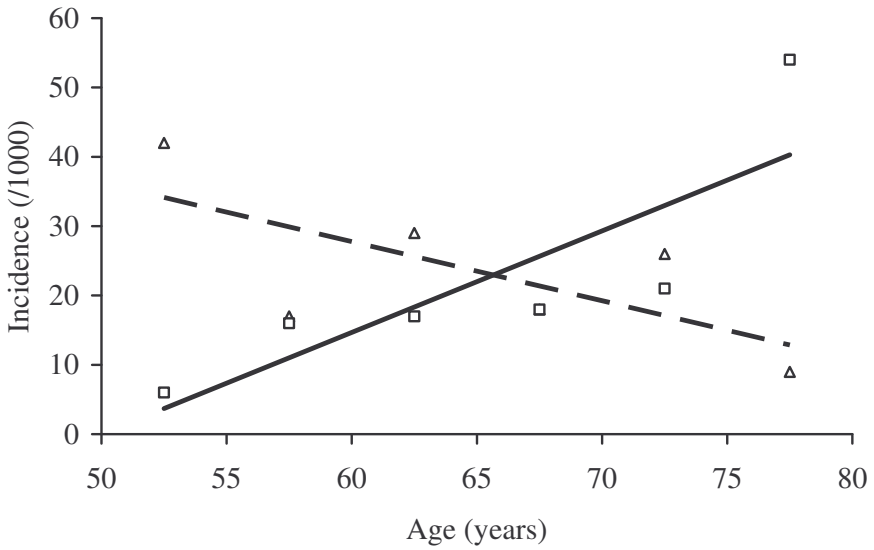

Figure 6. Incidence of deterioration (squares, continuous linear trend line) and recovery (triangles, dotted linear trend line) by age

5.5. Chronic diseases and nocturia

The incidence of mild nocturia was higher in men with diabetes, heart disease or arthritis than in those free of such diseases in the age-adjusted analysis (Table 7). No statistically significant associations with mild nocturia were found for hypertension, cerebrovascular disease, pulmonary disease, depressive symptoms, or the use of non-steroidal anti-inflammatory drugs, antidepressants or antipsychotic drugs.

The incidence of moderate or severe nocturia was associated with heart disease, arthritis, depressive symptoms and use of non-steroidal anti-inflammatory drugs in the age-adjusted analysis. A dose-response relation was found between the severity of depressive symptoms at baseline and the incidence of moderate or severe nocturia. Men with mild to moderate depressive symptoms at entry were at 3 times (95% CI 1.6-5.7) and those with moderate or severe depressive symptoms at 6.7 times (95% CI 2.4-18.5) higher risk of moderate or severe nocturia than men free of depressive symptoms. Diabetes, hypertension, cerebrovascular disease, pulmonary disease, and the use of antidepressant or antipsychotic drugs were not statistically significantly associated with the incidence of moderate or severe nocturia.

Table 7. Age-adjusted incidence rate ratio (RR) of mild, and moderate or severe nocturia according to medical conditions.

Medical conditions	Mild				Moderate or severe			
	No. of men	Incident cases	RR	95% CI	No. of men	Incident cases	RR	95% CI
Diabetes								
No	701	211	1		1475	61	1	
Yes	44	23	2.0	1.3-3.1	105	9	1.8	0.9-3.6
Heart disease								
No	660	199	1		1330	48	1	
Yes	85	35	1.5	1.0-2.1	250	22	1.8	1.1-3.1
Hypertension								
No	557	174	1		1126	47	1	
Yes	188	60	1.0	0.7-1.4	454	23	1.1	0.7-1.8
Cerebrovascular disease								
No	715	221	1		1497	62	1	
Yes	30	13	1.5	0.8-2.6	83	8	1.8	0.9-3.9
Pulmonary disease								
No	696	214	1		1430	59	1	
Yes	49	20	1.4	0.9-2.2	150	11	1.4	0.7-2.7
Arthritis								
No	580	169	1		1163	35	1	
Yes	164	65	1.4	1.1-1.9	416	35	1.3	1.1-1.6
Depressive symptoms								
No	666	206	1		1351	48	1	
Mild to moderate	43	12	0.9	0.5-1.6	126	12	3.0	1.6-5.7
Moderate to severe	9	3	1.1	0.3-3.4	19	4	6.7	2.4-18.5
Depressive symptoms and antidepressive use								
None	655	201	1		1327	45	1	
Untreated depressive symptoms	36	12	1.1	0.6-2.0	114	14	4.0	2.2-7.3
Only antidepressive use	11	5	1.5	0.6-3.6	24	3	3.7	1.1-12.0
Both symptom and treatment	16	3	0.6	0.2-1.9	31	2	2.3	0.5-9.7
Medication use								
Non-steroidal anti-inflammatory drug								
No	699	220	1		1396	50	1	
Yes	46	14	1.0	0.5-1.6	184	20	2.5	1.4-4.2
Antidepressant or antipsychotic drug								
No	717	225	1		1521	65	1	
Yes	28	9	1.0	0.5-2.0	59	5	2.2	0.9-5.5

After adjustment for other covariates, the risk of mild nocturia was higher in men with diabetes (RR 1.6, 95% CI 1.0-2.7) or arthritis (RR 1.4, 95% CI 1.0-1.9) than in subjects without such a disease (Table 8). Men with mild to severe depressive symptoms at entry were at 2.8 times (95% CI 1.5-5.2) higher risk of moderate or severe nocturia compared with those free of depressive symptoms. Only untreated depressive symptoms increased the incidence of moderate or severe nocturia (adjusted RR 3.3, 95% CI 1.7-6.2) while men with depressive symptoms and antidepressive medication did not show an increased risk (adjusted RR 1.7, 95% CI 0.4-7.4). The risk of moderate or severe nocturia increased with the severity of depressive symptoms at baseline. Each unit increment in the MHI-5 score increased the incidence rate ratio of moderate or severe nocturia by 10% (95% CI 4-16).

Table 8. Incidence rate ratio (RR) of mild nocturia and moderate or severe nocturia, according to medical conditions. Adjusted for age, chronic diseases and medication.

Characteristic	Mild		Moderate or severe	
	RR	95% CI	RR	95% CI
Age (continuous, per year)	1.02	0.99-1.04	1.07	1.03-1.10
Medical conditions				
Diabetes	1.6	1.0-2.7	1.4	0.6-3.1
Heart disease	1.2	0.8-1.8	1.5	0.8-2.7
Pulmonary disease	1.3	0.8-2.1	1.6	0.8-3.1
Arthritis	1.4	1.0-1.9	1.2	0.9-1.6
Depressive symptoms				
None vs. mild, moderate or severe	1.0	0.5-1.8	2.8	1.5-5.2
MHI-5 score (continuous)	1.01	0.97-1.05	1.10	1.04-1.16
Depressive symptoms and the use of antidepressive medication				
None	1		1	
Untreated depressive symptoms	1.2	0.6-2.1	3.3	1.7-6.2
Only antidepressive use	1.2	0.5-2.9	2.6	0.7-8.8
Both symptom and treatment	0.6	0.2-1.8	1.7	0.4-7.4
Medication use				
Non-steroidal anti-inflammatory drugs	0.9	0.4-2.0	1.6	0.8-2.9
Antidepressive or antipsychotic medications	0.7	0.4-1.4	1.1	0.4-3.0

Among 1,229 men free of depressive symptoms at baseline, 74 subjects developed depressive symptoms during follow-up, corresponding to an incidence of depressive symptoms of 9 cases (95% CI 7-11) per 1,000 person-years. Nocturia at entry had no significant effect on the development of depressive symptoms during the follow-up.

5.6. Bother index

Information on both symptom and the bother it caused was available for 1,803 (64%) to 2,046 (72%) men depending on the symptom. Prevalence of at least mild symptoms (symptom score ≥ 1) varied from 68% in urgency, to 8% in stress incontinence and in overflow or other incontinence (Table 6). The cumulative prevalence of bother was also highest in urgency, 46% and lowest, 7% in incontinence symptoms other than urge incontinence, in which it was 17%.

The bother index (BI) for all reported symptoms together was 0.27 i.e. the frequency or severity of the urinary symptom was rated higher than the bother it caused by four out of five men in those who rated the symptom score differently from the bother score. BI ranged from 0.06 in straining to 3.7 in overflow or other incontinence (Table 9). All types of incontinence and also weak stream had a high BI. Straining, post-micturition dribble and hesitancy were the best tolerated symptoms with a very low BI. The cumulative prevalence of symptom was higher than that of bother in all individual symptoms (Table 9). Relative prevalence of the symptoms (RR), i.e. cumulative bother score divided by cumulative symptom score, showed much less variation (from 0.5 to 0.9) than BI (from 0.06 to 3.70).

Table 9. Cumulative prevalence of symptom and bother scores (men with score > 0 in total men), relative prevalence (RR) and bother index (BI) by urinary symptoms.

Symptom	Cumulative prevalence (%) of		RR	BI
	symptom	bother		
Overflow or other incontinence	7.6	6.8	0.89	3.70
Urge incontinence	19.9	17.4	0.87	2.44
Stress incontinence	8.4	7.3	0.87	1.79
Weak stream	25.9	20.8	0.80	1.14
Daytime frequency	34.9	23.1	0.66	0.72
Dysuria	18.3	12.1	0.66	0.34
Nocturia	57.3	36.0	0.63	0.33
Urgency	68.0	46.2	0.68	0.18
Incomplete emptying	43.3	27.6	0.64	0.13
Hesitancy	46.9	23.9	0.51	0.06
Post-micturition dribble	60.0	42.0	0.70	0.06
Straining	46.4	24.6	0.53	0.06
All symptoms	35.9	23.7	0.66	0.27

6. Discussion

This dissertation gathers the results of four analyses based on the Tampere Ageing Male Urologic Study (TAMUS). The main results concerning descriptive epidemiology are the estimation of nocturia incidence and change in prevalence. Incidence of nocturia has not been published earlier in the scientific literature. Ten-year follow-up of urinary symptoms is also unprecedented in Finland.

From the analytical epidemiology point of view the most salient result is the finding that depressive symptoms increase the incidence of nocturia. It is in accordance with the earlier cross-sectional results of Asplund et al. (2004) in Sweden and supports the hypothesis that there is a causal relationship between depression and nocturia.

Nocturia is an inconvenient symptom of the elderly. The spectrum of the consequences it causes varies from slight bother to severe morbidity that may be life-threatening. Nocturia is one of the diseases that will become more and more common in societies due to increasing life expectancy and the number of elderly citizens. It increases resource needs and financial consequences in social and health care organisations by the ever-growing need for treatment and care. In urology, a broad consensus exists that nocturia needs more attention in clinical and scientific settings if the results of the treatment of LUTS are to be improved (Tubaro et al. 2006).

6.1. Participation and methodology

The response rates in TAMUS have been relatively high, 70% at baseline, 75% and 76% in consecutive follow-ups. The response rate in the 1994-99 follow-up survey was 58%, which is similar to that in earlier studies (Diokno et al. 1992, Jacobsen et al. 1996, Lee AJ et al. 1998). In the second follow-up from 1999 to 2004 the proportion of the men with data both at baseline and follow-up was even a little higher, 64%.

Comparing the men with and without follow-up information on nocturia, those responding both at baseline and at follow-up were older and suffered more often from chronic diseases as diabetes, arthritis and depressive symptoms, thus

being obviously at greater risk of nocturia. This may have caused a minor incidence underestimation in the target population. However, the design in this study with internal comparisons of the incidence rates diminished the possible bias. In this follow-up study, we evaluated the effect of chronic diseases on the incidence of nocturia. With the longitudinal set-up we were able to evaluate the data of risk factors collected prior to onset of the symptom and recall bias in reporting earlier conditions was avoided. A sufficiently long follow-up also enabled the detection of weak, but cumulative effects. Our findings are based on relatively small numbers of men and events, but the statistical significance and internal consistency of the findings suggest true effects, which are hardly attributable to chance.

The basic source of urinary symptom information in this study was the DAN-PSS-1 questionnaire. In the BI study in 1999 (IV), the whole set of LUTS questions was used and in the nocturia studies the nocturia question only. The Danish Prostatic Symptom Score (DAN-PSS-1) was published by Hald et al. in 1991. The questionnaire was the first in which not only occurrence but also bother of the symptom was assessed by the subject at the same time. This evaluation of the symptom-specific bothersomeness also became possible later with IPSS after the publication of the Symptom Problem Index (SPI) in 1995 by the American Urological Association (AUA) (Barry et al. 1995). Until this the SPI has not been widely used and use of IPSS with the one original QoL question is still recommended (Madersbacher et al. 2004). Overall, the importance of evaluation of disease or symptom specific QoL has become increasingly discussed and a symptom specific QoL questionnaire was recently introduced also for nocturia (Abraham et al. 2004). Such specific questionnaires probably give a better view of the bothersomeness of a concrete symptom like nocturia. Other potential instruments for the evaluation of nocturia and its impact on QoL are sleep diaries and measuring the time from falling asleep to the first awakening to void, i.e. hours of undisturbed sleep (HUS) (Chapple et al. 2006).

Although the correlation of symptom score with bother score in DAN-PSS-1 and IPSS was good, the symptom and bother questions do not elicit the same information, and the variability between the two scales has been high (Barry et al. 1995, Eckhardt et al. 2001, Engström et al. 2004, Perrin et al. 2005). This means that both symptom and bother questions are needed in questionnaires intended for clinical use or epidemiological studies considering not only prevalence but also the impact of LUTS on population. DAN-PSS-1 with a wide range of symptoms is suitable for both clinical and research use. Each symptom can be analysed separately with or without bother score, or combined into an LUTS score. The original Danish version has been validated and used in many epidemiological surveys and clinical trials (Meyhoff et al. 1993, Hansen et al. 1995, Koskimäki et al. 1998, Kay et al. 1999, Engström et al. 2004).

The nocturia question in the DAN-PSS-1 questionnaire is consistent with the International Continence Society's definition for nocturia (van Kerrebroeck et al. 2002). The response alternatives do not discriminate solitary nocturia from two voids per night. This can be considered a weakness, because one void per night is often considered as a part of the normal ageing process. In IPSS -questionnaire the response alternatives represent the mean number of nightly voids during the study period, which is usually four weeks. In its apparent simplicity this may increase recall bias: the person has to remember the number of nightly voids, and also make an approximation of the mean frequency. Classification of nocturia into three grades, as in the DAN-PSS-1, may describe the fluctuation of the actual number of nightly micturitions (Yoshimura and Terai 2005) better than the mean number of nocturia episodes and thus decrease the recall bias (Hunskaar 2005).

Prevalence as a measure of disease occurrence gives a good picture of the total burden of the condition in population. For etiological purposes incidence is superior, because in a longitudinal study with multiple measuring time-points exposure to the risk factors can be better controlled for. Accordingly, incidence is ideal for the assessment of irreversible events. In nocturia, especially in its mild stage the number of voids fluctuates and deterioration as well as recovery has been reported (Lee AJ et al. 1998, Yoshimura and Terai 2005). However, in our study in the cross-sectional analysis 80% of the men with nocturia had no change in symptom score during follow-up. For the calculation of incidence rates, we dichotomized nocturia into presence or absence of the symptom. This resulted in loss of information, thus impairing accuracy. Another methodological weakness was our assessment of the symptoms at only two time points during the study, baseline and at five-year follow-up. We did not have any information on the time of symptom onset or acerbation. Therefore, we had to assume that the transition occurred on average at the midpoint of the follow-up period. This may have caused inaccuracy in incidence estimates, because the prevalence of transitions probably increases with age, which leads to a skewed distribution of event times.

6.2. Prevalence and incidence of nocturia

In the TAMUS target population, the overall prevalence of nocturia was 56% at baseline and 60% after 5-year follow-up and 74% after 10-year follow-up. These figures are comparable with earlier studies and very similar with another Finnish nocturia study (Tikkinen et al. 2006b). A clear age-related increase was seen in follow-up in the prevalence of nocturia. The marked age-dependence of the symptom became further enhanced by the fact that there was also a prominent increase in prevalence within each age group. Only in the oldest group did the

prevalence of mild nocturia reach a plateau but moderate and severe symptoms continued to increase.

In Study II we estimated the incidence rates of nocturia in a sample of originally 50 to 70-year old men. The follow-up time was reasonably long, ten years with a query at 5 and 10 years. The crude incidence of any nocturia was 75 new cases per 1,000 men annually during the first 5-year follow-up period and 126 during the second period. The incidences of moderate to severe symptoms also almost doubled with age but severe symptoms were generally uncommon in the study population. In multivariate logistic regression analysis after the adjustment for age, chronic diseases and medications, age was significantly associated with moderate or severe nocturia with a 7% annual increase in incidence, but not with mild nocturia (Table 8). In the literature there are no earlier incidence estimations for comparison in different populations.

Nine out of ten of the men with nocturia reported only one or two voids per night. Nocturia, especially in its mildest forms, is often perceived as an unavoidable of even normal phenomenon in ageing (Lundgren 2004). This is a logical conclusion with a symptom as prevalent as nocturia in the elderly. There is also some pathophysiological support for this assumption, because mechanisms behind nocturia like decrease in the sensitivity of vasopressin receptors in the kidney and increase in bladder over activity is strongly associated with ageing (Milsom et al. 2001, Robertson and Nørgaard 2002). Although mild symptoms predominate, 10% of the men with nocturia reported three or more voids per night. Most of them are very old men and have multiple factors leading to nocturia. These men need to be properly examined and treated.

Changes in the severity of the urinary symptoms have been previously evaluated in only few studies (Jacobsen et al. 1996, Lee AJ et al. 1998, Temml et al. 2003). In the TAMUS population, symptom recovery was more common and symptom deterioration less usual than in earlier studies. Comparison with other studies, however, is not very fruitful because of major differences in study design. In the Olmsted study all men with a history of prostatectomy, prostate cancer or other medical condition (other than BPH) known to interfere with voiding function were excluded and in the Scottish study only patients with a diagnosis but without treatment for BPH were included in follow-up. None of the studies utilised the DAN-PSS-1 questionnaire.

The fluctuating nature of nocturia has been shown in earlier studies (Temml et al. 2003, Yoshimura and Terai 2005). Spontaneous improvement or fluctuation of the symptom possibly explains part of the recovery in our study, too because only 10% of the men reported any prostate or urinary symptom-specific treatment during the follow-up (I). The almost twofold incidence of medical treatments of LUTS during the second follow-up period may have had an effect on recovery. Although in the first follow-up there was an increase in the

prevalence of nocturia, improvement was more frequent than deterioration. This means that initially symptom-free men contributed substantially to the prevalence, which is seen in Study II, where the incidence of mild nocturia was high and increased markedly in late middle age. Roughly 10% of the men in the target population started nightly voiding annually. The recovery-deterioration fluctuation is widest in middle-aged men, which is clearly seen in the trend lines of the age-specific incidences in Figure 6. Recovery is most usual in young age groups and deterioration conversely rare. However, the overall nocturia incidence is high and increasing dramatically. Moreover, the prevalence of deterioration exceeds the prevalence of recovery in 10-year follow-up and the overall trend in nocturia is increase in prevalence and a gradual tendency to more severe symptoms with age. Strikingly, in the oldest men, over 75 years, nocturia is often severe and the incidence of deterioration is high and recovery happens rarely. This is in line with increasing burden of prostatic and chronic systemic disease affecting urinary functioning at that age (Emberton et al. 2003).

Nocturia is seldom a symptom of a fatal disease and therefore its prevalence increases even if the incidence does not. Our study revealed only a moderate increase in the incidence of nocturia by age. A statistically significant 50 to 60% increase in IDR was seen in two older age groups when compared with the youngest one in mild nocturia. However, IDR did not continue to increase in older age groups, indicating that the risk of mild nocturia did not increase markedly after the age of 60 years. The incidence of moderate or severe nocturia increased rapidly with age but the overall number of cases was low.

The overall drift to more detected nocturia was seen in the three consecutive surveys of this population. The prevalence of many other urinary symptoms increased over time and showed a cohort effect (I). In Study II the same phenomenon was seen in the incidence of mild nocturia during two consecutive follow-up periods and there was a substantial increase over calendar time, which was 200 to 300% within 5 years. This may to some extent be due to an increasing sensitivity to reporting mild symptoms in repeated surveys. Also, increasing awareness of the high prevalence of urinary symptoms in the community and emerging non-surgical treatments during the study period may have encouraged men to report their symptoms more precisely.

6.3. Nocturia, depression and chronic diseases

Despite recent increasing interest in nocturia and numerous prevalence studies, there is a need for more advanced epidemiological analysis of the risk factors of nocturia (Hunskaar 2005). Longitudinal set-up and the estimation of the effects

of risk factors with incidence rates is the method of choice for these etiological purposes.

The main result of Study III was the finding that severe and untreated depressive symptoms increase the incidence of moderate or severe nocturia. This finding was strengthened with a positive dose-response effect and a unidirectional effect of depressive symptoms. Among the other chronic medical conditions, diabetes and arthritis increase the incidence of mild nocturia.

After adjustment for the most common confounders the risk of moderate or severe nocturia (≥ 3 voids per night) was 2.8 times higher in men with depressive symptoms than in non-depressed men. Asplund et al. (2004) reported a 6.5 (95% CI 2.6-15.6) times higher prevalence of nocturia in men with major depression than in those free of depression (Asplund et al. 2004), but their study was cross-sectional prevalence study. However, their results are consistent with our finding of higher incidence of moderate or severe nocturia in men with moderate or severe depressive symptoms compared with those free of depressive symptoms at entry.

Loss of circadian rhythm and absence of nocturnal increase in arginine vasopressin (AVP) plasma levels leads to an increase in nightly urine production and nocturia (Asplund and Åberg 1991). In depressed patients both the synthesis and release of AVP in suprachiasmatic nucleus in the hypothalamus has been reported to be reduced (Zhou et al. 2001). On the other hand, high AVP levels have been connected to affective disorders and depression, but high AVP levels in the severely depressed patients had no circadian changes (van Londen et al. 1997). In addition, in experimental animals reduction of monoamines like serotonin and noradrenalin in central nervous system (CNS) caused both depression and overactive bladder (OAB) (Steers and Lee 2001). Thus, depression and nocturia may have common pathogenetic mechanisms leading to either NP or OAB. Depressed people often suffer from insomnia, which is an independent risk factor for nocturia (Kageyama et al. 2000).

Earlier studies have reported contradictory findings on the associations between chronic medical conditions and nocturia. Hypertension, cardiovascular disease or diabetes mellitus were associated with the prevalence of nocturia in some studies (Asplund 2002b, Seim et al. 2003, Yoshimura et al. 2004, Johnson et al. 2005) but not in all (Blanker et al. 2000, Rembratt et al. 2003). A follow-up study did not show associations between hypertension or diabetes and the incidence of nocturia (Johnson et al. 2005). Poor glucose control in diabetes is a common cause of nocturia (Samos and Roos 1998). In our study, diabetes was associated with increased risk of only mild nocturia (1-2 voids per night), but not with moderate or severe nocturia. An association between arthritis and nocturia has not previously been reported. The effect of arthritis on nocturia may be due to other comorbidities, chronic pain or the side effects of medications.

6.4. Bother index

The basic measures of the DAN-PPS-1 scoring system are frequency or severity of urinary symptoms and the inconvenience they cause. These two components were presented separately and independently in the original paper by Meyhoff et al. (1993) as was done in subsequent studies. The total or LUTS score uses both the symptom and bother scores simultaneously but without distinguishing their relative weight. BI as constructed in this study weights the relative importance of bother to symptom simultaneously in the same individual. BI describes the odds that a person reported a higher bother score than severity or frequency score in relation to the odds of having a bother score less than the symptom score. The higher the BI is, the more inconvenient the symptom is considered relative to its severity. As subjective bother and objective frequency (severity) cannot be directly compared, the BI as such has only a limited interpretation. This is true for any indicator comparing bother and symptom including the ratio of prevalences. These cannot be used as traditional symptom scores describing the burden of the disease in population or individual patients. The use of BI is to compare different urinary symptoms or different populations evaluated with the same scoring system.

A good correlation of symptom score with bother score overall as well as in individual urinary symptoms in the DAN-PSS-1 questionnaire has been shown (Hansen et al. 1995, Engström et al. 2004). BI cannot supersede any previous method of validating symptom scores, but it includes information impossible to achieve with traditional methods. In Study IV, we evaluated the perceived bothersomeness of the urinary symptoms included in the DAN-PSS-1 questionnaire in a population-based sample and compared it to the severity of the same symptom by means of BI. The BI detected the symptoms which were frequently considered extremely annoying (high BI) and also those with low bothersomeness (low BI) in comparison to the severity or frequency of the symptom. Therefore, the odds or BI is a more informative indicator of bothersomeness than, for example, the prevalence of bother or the ratio of prevalence of bother to that of severity. In the target population the cumulative prevalence of a symptom was higher than the corresponding prevalence of bother for all symptoms (RR<1) while the BI ranged from 0.06 to 3.7. There was a less than 100% and an inverse correlation between the prevalence of the symptom and its bothersomeness, indicating that BI provides information on LUTS that cannot be described by prevalence or prevalence ratio only.

The prevalence of most urinary symptoms in our material was high and comparable with previous cross-sectional DAN-PSS-1 surveys (Koskimäki et al. 1998, Kay et al. 1999, Engström et al. 2004). The higher prevalence compared to the Kay et al. (1999) study may be due to the older population in our survey and lower prevalence compared to that of Engström et al. (2004) because of different

sampling of the target population. Voiding symptoms had lower BI than typical storage symptoms. This is consistent with previous knowledge (Peters et al. 1997). All types of incontinence had high BI. In previous IPSS studies urgency has been one of the most bothersome symptoms, but weak stream quite tolerable (Eckhardt et al. 2001, Perrin et al. 2005). Engström et al. found weak stream overall fairly well tolerated, but all the men affected by 'very weak' or 'dribbling' urinary stream in their study reported major distress (Engström et al. 2004). They used the DAN-PSS-1 questionnaire and against this background our high BI for weak stream is understandable. Obviously the DAN-PSS-1 questionnaire detects diminished urinary stream sensitively. Nocturia is one of the most bothersome storage symptoms (Asplund 2005). The low BI in the present study may be due to the fact that DAN-PSS-1 combines one and two nightly voidings into the mildest score and that 90% of the men with nocturia in our population fell into this category. Men with only one nocturia episode probably wake up to void during the early morning hours and the important hours of undisturbed sleep just after falling asleep are unaffected.

In earlier studies the symptom and the inconvenience have not been considered simultaneously as a pair, as we did in the analysis that did not simply combine symptom and bother into a total score. Our comparison of two approaches (RR and BI) demonstrates that they provide supportive and independent information of the symptom. RR shows less variation than BI, indicating that the distributions of the symptom score and bother score do not fully disclose the role of bother. RR gives only the overall impression that the frequency of the symptom is more important, whereas BI demonstrates that there are many individual men in the population who perceive the symptom more bothersome than its frequency would suggest. Further, the symptoms have an objective ranking of bothersomeness in the BI that goes over and above the simple prevalence only.

6.5. Strengths and shortcomings of the study

The target population of TAMUS consists of a stratified random cohort of men in twelve municipalities in Pirkanmaa, southern Finland. The target population includes 11% of all men 50 years old or older in the source population. The target population is truly population-based and reflects the composition of the Finnish elderly male population at large. The participation rate of the study was fairly good, 70% or over in each study round. A proportion of 80% and 73% of the men with nocturia information at baseline were eligible in 5 and 10 year follow-up respectively.

With a longitudinal study, we were able to evaluate the temporal relationships of exposures to outcomes, which is not possible in cross-sectional

prevalence studies. Temporal relationship is especially important in exposures like chronic diseases. Without a longitudinal study, it is impossible to ascertain whether depression causes nocturia or nocturia with possible sleep deprivation is the reason for depressive symptoms.

There were differences between the responders and non-responders in the study. Non-responders were older than those on whom the nocturia information was available both at baseline and follow-up. They also had more chronic diseases, and thus possibly more nocturia than responders. Therefore the incidence rates of the study may underestimate the true nocturia incidence in the population. However, the incidence rate ratios are likely to be unbiased.

For the estimations of incidence rates we had only two cross-sectional interviews; baseline and follow-up. With this setting we could not know the exact point in time when incident condition occurred. Thus person-years for incident cases were not exact due to approximations. The fluctuation of the symptom may also hamper the incidence rate estimation with this long inquiry interval.

Self-administered postal questionnaires are prone to biased information. The responses may be affected by other family members and complicated questions are not always well understood by the respondent. However, self-administered questionnaires have been found more reliable than personal or telephone inquiries. Although linguistically validated Finnish versions of many widely used questionnaires are available, the quality if the translations may vary and comparability with the original may be questioned. A clear weakness of the TAMUS project is that it includes only male population.

6.6. Future aspects

The TAMUS follow-up study project should continue. The further evaluation of the risk factors of nocturia as well as other LUTS is ongoing with chronic conditions and modifiable life-style factors. The effects of nocturia on subjects' QoL should be analysed in the data already collected. The quality of the incidence estimations in the present study could be studied with a follow-up of a sub-group of our target population with multiple short interval interviews. In future study rounds symptom-specific QoL questionnaires should be utilised.

7. Conclusions

On the basis of the TAMUS follow-up study and the analysis of the nocturia data the following conclusions can be drawn.

1. Nocturia is a common condition in ageing male population in Finland. Prevalence and incidence rates are comparable with those of other western countries. The prevalence and incidence of nocturia increase with age, but the increase is not constant. In late middle age the incidence of mild nocturia increases, leading to a steady growth in prevalence. In older age the incidence increase slows down but symptom deterioration and the non-malignant nature of nocturia keeps the prevalence high. Severe nocturia is rare, but much more common in old men than in younger men.

2. Nocturia is a progressive symptom. Its prevalence and severity increase with age. The incidence of deterioration increases and the incidence of recovery decreases with age. Worsening of the symptom is most prominent in the oldest men. Mild nocturia, especially in middle aged men, may diminish spontaneously.

3. Depressive symptoms are a risk factor for nocturia. The effect is unidirectional, nocturia does not increase the incidence of depressive symptoms. The effect is also dose-related, an increase in depressive symptoms increasing the incidence of nocturia. Untreated depression has a greater effect on the incidence of nocturia than depressive symptoms during medical treatment. The effects of other chronic diseases on the incidence of nocturia are weak. Diabetes and arthritis were the only significant risk factors for mild nocturia.

4. The bothersomeness of a urinary symptom is an independent contribution in the assessment of LUTS. The bother index (BI) may be a useful indicator of bothersomeness of urinary symptoms.

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References

Abraham L, Hareendran A, Mills IW, Martin ML, Abrams P, Drake MJ, MacDonagh RP and Noble JG (2004): Development and validation of a quality-of-life measure for men with nocturia. Urology 63: 481-486

Abrams P, Mattiasson A, Lose GR and Robertson GL (2002): The role of desmopressin in the treatment of adult nocturia. BJU Int 90 Suppl 3: 32-36

Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, Van Kerrebroeck P, Victor A and Wein A (2003): The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. Urology 61: 37-49

Andersson KE (2002): The pharmacological treatment of nocturia. BJU Int 90 (Suppl 3): 25-27

Andersson SO, Rashidkhani B, Karlberg L, Wolk A and Johansson JE (2004): Prevalence of lower urinary tract symptoms in men aged 45-79 years: a population-based study of 40 000 Swedish men. BJU Int 94: 327-331

Asplund R (1995): The nocturnal polyuria syndrome (NPS). Gen Pharmacol 26: 1203-1209

Asplund R (1996): Daytime sleepiness and napping amongst the elderly in relation to somatic health and medical treatment. J Intern Med 239: 261-267

Asplund R (1999): Mortality in the elderly in relation to nocturnal micturition. BJU Int 84: 297-301

Asplund R (2002a): Diuresis pattern, plasma vasopressin and blood pressure in healthy elderly persons with nocturia and nocturnal polyuria. Neth J Med 60: 276-280

Asplund R (2002b): Nocturia in relation to sleep, somatic diseases and medical treatment in the elderly. BJU Int 90: 533-536

Asplund R (2004): Nocturia, nocturnal polyuria, and sleep quality in the elderly. J Psychosom Res 56: 517-525

Asplund R (2005): Nocturia: consequences for sleep and daytime activities and associated risks. Eur Urol Suppl 3: 24-32

Asplund R and Åberg H (1991): Diurnal variation in the levels of antidiuretic hormone in the elderly. J Intern Med 229: 131-134

Asplund R and Åberg H (1992): Health of the elderly with regard to sleep and nocturnal micturition. Scand J Prim Health Care 10: 98-104

Asplund R, Sundberg B and Bengtsson P (1999): Oral desmopressin for nocturnal polyuria in elderly subjects: a double-blind, placebo-controlled randomized exploratory study. BJU Int 83: 591-595

Asplund R, Henriksson S, Johansson S and Isacsson G (2004): Nocturia and depression. BJU Int 93: 1253-1256

Barker JC and Mitteness LS (1988): Nocturia in the elderly. Gerontologist 28: 99-104

Barry MJ, Fowler FJ Jr., O'Leary MP, Bruskewitz RC, Holtgrewe HL and Mebust WK (1995): Measuring disease-specific health status in men with benign prostatic hyperplasia. Measurement Committee of The American Urological Association. Med Care 33: 145-155

Beier-Holgersen R and Bruun J (1990): Voiding pattern of men 60 to 70 years old: population study in an urban population. J Urol 143: 531-532

Bertaccini A, Vassallo F, Martino F, Luzzi L, Rocca Rossetti S, Di Silverio F and Comunale L (2001): Symptoms, bothersomeness and quality of life in patients with LUTS suggestive of BPH. Eur Urol 40 (Suppl 1): 13-18

Berwick DM, Murphy JM, Goldman PA, Ware JE, Jr., Barsky AJ and Weinstein MC (1991): Performance of a five-item mental health screening test. Med Care 29: 169-176

Bing MH, Moller LA, Jennum P, Mortensen S, Skovgaard LT and Lose G (2006): Prevalence and bother of nocturia, and causes of sleep interruption in a Danish population of men and women aged 60-80 years. BJU Int 98: 599-604

Blanker MH, Bohnen AM, Groeneveld FP, Bernsen RM, Prins A and Ruud Bosch JL (2000): Normal voiding patterns and determinants of increased diurnal and nocturnal voiding frequency in elderly men. J Urol 164: 1201-1205

Blanker MH, Bernsen RM, Ruud Bosch JL, Thomas S, Groeneveld FP, Prins A and Bohnen AM (2002): Normal values and determinants of circadian urine production in older men: a population based study. J Urol 168: 1453-1457

Bosch JL, Hop WC, Kirkels WJ and Schröder FH (1995): 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 75: 622-630

Boyle P, Robertson C, Mazzetta C, Keech M, Hobbs R, Fourcade R, Kiemeney L and Lee C (2003): The relationship between lower urinary tract symptoms and health status: the UREPIK study. BJU Int 92: 575-580

Brazzelli M, Murray A and Fraser C (2006): Efficacy and safety of sacral nerve stimulation for urinary urge incontinence: a systematic review. J Urol 175: 835-841

Britton JP, Dowell AC and Whelan P (1990): Prevalence of urinary symptoms in men aged over 60. Br J Urol 66: 175-176

Bruskewitz RC, Larsen EH, Madsen PO and Dorflinger T (1986): 3-year followup of urinary symptoms after transurethral resection of the prostate. J Urol 136: 613-615

Burgio KL, Engel BT and Locher JL (1991): Normative patterns of diurnal urination across 6 age decades. J Urol 145: 728-731

Cai T, Gardener N, Abraham L, Boddi V, Abrams P and Bartoletti R (2006): Impact of surgical treatment on nocturia in men with benign prostatic obstruction. BJU Int 98: 799-805

Callreus T, Ekman E and Andersen M (2005): Hyponatremia in elderly patients treated with desmopressin for nocturia: a review of a case series. Eur J Clin Pharmacol 61: 281-284

Chang SC, Lin AT, Chen KK and Chang LS (2006): Multifactorial nature of male nocturia. Urology 67: 541-544

Chapple CR, Batista JE, Berges R, Chartier-Kastler E, Tubaro A, Van Kerrebroeck P and Stoevelaar H (2006): The impact of nocturia in patients with LUTS/BPH: need for new recommendations. Eur Urol Suppl 5: 12-18

Chartier-Kastler E and Chapple CR (2006): LUTS/BPH in clinical practice: the importance of nocturia and quality of sleep. BJU Int 98 (Suppl 2): 3-8

Chute CG, Panser LA, Girman CJ, Oesterling JE, Guess HA, Jacobsen SJ and Lieber MM (1993): The prevalence of prostatism: a population-based survey of urinary symptoms. J Urol 150: 85-89

Chyou PH, Nomura AM, Stemmermann GN and Hankin JH (1993): A prospective study of alcohol, diet, and other lifestyle factors in relation to obstructive uropathy. Prostate 22: 253-264

Coyne KS, Zhou Z, Bhattacharyya SK, Thompson CL, Dhawan R and Versi E (2003): The prevalence of nocturia and its effect on health-related quality of life and sleep in a community sample in the USA. BJU Int 92: 948-954

van Dijk L, Kooij DG and Schellevis FG (2002): Nocturia in the Dutch adult population. BJU Int 90: 644-648

Diokno AC, Brown MB, Goldstein N and Herzog AR (1992): Epidemiology of bladder emptying symptoms in elderly men. J Urol 148: 1817-1821

Donahue JL and Lowenthal DT (1997): Nocturnal polyuria in the elderly person. Am J Med Sci 314: 232-238

Drake MJ, Mills IW and Noble JG (2004): Melatonin pharmacotherapy for nocturia in men with benign prostatic enlargement. J Urol 171: 1199-1202

DuBeau CE (2006): The aging lower urinary tract. J Urol 175: S11-15

DuBeau CE, Yalla SV and Resnick NM (1995): Implications of the most bothersome prostatism symptom for clinical care and outcomes research. J Am Geriatr Soc 43: 985-992

Eckhardt MD, van Venrooij GE, van Melick HH and Boon TA (2001): Prevalence and bothersomeness of lower urinary tract symptoms in benign prostatic hyperplasia and their impact on well-being. J Urol 166: 563-568

Emberton M, Andriole GL, de la Rosette J, Djavan B, Hoefner K, Vela Navarrete R, Nordling J, Roehrborn C, Schulman C, Teillac P, Tubaro A and Nickel JC (2003): Benign prostatic hyperplasia: a progressive disease of aging men. Urology 61: 267-273

Engström G, Walker-Engström ML, Henningsohn L, Lööf L and Leppert J (2004): Prevalence of distress and symptom severity from the lower urinary tract in men: a population-based study with the DAN-PSS questionnaire. Fam Pract 21: 617-622

Fuxe K, Andersson K, Eneroth P, Harfstrand A and Agnati LF (1989): Neuroendocrine actions of nicotine and of exposure to cigarette smoke: medical implications. Psychoneuroendocrinology 14: 19-41

Garraway WM, Collins GN and Lee RJ (1991): High prevalence of benign prostatic hypertrophy in the community. Lancet 338: 469-471

George CP, Messerli FH, Genest J, Nowaczynski W, Boucher R and Kuchel Orofo-Oftega M (1975): Diurnal variation of plasma vasopressin in man. J Clin Endocrinol Metab 41: 332-338

Gourova LW, van de Beek C, Spigt MG, Nieman FH and van Kerrebroeck PE (2006): Predictive factors for nocturia in elderly men: a cross-sectional study in 21 general practices. BJU Int 97: 528-532

Griffiths DJ, McCracken PN, Harrison GM and Gormley EA (1992): Characteristics of urinary incontinence in elderly patients studied by 24-hour monitoring and urodynamic testing. Age Ageing 21: 195-201

Griffiths DJ, McCracken PN, Harrison GM, Gormley EA, Moore K, Hooper R, McEwan AJ and Triscott J (1994): Cerebral aetiology of urinary urge incontinence in elderly people. Age Ageing 23: 246-250

Guilleminault C, Lin CM, Goncalves MA and Ramos E (2004): A prospective study of nocturia and the quality of life of elderly patients with obstructive sleep apnea or sleep onset insomnia. J Psychosom Res 56: 511-515

Hakenberg OW, Pinnock CB and Marshall VR (1999): The follow-up of patients with unfavourable early results of transurethral prostatectomy. BJU Int 84: 799-804

Hald T, Nordling J, Andersen JT, Bilde T, Meyhoff H-H and Walter S (1991): A patient weighted symptom score system in the evaluation of uncomplicated benign prostatic hyperplasia. Scand J Urol Nephrol Suppl 138: 59-62

Hansen BJ, Flyger H, Brasso K, Schou J, Nordling J, Andersen JT, Mortensen S, Meyhoff H-H, Walter S and Hald T (1995): Validation of the self-administered Danish Prostatic Symptom Score (DAN-PSS-1) system for use in benign prostatic hyperplasia. Br J Urol 76: 451-458

Hansen MV, Zdanowski A and Spångberg A (1994): Prostatism symptoms in a randomly selected population: introduction of a patient administered population based symptom evaluation score. Scand J Urol Nephrol 28: 371-378

Hetta J (1999): The impact of sleep deprivation caused by nocturia. BJU Int 84 (Suppl 1): 27-28

Hirayama A, Fujimoto K, Matsumoto Y and Hirao Y (2005): Nocturia in men with lower urinary tract symptoms is associated with both nocturnal polyuria and detrusor overactivity with positive response to ice water test. Urology 65: 1064-1069

Homma Y (2005): Classification of nocturia in the adult and elderly patient: a review of clinical criteria and selected literature. BJU Int 96 Suppl 1: 8-14

Homma Y, Kawabe K, Tsukamoto T, Yamanaka H, Okada K, Okajima E, Yoshida O, Kumazawa J, Gu FL, Lee C, Hsu TC, dela Cruz RC, Tantiwang A, Lim PH, Sheikh MA, Bapat SD, Marshall VR, Tajima K and Aso Y (1997): Epidemiologic survey of lower urinary tract symptoms in Asia and Australia using the international prostate symptom score. Int J Urol 4: 40-46

Homma Y, Yamaguchi O, Kageyama S, Nishizawa O, Yoshida M and Kawabe K (2000): Nocturia in the adult: classification on the basis of largest voided volume and nocturnal urine production. J Urol 163: 777-781

Homma Y, Yamaguchi T, Kondo Y, Horie S, Takahashi S and Kitamura T (2002): Significance of nocturia in the International Prostate Symptom Score for benign prostatic hyperplasia. J Urol 167: 172-176

Hunskaar S (2005): Epidemiology of nocturia. BJU Int 96 (Suppl 1): 4-7

Jackson S (1999): Lower urinary tract symptoms and nocturia in men and women: prevalence, aetiology and diagnosis. BJU Int 84 (Suppl 1): 5-8

Jacobsen SJ, Girman CJ, Guess HA, Rhodes T, Oesterling JE and Lieber MM (1996): Natural history of prostatism: longitudinal changes in voiding symptoms in community dwelling men. J Urol 155: 595-600

Jennum P (2002): Sleep and nocturia. BJU Int 90 (Suppl 3): 21-24

Johnson TM 2nd, Jones K, Williford WO, Kutner MH, Issa MM and Lepor H (2003): Changes in nocturia from medical treatment of benign prostatic

hyperplasia: secondary analysis of the Department of Veterans Affairs Cooperative Study Trial. J Urol 170: 145-148

Johnson TM 2nd, Sattin RW, Parmelee P, Fultz NH and Ouslander JG (2005): Evaluating potentially modifiable risk factors for prevalent and incident nocturia in older adults. J Am Geriatr Soc 53: 1011-1016

Jolleys JV, Donovan JL, Nanchahal K, Peters TJ and Abrams P (1994): Urinary symptoms in the community: how bothersome are they? Br J Urol 74: 551-555

Kageyama T, Kabuto M, Nitta H, Kurokawa Y, Taira K, Suzuki S and Takemoto T (2000): Prevalence of nocturia among Japanese adults. Psychiatry Clin Neurosci 54: 299-300

Kay L, Stigsby B, Brasso K, Mortensen SO and Munkgaard S (1999): Lower urinary tract symptoms. A population survey using the Danish Prostatic Symptom Score (DAN-PSS) questionnaire. Scand J Urol Nephrol 33: 94-99

Kelleher CJ, Cardozo L, Chapple CR, Haab F and Ridder AM (2005): Improved quality of life in patients with overactive bladder symptoms treated with solifenacin. BJU Int 95: 81-85

van Kerrebroeck P and Weiss J (1999): Standardization and terminology of nocturia. BJU Int 84 (Suppl 1): 1-4

van Kerrebroeck P, Abrams P, Chaikin D, Donovan J, Fonda D, Jackson S, Jennum P, Johnson T, Lose G, Mattiasson A, Robertson G and Weiss J (2002): The standardisation of terminology in nocturia: report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urodyn 21: 179-183

Kirkland JL, Lye M, Levy DW and Banerjee AK (1983): Patterns of urine flow and electrolyte excretion in healthy elderly people. Br Med J (Clin Res Ed) 287: 1665-1667

Kobelt G, Borgstrom F and Mattiasson A (2003): Productivity, vitality and utility in a group of healthy professionally active individuals with nocturia. BJU Int 91: 190-195

Koskimäki J (1997): Lower urinary tract symptoms in men [Dissertation]. University of Tampere, Tampere

Koskimäki J, Hakama M, Huhtala H and Tammela TLJ (1998): Prevalence of lower urinary tract symptoms in Finnish men: a population-based study. Br J Urol 81: 364-369

Koskimäki J, Hakama M, Huhtala H and Tammela TLJ (2001): Is reduced quality of life in men with lower urinary tract symptoms due to concomitant diseases? Eur Urol 40: 661-665

Krieger J, Petiau C, Sforza E, Delanoe C, Hecht MT and Chamouard V (1993): Nocturnal pollacisuria is a symptom of obstructive sleep apnea. Urol Int 50: 93-97

Kuo HC (2002): Efficacy of desmopressin in treatment of refractory nocturia in patients older than 65 years. Urology 59: 485-489

Lee AJ, Russell EB, Garraway WM and Prescott RJ (1996): Three-year follow-up of a community-based cohort of men with untreated benign prostatic hyperplasia. Eur Urol 30: 11-17

Lee AJ, Garraway WM, Simpson RJ, Fisher W and King D (1998): The natural history of untreated lower urinary tract symptoms in middle-aged and elderly men over a period of five years. Eur Urol 34: 325-332

Lee E, Yoo KY, Kim Y, Shin Y and Lee C (1998): Prevalence of lower urinary tract symptoms in Korean men in a community-based study. Eur Urol 33: 17-21

Liew LC, Tiong HY, Wong ML, Png DC and Tan JK (2006): A population study of nocturia in Singapore. BJU Int 97: 109-112

Lin CC, Tsan KW and Lin CY (1993): Plasma levels of atrial natriuretic factor in moderate to severe obstructive sleep apnea syndrome. Sleep 16: 37-39

Logie J, Clifford GM and Farmer RD (2005): Incidence, prevalence and management of lower urinary tract symptoms in men in the UK. BJU Int 95: 557-562

van Londen L, Goekoop JG, van Kempen GM, Frankhuijzen-Sierevogel AC, Wiegant VM, van der Velde EA and De Wied D (1997): Plasma levels of arginine vasopressin elevated in patients with major depression. Neuropsychopharmacology 17: 284-292

Lucassen PJ, Van Heerikhuize JJ, Guldenaar SE, Pool CW, Hofman MA and Swaab DF (1997): Unchanged amounts of vasopressin mRNA in the supraoptic and paraventricular nucleus during aging and in Alzheimer's disease. J Neuroendocrinol 9: 297-305

Lundgren R (2004): Nocturia: a new perspective on an old symptom. Scand J Urol Nephrol 38: 112-116

Madersbacher S, Alivizatos G, Nordling J, Sanz CR, Emberton M and de la Rosette JJ (2004): EAU 2004 guidelines on assessment, therapy and follow-up of men with lower urinary tract symptoms suggestive of benign prostatic obstruction (BPH guidelines). Eur Urol 46: 547-554

Malmsten UG, Milsom I, Molander U and Norlen LJ (1997): Urinary incontinence and lower urinary tract symptoms: an epidemiological study of men aged 45 to 99 years. J Urol 158: 1733-1737

Marinkovic SP, Gillen LM and Stanton SL (2004): Managing nocturia. BMJ 328: 1063-1066

Marschall-Kehrel D (2004): Update on nocturia: the best of rest is sleep. Urology 64: 21-24

Matthiesen TB, Rittig S, Nørgaard JP, Pedersen EB and Djurhuus JC (1996): Nocturnal polyuria and natriuresis in male patients with nocturia and lower urinary tract symptoms. J Urol 156: 1292-1299

Mattiasson A, Abrams P, Van Kerrebroeck P, Walter S and Weiss J (2002): Efficacy of desmopressin in the treatment of nocturia: a double-blind placebo-controlled study in men. BJU Int 89: 855-862

Matzkin H, Greenstein A, Prager-Geller T, Sofer M and Braf Z (1996): Do reported micturition symptoms on the American Urological Association Questionnaire correlate with 24-hour home uroflowmetry recordings? J Urol 155: 197-199

McGrother CW, Donaldson MM, Shaw C, Matthews RJ, Hayward TA, Dallosso HM, Jagger C, Clarke M and Castleden CM (2004): Storage symptoms of the bladder: prevalence, incidence and need for services in the UK. BJU Int 93: 763-769

McKeigue PM and Reynard JM (2000): Relation of nocturnal polyuria of the elderly to essential hypertension. Lancet 355: 486-488

Meyhoff H-H, Hald T, Nordling J, Andersen JT, Bilde T and Walter S (1993): A new patient weighted symptom score system (DAN-PSS-1). Clinical assessment of indications and outcomes of transurethral prostatectomy for uncomplicated benign prostatic hyperplasia. Scand J Urol Nephrol 27: 493-499

Middelkoop HA, Smilde-van den Doel DA, Neven AK, Kamphuisen HA and Springer CP (1996): Subjective sleep characteristics of 1,485 males and females aged 50-93: effects of sex and age, and factors related to self-evaluated quality of sleep. J Gerontol A Biol Sci Med Sci 51: 108-115

Miller M (1997): Fluid and electrolyte homeostasis in the elderly: physiological changes of ageing and clinical consequences. Baillieres Clin Endocrinol Metab 11: 367-387

Miller M (2000): Nocturnal polyuria in older people: pathophysiology and clinical implications. J Am Geriatr Soc 48: 1321-1329

Milsom I, Abrams P, Cardozo L, Roberts RG, Thuroff J and Wein AJ (2001): How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. BJU Int 87: 760-766

Moon DG, Jin MH, Lee JG, Kim JJ, Kim MG and Cha DR (2004): Antidiuretic hormone in elderly male patients with severe nocturia: a circadian study. BJU Int 94: 571-575

Morley J (2000): Water, water everywhere and not a drop to drink. J Gerontol A Biol Sci Med Sci 55: M359-360

Nadal M (1996): Secretory rhythm of vasopressin in healthy subjects with inversed sleep--wake cycle: evidence for the existence of an intrinsic regulation. Eur J Endocrinol 134: 174-176

Nakamura S, Kobayashi Y, Tozuka K, Tokue A, Kimura A and Hamada C (1996): Circadian changes in urine volume and frequency in elderly men. J Urol 156: 1275-1279

Namiki S, Saito S, Ishidoya S, Tochigi T, Ioritani N, Yoshimura K, Terai A and Arai Y (2005): Adverse effect of radical prostatectomy on nocturia and voiding frequency symptoms. Urology 66: 147-151

Norman RW, Nickel JC, Fish D and Pickett SN (1994): 'Prostate-related symptoms' in Canadian men 50 years of age or older: prevalence and relationships among symptoms. Br J Urol 74: 542-550

Ouslander JG, Nasr SZ, Miller M, Withington W, Lee CS, Wiltshire-Clement M, Cruise P and Schnelle JF (1998): Arginine vasopressin levels in nursing home residents with nighttime urinary incontinence. J Am Geriatr Soc 46: 1274-1279

Oztura I, Kaynak D and Kaynak HC (2006): Nocturia in sleep-disordered breathing. Sleep Med 7: 362-367

Paick JS, Ku JH, Shin JW, Yang JH and Kim SW (2006): Alpha-blocker monotherapy in the treatment of nocturia in men with lower urinary tract symptoms: a prospective study of response prediction. BJU Int 97: 1017-1023

Pannek J, Berges RR, Haupt G and Senge T (1998): Value of the Danish Prostate Symptom Score compared to the AUA symptom score and pressure/flow studies in the preoperative evaluation of men with symptomatic benign prostatic hyperplasia. Neurourol Urodyn 17: 9-18

Perrin P, Marionneau N, Cucherat M and Taieb C (2005): Relationship between lower urinary tract symptoms frequency assessed by the IPSS and bothersomeness (SPI) among men older than 50 years old. Eur Urol 48: 601-607

Peters TJ, Donovan JL, Kay HE, Abrams P, de la Rosette JJ, Porru D and Thuroff JW (1997): The International Continence Society "Benign Prostatic Hyperplasia" Study: the bothersomeness of urinary symptoms. J Urol 157: 885-889

Pinnock C and Marshall VR (1997): Troublesome lower urinary tract symptoms in the community: a prevalence study. Med J Aust 167: 72-75

Platz EA, Smit E, Curhan GC, Nyberg LM and Giovannucci E (2002): Prevalence of and racial/ethnic variation in lower urinary tract symptoms and noncancer prostate surgery in U.S. men. Urology 59: 877-883

Pollak CP and Perlick D (1991): Sleep problems and institutionalization of the elderly. J Geriatr Psychiatry Neurol 4: 204-210

Prasad VK, Häkkinen JT, Shiri R and Al Ansari A (2006): Prevalence and determinants of lower urinary tract symptoms among expatriate male workers in Qatar. Indian J Urol 22: 27-31

Pressman MR, Figueroa WG, Kendrick-Mohamed J, Greenspon LW and Peterson DD (1996): Nocturia. A rarely recognized symptom of sleep apnea and other occult sleep disorders. Arch Intern Med 156: 545-550

Quinn N (1989): Multiple system atrophy--the nature of the beast. J Neurol Neurosurg Psychiatry Special Suppl: 78-89

Rembratt A, Norgaard JP and Andersson KE (2002): What is nocturnal polyuria? BJU Int 90 (Suppl 3): 18-20

Rembratt A, Norgaard JP and Andersson KE (2003): Nocturia and associated morbidity in a community-dwelling elderly population. BJU Int 92: 726-730

Rembratt A, Riis A and Norgaard JP (2006): Desmopressin treatment in nocturia; an analysis of risk factors for hyponatremia. Neurourol Urodyn 25: 105-109

Resnick NM, Yalla SV and Laurino E (1989): The pathophysiology of urinary incontinence among institutionalized elderly persons. N Engl J Med 320: 1-7

Reynard JM, Cannon A, Yang Q and Abrams P (1998): A novel therapy for nocturnal polyuria: a double-blind randomized trial of frusemide against placebo. Br J Urol 81: 215-218

Rittig S, Knudsen UB, Norgaard JP, Pedersen EB and Djurhuus JC (1989): Abnormal diurnal rhythm of plasma vasopressin and urinary output in patients with enuresis. Am J Physiol 256: 664-671

Robertson G and Berl T (2000): Pathophysiology of water metabolism. In: The Kidney, 6th ed. Brenner B (ed.). Philadelphia, WB Saunders**:** 866-924

Robertson GL and Nørgaard JP (2002): Renal regulation of urine volume: potential implications for nocturia. BJU Int 90 (Suppl 3): 7-10

Rosen RC, Cappelleri JC, Smith MD, Lipsky J and Pena BM (1999): Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. Int J Impot Res 11: 319-326

Rumpf HJ, Meyer C, Hapke U and John U (2001): Screening for mental health: validity of the MHI-5 using DSM-IV Axis I psychiatric disorders as gold standard. Psychiatry Res 105: 243-253

Sagnier PP, MacFarlane G, Richard F, Botto H, Teillac P and Boyle P (1994): Results of an epidemiological survey using a modified American Urological Association symptom index for benign prostatic hyperplasia in France. J Urol 151: 1266-1270

Sagnier PP, MacFarlane G, Teillac P, Botto H, Richard F and Boyle P (1995): Impact of symptoms of prostatism on level of bother and quality of life of men in the French community. J Urol 153: 669-673

Sagnier PP, Girman CJ, Garraway M, Kumamoto Y, Lieber MM, Richard F, MacFarlane G, Guess HA, Jacobsen SJ, Tsukamoto T and Boyle P (1996): International comparison of the community prevalence of symptoms of prostatism in four countries. Eur Urol 29: 15-20

Saito M, Kondo A, Kato T and Yamada Y (1993): Frequency-volume charts: comparison of frequency between elderly and adult patients. Br J Urol 72: 38-41

Samos LF and Roos BA (1998): Diabetes mellitus in older persons. Med Clin North Am 82: 791-803

Schatzl G, Temml C, Schmidbauer J, Dolezal B, Haidinger G and Madersbacher S (2000): Cross-sectional study of nocturia in both sexes: analysis of a voluntary health screening project. Urology 56: 71-75

Schneider DL (2002): Insomnia. Safe and effective therapy for sleep problems in the older patient. Geriatrics 57: 24-26

Seim A, Hoyo C, Ostbye T and Vatten L (2003): Prevalence and correlates of nocturia in men - a large community based study. ICS 2003, Florence, Italy. Abstract 63. [cited 3.1. 2007]. Available at: http://www.icsoffice.org/publications/2003/PDF/063.PDF

Seim A, Hoyo C, Ostbye T and Vatten L (2005): The prevalence and correlates of urinary tract symptoms in Norwegian men: the HUNT study. BJU Int 96: 88-92

Sintonen H and Pekurinen M (1989): A generic 15 dimensional measure of health-related quality of life (15D). J Soc Med 26: 85-96

Sommer P, Nielsen KK, Bauer T, Kristensen ES, Hermann GG, Steven K and Nordling J (1990): Voiding patterns in men evaluated by a questionnaire survey. Br J Urol 65: 155-160

Spinelli M, Giardiello G, Gerber M, Arduini A, van den Hombergh U and Malaguti S (2003): New sacral neuromodulation lead for percutaneous implantation using local anesthesia: description and first experience. J Urol 170: 1905-1907

Stanley N (2005): The physiology of sleep and the impact of ageing. Eur Urol Suppl 3: 17-23

Statistics Finland (2006): Väestötilastot. [WWW]. Statistics Finland. [cited 5.10. 2006]. Available at: http://pxweb2.stat.fi/database/V%E4est%F6/V%E4est%F6rakenne/V%E4est%F6rakenne.asp

Steers WD and Lee KS (2001): Depression and incontinence. World J Urol 19: 351-357

Stewart RB, Moore MT, May FE, Marks RG and Hale WE (1992): Nocturia: a risk factor for falls in the elderly. J Am Geriatr Soc 40: 1217-1220

Tan HY, Choo WC, Archibald C and Esuvaranathan K (1997): A community based study of prostatic symptoms in Singapore. J Urol 157: 890-893

Tanaka Y, Kawauchi A, Watanabe H and Imada N (1998): Relationship between nocturnal urinary frequency and sleep disturbances in aged men. Psychiatry Clin Neurosci 52: 189-190

Temml C, Brossner C, Schatzl G, Ponholzer A, Knoepp L and Madersbacher S (2003): The natural history of lower urinary tract symptoms over five years. Eur Urol 43: 374-380

Tikkinen KA, Auvinen A, Huhtala H and Tammela TL (2006a): Nocturia and obesity: a population-based study in Finland. Am J Epidemiol 163: 1003-1011

Tikkinen KA, Tammela TL, Huhtala H and Auvinen A (2006b): Is nocturia equally common among men and women? A population based study in Finland. J Urol 175: 596-600

Tsukamoto T, Kumamoto Y, Masumori N, Miyake H, Rhodes T, Girman CJ, Guess HA, Jacobsen SJ and Lieber MM (1995): Prevalence of prostatism in Japanese men in a community-based study with comparison to a similar American study. J Urol 154: 391-395

Tubaro A, Batista JE, Berges R, Chartier-Kastler E, van Kerrebroeck P, Chapple C and Stoevelaar H (2006): Future directions in evaluating nocturia and its impact in patients with LUTS/BPH. Eur Urol Suppl 5: 19-21

Umlauf MG, Chasens ER, Greevy RA, Arnold J, Burgio KL and Pillion DJ (2004): Obstructive sleep apnea, nocturia and polyuria in older adults. Sleep 27: 139-144

Uygur MC, Ergen A and Remzi D (1995): Enuresis nocturna: new concepts in pathophysiology. Int Urol Nephrol 27: 439-443

Weatherall M (2004): The risk of hyponatremia in older adults using desmopressin for nocturia: a systematic review and meta-analysis. Neurourol Urodyn 23: 302-305

Wein A and Abrams P (2002): Statement from the First International Consultation on Nocturia: reaching for a consensus. BJU Int 90 (Suppl 3): 37

Weiss JP (2006): Nocturia: "do the math". J Urol 175: S16-18

Weiss JP and Blaivas JG (2000): Nocturia. J Urol 163: 5-12

Weiss JP and Blaivas JG (2002): Nocturnal polyuria versus overactive bladder in nocturia. Urology 60: 28-32

Weiss JP and Blaivas JG (2003): Nocturia. Adv Exp Med Biol 539: 751-772

Weiss JP, Blaivas JG, Stember DS and Brooks MM (1998): Nocturia in adults: etiology and classification. Neurourol Urodyn 17: 467-472

Verhamme KM, Dieleman JP, Bleumink GS, van der Lei J, Sturkenboom MC, Artibani W, Begaud B, Berges R, Borkowski A, Chappel CR, Costello A, Dobronski P, Farmer RD, Jimenez Cruz F, Jonas U, MacRae K, Pientka L, Rutten FF, van Schayck CP, Speakman MJ, Sturkenboom MC, Tiellac P, Tubaro A, Vallencien G and Vela Navarrete R (2002): Incidence and prevalence of lower urinary tract symptoms suggestive of benign prostatic hyperplasia in primary care--the Triumph project. Eur Urol 42: 323-328

Williamson AM and Feyer AM (2000): Moderate sleep deprivation produces impairments in cognitive and motor performance equivalent to legally

prescribed levels of alcohol intoxication. Occup Environ Med 57: 649-655

Wolfs GG, Knottnerus JA and Janknegt RA (1994): Prevalence and detection of micturition problems among 2,734 elderly men. J Urol 152: 1467-1470

Yalkut D, Lee LY, Grider J, Jorgensen M, Jackson B and Ott C (1996): Mechanism of atrial natriuretic peptide release with increased inspiratory resistance. J Lab Clin Med 128: 322-328

Yoshimura K and Terai A (2005): Fluctuation of night time frequency in patients with symptomatic nocturia. Int J Urol 12: 469-473

Yoshimura K, Ohara H, Ichioka K, Terada N, Matsui Y, Terai A and Arai Y (2003): Nocturia and benign prostatic hyperplasia. Urology 61: 786-790

Yoshimura K, Terada N, Matsui Y, Terai A, Kinukawa N and Arai Y (2004): Prevalence of and risk factors for nocturia: Analysis of a health screening program. Int J Urol 11: 282-287

Yu HJ, Chen TH, Chie WC, Liu CY, Tung TH and Huang SW (2005): Prevalence and associated factors of nocturia among adult residents of the Matsu area of Taiwan. J Formos Med Assoc 104: 444-447

Zhou JN, Riemersma RF, Unmehopa UA, Hoogendijk WJ, van Heerikhuize JJ, Hofman MA and Swaab DF (2001): Alterations in arginine vasopressin neurons in the suprachiasmatic nucleus in depression. Arch Gen Psychiatry 58: 655-662

Åkerstedt T and Nilsson PM (2003): Sleep as restitution: an introduction. J Intern Med 254: 6-12

Appendix 1

The 1999 original TAMUS questionnaire:
(See next page.)

MIESTEN VIRTSAVAIVAT
KYSELYLOMAKE OSA I

Olkaa hyvä ja vastatkaa alla oleviin kysymyksiin rastittamalla sopiva vaihtoehto tai täydentämällä kysymykseen liittyvä vastaustila.

1 **HENKILÖTIEDOT**

SUKUNIMI (vapaaehtoinen)

ETUNIMET (vapaaehtoinen)

SYNTYMÄAIKA / / 19
päivä kuukausi vuosi

2 **AMMATTI**

0 Olen työelämässä ja ammattini on (kirjoittakaa ruutuun)

1 Olen eläkkeellä, ammattini oli

2 Olen työttömänä, ammattikoulutukseni on

3 **SIVIILISÄÄTY**

Olen
0 Naimisissa
1 Eronnut
2 Leski
3 Avoliitossa
4 Naimaton

5 Elän vakituisessa parisuhteessa

4 **TERVEYS**

Viimeisen viiden vuoden aikana terveyteni on

0 Huonontunut voimakkaasti
1 Huonontunut hieman
2 Pysynyt ennallaan
3 Parantunut hieman
4 Parantunut selvästi

5 PITUUS JA PAINO

Pituuteni on [ ] cm Painoni on [ ] kg

6 TUPAKOINTI

Tupakoitteko nykyään tai oletteko koskaan tupakoinut säännöllisesti?

[0] **En** Voitte siirtyä kysymysryhmään 7.
[1] **Kyllä** Vastatkaa vielä alla oleviin tarkentaviin kysymyksiin.

Minä vuonna aloititte **säännöllisen** tupakoinnin? 19_____
Jos olette lopettanut tupakoinnin, minä vuonna? 19_____
Kuinka paljon poltatte **päivittäin** nykyään? Tai, kuinka paljon poltitte päivittäin ennen lopettamista?

Savukkeita tai pikkusikareja	[ ]	kpl
Piippua	[ ]	pesällistä
Sikareja	[ ]	kpl
Käytän nuuskaa päivittäin	[ ]	kertaa

7 MUUT NAUTINTOAINEET

Juotteko kahvia tai teetä päivittäin?

[0] **En**
[1] **Kyllä**, _____ kuppia kahvia päivässä.
[2] **Kyllä**, _____ kuppia teetä päivässä.

Juotteko alkoholipitoisia juomia?

[3] **En lainkaan.** Voitte siirtyä kysymysryhmään 8.
[4] **Kyllä, satunnaisesti, mutta en joka viikko.**
[5] **Kyllä, viikoittain**
Jos käytätte alkoholia viikoittain, arvioikaa keskimääräinen kulutuksenne tässä.

Olutta	_____	pulloa (1/3 l)		
Viiniä	_____	pulloa (3/4 l), tai	____(12 cl)	lasillista
Väkeviä	_____	pulloa (1/2 l), tai	____ (4 cl)	lasillista

8 LÄÄKKEET

Käytättekö säännöllisesti lääkkeitä?

[0] **En käytä**. Voitte siirtyä seuraavalle sivulle kysymysryhmään 9.
[1] **Kyllä käytän**. Merkitkää alla olevista lääkeryhmistä ne, joihin käytössänne olevat lääkkeet kuuluvat.

[2]	Sydänlääkkeet	[6]	Nesteenpoistolääkkeet
[3]	Verenpainelääkkeet	[7]	Virtsaamisvaivojen lääkkeet
[4]	Kipulääkkeet	[9]	Impotenssin lääkkeet
[5]	Mielenterveyslääkkeet	[10]	Hormonilääkkeet

9 SAIRAUDET JA VAMMAT

Sairastatteko tai oletteko joskus sairastanut jotain seuraavista sairauksista? (Rastittakaa Teillä olevat tai olleet sairaudet.)

- [0] En sairasta, enkä ole sairastanut mitään näistä sairauksista.

- [1] Sokeritauti
- [2] Kohonnut verenpaine
- [3] Sydänsairaus
- [4] Nivelkulumia
- [5] Ummetusta
- [6] Ulosteen pidätyskyvyttömyyttä
- [7] Hengityselinsairaus
- [8] Neurologinen sairaus
- [9] Aivojen verenkiertohäiriö
- [10] Halvaus
- [11] Selkäsairaus
- [12] Selkäytimen vamma
- [13] Virtsateiden vamma
- [14] Virtsatiekivi
- [15] Virtsaumpi
- [16] Virtsatietulehdus
- [17] Virtsaputken kurouma
- [18] Syöpä
- [19] Nivustyrä
- [20] Muu, mikä

10 TUTKIMUKSET JA LEIKKAUKSET

Onko Teille tehty viimeisen viiden vuoden aikana jokin seuraavista tutkimuksista tai leikkauksista? (Merkitkää rastilla.)

- [0] Ei mitään tässä luetelluista.
- [1] Peräsuolen poistoleikkaus
- [2] Virtsan tai ulosteen pidätyskykyä parantava leikkaus
- [3] Selkäleikkaus
- [4] Vatsa-aortan pullistuman (aneurysman) leikkaus
- [5] Aivo- tai selkäydinleikkaus
- [6] Eturauhasen höyläysleikkaus (TURP)
- [7] Eturauhasen liikakasvun avoleikkaus
- [8] Muu eturauhasta pienentävä toimenpide
- [9] Eturauhasen poistoleikkaus syövän vuoksi
- [10] Virtsarakkoon kohdistunut leikkaus (avoin tai tähystysleikkaus)
- [11] Virtsaputkeen kohdistunut leikkaus (avoin tai tähystysleikkaus)
- [12] Virtsarakon tähystys
- [13] Virtsateiden ultraääni- tai röntgentutkimus
- [14] Virtsanvirtausmittaus
- [15] Urodynaaminen tutkimus

11 MUU HOITO

Oletteko viimeisen viiden vuoden aikana saanut hoitoa

Virtsavaivojen vuoksi?

- [0] **Kyllä**
- [1] **En**

Impotenssin vuoksi?

- [2] **Kyllä**
- [3] **En**

12 **LÄÄKELISTA**

Pyydämme Teitä vielä kirjoittamaan alla oleville riveille
<u>kaikki</u> säännöllisesti käyttämänne lääkkeet annostuksineen.

LÄÄKE	ANNOS

Nyt voitte siirtyä kyselyn seuraaviin osiin, joissa kysytään yksityiskohtaisia virtsaamiseen, sukupuolielämään ja yleiseen elämän laatuun liittyviä asioita.

OSA II

VIRTSAAMISEEN JA SUKUPUOLITOIMINTOIHIN LIITTYVÄT KYSYMYKSET:

Tämä kysely koostuu kahdenlaisista kysymyksistä:

A-kysymyksissä kysytään, kuinka **voimakas** kyseinen oire Teillä on.

B-kysymyksissä kysytään, kuinka paljon **haittaa** Teille on oireesta.

Vastatkaa jokaiseen kysymykseen merkitsemällä rasti sopivan vastausvaihtoehdon kohdalle.
Jos kuitenkin valitsette A kohdassa ensimmäisen vaihtoehdon eli Teillä ei ole kysymyksen oiretta, voitte jättää B kysymyksen vastaamatta.

1 A	**Täytyykö virtsaamisen alkamista odottaa?** ☐ Ei koskaan ☐ Harvoin ☐ Usein ☐ Aina	1 B	**Mikäli joudutte odottamaan virtsaamisen alkamista, kuinka paljon siitä on Teille haittaa?** ☐ Ei lainkaan ☐ Vähän ☐ Kohtalaisesti ☐ Hyvin paljon
2 A	**Tuleeko virtsa omasta mielestänne:** ☐ Normaalisti ☐ Heikosti ☐ Hyvin heikosti ☐ Tipoittain	2 B	**Mikäli virtsa tulee heikosti, kuinka paljon siitä on Teille haittaa?** ☐ Ei lainkaan ☐ Vähän ☐ Kohtalaisesti ☐ Hyvin paljon
3 A	**Tuntuuko, että virtsatessanne rakko tyhjenee täysin?** ☐ Kyllä, aina ☐ Usein ☐ Harvoin ☐ Ei koskaan	3 B	**Mikäli tunnette, ettei rakko tyhjene täysin, kuinka paljon siitä on Teille haittaa?** ☐ Ei lainkaan ☐ Vähän ☐ Kohtalaisesti ☐ Hyvin paljon
4 A	**Joudutteko ponnistamaan virtsaamisen aloittamiseksi tai virtsaamisen jatkamiseksi?** ☐ En koskaan ☐ Harvoin ☐ Usein ☐ Aina	4 B	**Mikäli joudutte ponnistelemaan, kuinka paljon siitä on Teille haittaa?** ☐ Ei lainkaan ☐ Vähän ☐ Kohtalaisesti ☐ Hyvin paljon
5A	**Tippuuko virtsa vielä, vaikka luulitte virtsaamisen loppuneen (jälkitippuminen)?** ☐ Ei koskaan ☐ Kyllä, WC:ssä ☐ Hieman alushousuihin ☐ Runsaasti alushousuihin	5B	**Mikäli jälkitippumista esiintyy kuinka paljon siitä on Teille haittaa?** ☐ Ei lainkaan ☐ Vähän ☐ Kohtalaisesti ☐ Hyvin paljon
6A	**Kuinka pitkä on pisin kahden virtsaamisen välinen aika päivällä?** ☐ Yli 3 tuntia ☐ 2-3 tuntia ☐ 1-2 tuntia ☐ Alle tunti	6B	**Mikäli joudutte virtsaamaan usein, kuinka paljon siitä on Teille haittaa?** ☐ Ei lainkaan ☐ Vähän ☐ Kohtalaisesti ☐ Hyvin paljon
7A	**Kuinka monta kertaa joudutte virtsaamaan yön aikana?** ☐ 0 kertaa ☐ 1-2 kertaa ☐ 3-4 kertaa ☐ 5 kertaa tai useammin	7B	**Mikäli joudutte virtsaamaan yöllä, kuinka paljon siitä on Teille haittaa?** ☐ Ei lainkaan ☐ Vähän ☐ Kohtalaisesti ☐ Hyvin paljon

8A	**Tuleeko Teille äkillinen virtsaamistarve?** ☐ Ei koskaan ☐ Harvoin ☐ Usein ☐ Aina	8B	**Mikäli Teille tulee äkillinen virtsaamistarve, kuinka paljon siitä on Teille haittaa?** ☐ Ei lainkaan ☐ Vähän ☐ Kohtalaisesti ☐ Hyvin paljon
9A	**Tuleeko virtsaamisen tarve niin voimakkaana että virtsa karkaa ennen kuin ehditte WC:hen?** ☐ Ei koskaan ☐ Harvoin ☐ Usein ☐ Aina	9B	**Mikäli virtsa karkaa ennen kuin ehditte WC:hen, kuinka paljon siitä on Teille haittaa?** ☐ Ei lainkaan ☐ Vähän ☐ Kohtalaisesti ☐ Hyvin paljon
10A	**Tunnetteko virtsatessanne kipua tai poltetta?** ☐ En koskaan ☐ Harvoin ☐ Usein ☐ Aina	10 B	**Mikäli virtsatessanne tuntuu kipua tai poltetta kuinka paljon siitä on Teille haittaa?** ☐ Ei lainkaan ☐ Vähän ☐ Kohtalaisesti ☐ Hyvin paljon
11 A	**Karkaako virtsaa fyysisen ponnistuksen aikana (esim. yskiessänne, aivastaessanne tai nostaessanne)?** ☐ Ei koskaan ☐ Harvoin ☐ Usein ☐ Aina	11 B	**Mikäli virtsaa karkaa fyysisen ponnistuksen aikana, kuinka paljon siitä on Teille haittaa?** ☐ Ei lainkaan ☐ Vähän ☐ Kohtalaisesti ☐ Hyvin paljon
12 A	**Karkaako virtsaa ilman fyysistä ponnistusta ja ilman virtsaustarvetta?** ☐ Ei koskaan ☐ Harvoin ☐ Usein ☐ Aina	12 B	**Mikäli virtsaa karkaa ilman fyysistä ponnistusta ja virtsaustarvetta, kuinka paljon siitä on Teille haittaa?** ☐ Ei lainkaan ☐ Vähän ☐ Kohtalaisesti ☐ Hyvin paljon
13.	**Kuinka tyytyväinen olette seksielämäänne?**		☐ Erittäin tyytyväinen ☐ Melko tyytyväinen ☐ En tyytyväinen enkä tyytymätön ☐ Melko tyytymätön ☐ Erittäin tyytymätön
14.	**Kuinka monta kertaa keskimäärin olette yhdynnässä viikon aikana?**		_____ kertaa
15.	**Onko Teillä ollut vaikeuksia saada siitin jäykistymään ennen yhdyntää?**		☐ Ei koskaan ☐ Joskus ☐ Melko usein ☐ Aina, yhdyntä ei onnistu lainkaan
16.	**Onko Teillä ollut vaikeuksia saada siitin pysymään jäykkänä yhdynnän aikana?**		☐ Ei koskaan ☐ Joskus ☐ Melko usein ☐ Aina, yhdyntä ei onnistu lainkaan
17.	**Kuinka usein herätessänne siittimenne on ollut täysin jäykkä?**		☐ Päivittäin ☐ 2-3 kertaa viikossa ☐ Kerran viikossa ☐ Harvemmin kuin kerran viikossa

OSA III

YLEISET ELÄMÄNLAATUKYSYMYKSET:

Seuraavissa kysymyksissä esitetään vaihtoehtoja, jotka kuvaavat mahdollisen sairautenne Teille aiheuttamaa haittaa ja toimintahäiriön astetta. Lukekaa ensin kunkin kysymyksen kaikki vastausvaihtoehdot huolellisesti läpi. Merkitkää sen jälkeen rastilla se vaihtoehto, joka parhaiten kuvaa terveydentilaanne tänään. **Jokaisesta kysymyksestä valitaan vain yksi vaihtoehto**.

1. **Liikuntakyky**
   - ☐ Pystyn kävelemään ja liikkumaan normaalisti (vaikeuksitta) sisällä, ulkona ja portaissa.
   - ☐ Pystyn kävelemään vaikeuksitta sisällä, mutta ulkona tai portaissa on pieniä vaikeuksia.
   - ☐ Pystyn kävelemään ilman apua sisällä (välinein tai ilman), mutta ulkona tai portaissa melkoisin vaikeuksin tai toisen avustamana.
   - ☐ Pystyn kävelemään sisälläkin vain toisen avustamana.
   - ☐ Olen täysin liikuntakyvytön ja vuoteen omana.
2. **Näkö**
   - ☐ Näen normaalisti, eli näen lukea lehteä ja TV:n tekstejä vaikeuksitta silmälaseilla tai ilman.
   - ☐ Näen lukea lehteä tai TV:n tekstejä pienin vaikeuksin silmälaseilla tai ilman.
   - ☐ Näen lukea lehteä tai TV:n tekstejä huomattavin vaikeuksin silmälaseilla tai ilman.
   - ☐ En näe lukea lehteä enkä TV:n tekstejä ilman silmälaseja tai niiden kanssa, mutta näen kulkea ilman opasta.
   - ☐ En näe kulkea ilman opasta eli olen lähes tai täysin sokea.
3. **Kuulo**
   - ☐ Kuulen normaalisti eli kuulen hyvin normaalia puheääntä kuulokojeen kanssa tai ilman sitä.
   - ☐ Kuulen normaalia puheääntä pienin vaikeuksin.
   - ☐ Kuulen normaalia puheääntä melkoisin vaikeuksin, keskustelussa on käytettävä normaalia kovempaa puheääntä.
   - ☐ Kuulen kovaakin puheääntä heikosti, olen melkein kuuro.
   - ☐ Olen täysin kuuro.
4. **Hengitys**
   - ☐ Pystyn hengittämään normaalisti eli minulla ei ole hengenahdistusta eikä muita hengitysvaikeuksia.
   - ☐ Minulla on hengenahdistusta raskaassa työssä tai urheillessa, reippaassa kävelyssä tasamaalla tai lievässä ylämäessä.
   - ☐ Minulla on hengenahdistusta kävellessä muitten samanikäisten vauhtia tasamaalla.
   - ☐ Minulla on hengenahdistusta pienenkin rasituksen jälkeen, esimerkiksi pukeutuessa, peseytyessä tai levossa.
   - ☐ Minulla on hengenahdistusta lähes koko ajan, myös levossa.
5. **Nukkuminen**
   - ☐ Nukun normaalisti, eikä minulla ole ongelmia unen suhteen.
   - ☐ Minulla on lieviä uniongelmia, esimerkiksi nukahtamisvaikeuksia tai heräilen satunnaisesti yöllä.
   - ☐ Minulla on melkoisia uniongelmia, esimerkiksi nukun levottomasti, uni ei tunnu riittävän.
   - ☐ Minulla on suuria uniongelmia, esimerkiksi joudun käyttämään usein tai säännöllisesti unilääkettä. Herään säännöllisesti yöllä tai aamuisin liian varhain.
   - ☐ Kärsin vaikeasta unettomuudesta, esimerkiksi unilääkkeiden runsaasta käytöstä huolimatta nukkuminen on lähes mahdotonta. Valvon suurimman osan yöstä.
6. **Syöminen**
   - ☐ Pystyn syömään normaalisti eli itse ilman mitään vaikeuksia.
   - ☐ Pystyn syömään pienin vaikeuksin, esimerkiksi hitaasti, kömpelösti, vapisten tai erityisapuneuvoin.
   - ☐ Tarvitsen hieman toisten apua syömisessä.
   - ☐ En pysty syömään itse lainkaan, vaan minua pitää syöttää.
   - ☐ En pysty syömään itse lainkaan, vaan minua pitää syöttää joko letkulla tai suonensisäisellä ravintoliuoksella.

7. **Puhuminen**
- ☐ Pystyn puhumaan normaalisti, eli selvästi, kuuluvasti ja sujuvasti.
- ☐ Puhuminen tuottaa minulle pieniä vaikeuksia, esimerkiksi sanoja on etsittävä tai ääni ei ole riittävän kuuluva tai se vaihtaa korkeutta.
- ☐ Pystyn puhumaan ymmärrettävästi, mutta katkonaisesti, ääni vavisten, sammaltaen tai änkyttäen.
- ☐ Muilla on vaikeuksia ymmärtää puhettani.
- ☐ Pystyn ilmaisemaan itseäni vain elein.

8. **Eritystoiminta**
- ☐ Virtsarakkoni ja suolistoni toimivat normaalisti ja ongelmitta
- ☐ Virtsarakkoni tai suolistoni toiminnassa on lieviä ongelmia, esimerkiksi minulla on virtsaamisvaikeuksia tai kova tai löysä vatsa.
- ☐ Virtsarakkoni tai suolistoni toiminnassa on melkoisia ongelmia, esimerkiksi minulla on satunnaisia virtsanpidätysvaikeuksia tai vaikea ummetus tai ripuli.
- ☐ Virtsarakkoni tai suolistoni toiminnassa on suuria ongelmia, esimerkiksi minulla on säännöllisesti "vahinkoja" tai peräruiskeiden tai katetroinnin tarvetta.
- ☐ En hallitse lainkaan virtsaamistani tai ulostamistani.

9. **Tavanomaiset toiminnot**
- ☐ Pystyn suoriutumaan normaalisti tavanomaisista toiminnoista, esimerkiksi ansiotyöstä, opiskelusta, kotityöstä ja vapaa-ajan toiminnoista.
- ☐ Pystyn suoriutumaan tavanomaisista toiminnoista hieman alentuneella teholla tai pienin vaikeuksin.
- ☐ Pystyn suoriutumaan tavanomaisista toiminnoista huomattavasti alentuneella teholla tai huomattavin vaikeuksin tai vain osittain.
- ☐ Pystyn suoriutumaan tavanomaisista toiminnoista vain pieneltä osin.
- ☐ En pysty suoriutumaan lainkaan tavanomaisista toiminnoista.

10. **Henkinen toiminta**
- ☐ Pystyn ajattelemaan selkeästi ja johdonmukaisesti, muistini toimii täysin moitteettomasti.
- ☐ Minulla on lieviä vaikeuksia ajatella selkeästi ja johdonmukaisesti, muistini ei toimi täysin moitteettomasti.
- ☐ Minulla on melkoisia vaikeuksia ajatella selkeästi ja johdonmukaisesti, minulla on jonkin verran muistinmenetystä.
- ☐ Minulla on suuria vaikeuksia ajatella selkeästi ja johdonmukaisesti, minulla on huomattavaa muistinmenetystä.
- ☐ Olen koko ajan sekaisin ja vailla ajan ja paikan tajua.

11. **Vaivat ja oireet**
- ☐ Minulla ei ole mitään vaivoja tai oireita, esim. kipua, särkyä, pahoinvointia, kutinaa jne.
- ☐ Minulla on lieviä vaivoja tai oireita, esimerkiksi kipua, särkyä, pahoinvointia, kutinaa jne.
- ☐ Minulla on melkoisia vaivoja tai oireita, esim. kipua, särkyä, pahoinvointia, kutinaa jne.
- ☐ Minulla on voimakkaita vaivoja tai oireita, esim. kipua, särkyä, pahoinvointia, kutinaa jne.
- ☐ Minulla on sietämättömiä vaivoja tai oireita, esim. kipua, särkyä, pahoinvointi, kutinaa jne.

12. **Masentuneisuus**
- ☐ En tunne itseäni lainkaan surulliseksi, alakuloiseksi tai masentuneeksi.
- ☐ Tunnen itseni hieman surulliseksi, alakuloiseksi tai masentuneeksi.
- ☐ Tunnen itseni melko surulliseksi, alakuloiseksi tai masentuneeksi.
- ☐ Tunnen itseni erittäin surulliseksi, alakuloiseksi tai masentuneeksi.
- ☐ Tunnen itseni äärimmäisen surulliseksi, alakuloiseksi tai masentuneeksi.

13. **Ahdistuneisuus**
- ☐ En tunne itseäni lainkaan ahdistuneeksi, jännittyneeksi tai hermostuneeksi.
- ☐ Tunnen itseni hieman ahdistuneeksi, jännittyneeksi tai hermostuneeksi.
- ☐ Tunnen itseni melko ahdistuneeksi, jännittyneeksi tai hermostuneeksi.
- ☐ Tunnen itseni erittäin ahdistuneeksi, jännittyneeksi tai hermostuneeksi.
- ☐ Tunnen itseni äärimmäisen ahdistuneeksi, jännittyneeksi tai hermostuneeksi.

14. **Energisyys**
- ☐ Tunnen itseni terveeksi ja elinvoimaiseksi.
- ☐ Tunnen itseni hieman uupuneeksi, väsyneeksi tai voimattomaksi.
- ☐ Tunnen itseni melko uupuneeksi, väsyneeksi tai voimattomaksi.
- ☐ Tunnen itseni hyvin uupuneeksi, väsyneeksi tai voimattomaksi, lähes "loppuun palaneeksi".
- ☐ Tunnen itseni äärimmäisen uupuneeksi, väsyneeksi tai voimattomaksi, täysin "loppuun palaneeksi".

15. **Sukupuolielämä**
- ☐ Terveydentilani ei mitenkään vaikeuta sukupuolielämääni.
- ☐ Terveydentilani vaikeuttaa hieman sukupuolielämääni.
- ☐ Terveydentilani vaikeuttaa huomattavasti sukupuolielämääni.
- ☐ Terveydentilani tekee sukupuolielämäni lähes mahdottomaksi.
- ☐ Terveydentilani tekee sukupuolielämän mahdottomaksi.

OSA IV
SUKUPUOLIELÄMÄN HÄIRIÖT:

Valitkaa ja merkitkää rastilla kunkin kysymyksen vastausvaihtoehdoista se, joka parhaiten kuvaa tilannettanne **viimeisen kuuden kuukauden aikana**. Valitkaa jokaiseen kysymykseen **ainoastaan yksi** vastaus!

1. **Millaiseksi arvioitte luottamuksenne siihen, että voitte saavuttaa erektion ja säilyttää sen yhdynnän ajan?**	1	Hyvin vähäiseksi
	2	Vähäiseksi
	3	Kohtalaiseksi
	4	Suureksi
	5	Hyvin suureksi

2. **Kun Teillä oli seksuaalisen kiihottumisen aikana erektioita, kuinka usein ne olivat tarpeeksi kovia yhdyntään?**	0	Ei seksuaalista toimintaa.
	1	Ei koskaan tai ei juuri koskaan.
	2	Muutaman kerran (harvemmin kuin joka toisella kerralla).
	3	Joskus (noin joka toisella kerralla).
	4	Useimmiten (useammin kuin joka toisella kerralla).
	5	Melkein aina tai aina.

3. **Kuinka usein pystyitte yhdynnässä ylläpitämään erektion sisään työntymisen jälkeen?**	0	Ei seksuaalista toimintaa.
	1	Ei koskaan tai ei juuri koskaan.
	2	Muutaman kerran (harvemmin kuin joka toisella kerralla).
	3	Joskus (noin joka toisella kerralla).
	4	Useimmiten (useammin kuin joka toisella kerralla).
	5	Melkein aina tai aina.

4. **Kuinka vaikeaa Teidän oli säilyttää erektionne yhdynnän loppuun saakka?**	0	En yrittänyt yhdyntää.
	1	Äärimmäisen vaikeaa.
	2	Hyvin vaikeaa.
	3	Vaikeaa
	4	Hieman vaikeaa.
	5	Ei lainkaan vaikeaa.

5. **Kun yrititte sukupuoliyhdyntää, kuinka usein saitte siitä tyydytystä?**	0	En yrittänyt yhdyntää.
	1	En koskaan tai en juuri koskaan.
	2	Muutaman kerran (harvemmin kuin joka toisella kerralla).
	3	Joskus (noin joka toisella kerralla).
	4	Useimmiten (useammin kuin joka toisella kerralla).
	5	Melkein aina tai aina.

OSA V

TERVEYDEN LISÄKYSYMYKSET:

Valitkaa kuhunkin kysymykseen yksi Teille sopiva vaihtoehto.
Kysymykset koskevat **viimeksi kulunutta kuukautta**.

	Koko ajan	Melkein aina	Enim-mäkseen	Melko harvoin	Harvoin	Ei koskaan
1. Yleinen terveydentila						
1. Onko Teillä kipuja tai särkyjä tai oletteko sairas?	0	1	2	3	4	5
2. Tunnetteko itsenne niin terveeksi että voitte tehdä mitä haluatte tai mitä Teidän täytyy tehdä?	0	1	2	3	4	5
3. Oletteko huolissanne tai peloissanne terveytenne vuoksi?	0	1	2	3	4	5
2. Yleinen mieliala						
1. Tunnetteko itsenne alakuloiseksi?	0	1	2	3	4	5
2. Tunnetteko itsenne hermostuneeksi?	0	1	2	3	4	5
3. Oletteko onnellinen ja tyytyväinen elämäänne?	0	1	2	3	4	5
4. Tunnetteko itsenne tasapainoiseksi ja rauhalliseksi?	0	1	2	3	4	5
5. Oletteko niin masentunut, että mikään ei tunnu minkään arvoiselta?	0	1	2	3	4	5
3. Huoli virtsaamisvaivoista ja potenssista						
1. Oletteko huolissanne potenssinne vuoksi?	0	1	2	3	4	5
2. Oletteko huolissanne virtsaamisenne vuoksi?	0	1	2	3	4	5
3. Oletteko tuntenut itsenne noloksi virtsaamisenne vuoksi?	0	1	2	3	4	5
4. Aktiivisuus						
1. Jaksatteko tehdä kotonanne kaikki välttämättömät ja haluamanne askareet?	0	1	2	3	4	5
2. Oletteko niin terve, että voitte käydä missä haluatte?	0	1	2	3	4	5
3. Oletteko niin hyvässä kunnossa, että voitte harrastaa haluamianne asioita?	0	1	2	3	4	5

5. Virtsavaivojen vaikutus aktiviteettiin?

Kuinka usein mahdolliset virtsavaivanne vaikuttavat seuraaviin asioihin?

	Ei koskaan	Joskus	Melko usein	Tavalli-sesti	Aina
1. Juominen ennen matkaa	0	1	2	3	4
2. Juominen ennen nukkumaan menoa	0	1	2	3	4
3. Autolla ajo 2 tuntia pysähtymättä	0	1	2	3	4
4. Riittävä unen saaminen	0	1	2	3	4
5. Käyminen paikoissa, joissa ei ole vessaa	0	1	2	3	4
6. Urheilun harrastaminen	0	1	2	3	4
7. Kirkossa, teatterissa, elokuvissa ym. käyminen	0	1	2	3	4

Kysely loppuu tähän.
Palauttakaa kysely oheisessa vastauskuoressa, postimaksu on maksettu puolestanne.
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Changes in Prevalence of Urinary Symptoms in Finnish Men

A Population-based 5-year Follow-up Study

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Objective: To describe changes in the prevalence and severity of urinary symptoms and the degree of interference they cause in the daily life of the Finnish male population by means of a 5-year follow-up study.
Material and Methods: A postal survey of a stratified random population sample of elderly men in Pirkanmaa County was carried out in 1994 and 1999. A total of 3143 men in 1994 and 2837 in 1999 received the questionnaire; 2198 (70%) and 2133 (75%) responded, respectively. The questionnaire included items on sociodemographic status, overall health and diseases, urinary symptoms (Danish Prostatic Symptom Score), sexual function and bothersomeness of symptoms. Data from those individuals who responded adequately to both inquiries were analysed.
Results: The most prevalent urinary symptoms were post-micturition dribble (64%), nocturia (62%), hesitancy (50%) and incomplete emptying (46%). At the 5-year follow-up, the prevalences of hesitancy, incomplete emptying, nocturia, urge incontinence and stress incontinence had increased statistically significantly. Subjects who had been symptomatic at baseline reported no change in 46–77% of cases, deterioration in 2–19% and improvement in 16–52%. The degree of interference in daily activities due to urinary symptoms increased significantly during follow-up. The mean interference index increased from 2.3 to 4.4.
Conclusion: Although urinary symptoms in elderly males are particularly common and their prevalence increases with age, they are mostly mild and also have a marked tendency to improve with time. The total burden of urinary symptoms nonetheless increases with age in the elderly male population.

Key words: benign prostatic hyperplasia, longitudinal survey, lower urinary tract symptoms, natural history, quality of life.

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The prevalence of lower urinary tract symptoms (LUTS) in males has been shown to be high worldwide (1–6). In individual surveys the prevalence of moderate-to-severe symptoms has varied with age from 13% to 30% and the proportion of men presenting at least one voiding symptom has been very high: 78–91% (1, 7–10). This substantial variation between studies has been explained by differences in the methods adopted. Although there have been numerous cross-sectional studies, population-based longitudinal surveys including evaluations of changes in the prevalence and severity of LUTS remain scarce. In order to chart the natural course of LUTS and evaluate the true burden of symptoms in the community, more unbiased and truly population-based follow-up studies are needed. The present survey forms part of the Tampere Aging Male Urologic Study (TAMUS) and we report here the results of a 5-year follow-up study of 1633 non-selected men, this being the first longitudinal study of the prevalence of LUTS in Finland.

MATERIAL AND METHODS

Details of the 1994 survey have been described elsewhere (4, 11). In brief, the basic study population comprised male inhabitants of the city of Tampere and 11 neighbouring municipalities in Pirkanmaa County, Finland. This group of 3143 men comprised all the males born in 1924, 1934 or 1944 who were living in the area at the beginning of the study. A corresponding register search was conducted 5 years later, excluding those who had moved into the area subsequent to the first search. At 5-year follow-up, 262 men had died, six had left the country and 36 had been institutionalized or

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lost to follow-up for other reasons. The 1999 study population thus comprised 2837 men (Fig. 1). The age distribution at baseline was 50 years, 44%, 60 years, 32% and 70 years, 24%; and 5 years later 55 years, 46%, 65 years, 33% and 75 years, 21%. This sample comprised 10% of the male population aged ≥50 years in the study area in 1994 and reflected the composition of the Finnish elderly male population at large.

Questionnaire

The questionnaire used in the 1999 survey consisted mainly of the same questions as the 1994 questionnaire. However, items on housing conditions and dietary habits were omitted. The complete Danish Prostatic Symptom Score (DAN-PSS-1) questionnaire (12) was included. Interference in activities of daily life due to urinary symptoms was mapped using seven questions (drinking before travelling, drinking before going to bed, driving for 2 h without stopping, getting enough sleep at night, going to places without a toilet, playing outdoor sports and going to movies, shows, church, etc.) devised by Epstein et al. (13).

Personally addressed correspondence was mailed to the men in May 1994 and May 1999. An identical questionnaire was sent 3 months later on each occasion as a reminder to non-responders. The total study period was 5 months. The number of responders was 2198 (70%) in 1994 and 2133 (75%) in 1999. The data from both surveys were combined using the social security number as a connecting link for each individual. During this merging phase the data on 62 (3%) men were lost because they completed the questionnaire anonymously.

There were some differences between the 1999 linguistically validated Finnish version of the DAN-PSS-1 questionnaire and the version used in 1994. Owing to this problem the research group made a stringent re-evaluation of the precise meaning of each question. The questions dealing with hesitancy, incomplete emptying, post-micturition dribble, nocturia, urge incontinence, dysuria and stress incontinence were found to be fully comparable and were accepted for further analysis. Questions concerning several important urinary symptoms (weak stream, straining, day-time frequency and urgency and other forms of incontinence), all of which are included in the original DAN-PSS-1 questionnaire, had to be omitted. Because of this we could use the total score of the original questionnaire (12). To overcome this limitation as far as possible we decided to analyse the symptoms individually. Although information was lost, changes in the prevalences of the symptoms used in the analysis described the trend quite well. Questions other than those from the DAN-PSS-1 questionnaire used in the survey were completely identical in 1994 and 1999.

Data and statistical methods

During data recording, if two alternatives were ticked instead of one for the DAN-PSS-1 questions, the worst alternative was considered. This happened in 131 cases, comprising 6% of all questionnaires returned. The aim of this manipulation was to minimize data loss. In most cases double ticking compromised only one of the items

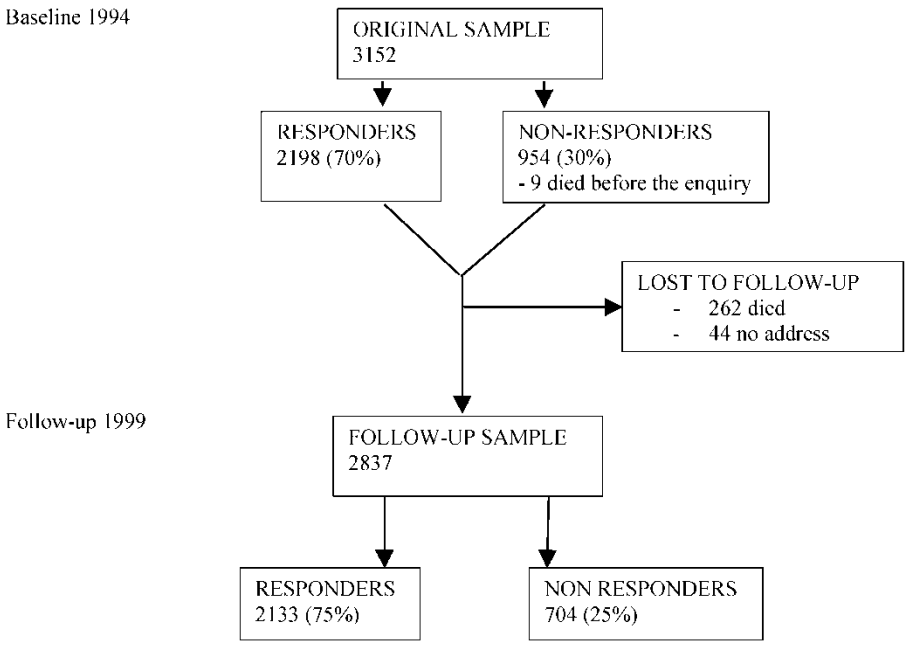

Fig. 1. Flow chart illustrating the study populations for the 1994 and 1999 surveys.

in the questionnaire. For analysis the DAN-PSS-1 symptom score data were recoded so that all "0" responses formed a new score of "no symptom" and responses "1, 2 and 3" were grouped together as a new "symptom-positive" score. The interference index was calculated by summing the scores and the degree of interference was categorized as either mild (interference index 0–2), moderate (3–8) or severe (9–28) interference (14).

The statistical significance of non-parametric binomial data was established by means of McNemar's test and 95% CIs are presented. The local ethics committee approved the study.

RESULTS

Information on urinary symptoms for both surveys was available for 1606–1633 men depending on the question. The highest number of responders, 1633 for the question on nocturia, comprised 58% of the 1999 study population. The mean age of the 1999 cohort was 62.5 years: 61.4 years for non-responders and 63.4 years for responders. The age distribution of the responder group was comparable to that of the original study population. Some changes in demographic data and health status took place during follow-up (Table I).

Table I. *Prevalence (%) of some demographic and health status characteristics in the study population (*n = *1633)*

Characteristic	1994	1999[a]
Marital status		
Married or cohabiting	82	79
Bachelor, widower or divorcee	18	20
Occupational status		
Retired	48	62
White-collar worker	18	12
Blue-collar worker	17	15
Self-employed	6	6
Unemployed	11	5
Education		
Elementary school	49	N/A
Intermediate stage	27	N/A
College or training centre	16	N/A
University	8	N/A
Overall health		
Same or better	N/A	46
Slightly worse	N/A	43
Much worse	N/A	11
Disease status		
Diabetes	7	9
Elevated blood pressure	29	34
Heart disease	16	20
Cancer	3	6
Surgery for BPH	2	6
Radical prostatectomy	1	2
Medical treatment for BPH	1	5

[a] All changes in prevalence, except in self-employees, were statistically significant at the $p < 0.05$ level.

Symptom prevalence

The prevalence of all analysed urinary symptoms, with the exception of dysuria, had increased at the 5-year follow-up survey (Table II). At baseline the most prevalent symptoms were post-micturition dribble (63%; 95% CI 61–66%), nocturia (54%; 52–57%) and hesitancy (47%; 44–49%); after 5 years the same order was observed: post-micturition dribble (64%; 62–66%), nocturia (62%; 59–64%) and hesitancy (50%; 48–53%).

A strong tendency towards a rising prevalence with age was found in all three age groups for most of the symptoms (Fig. 2). Post-micturition dribble had the highest prevalence (69%) among men aged 70 years. This symptom increased from 60% at 50 years to 64% at 55 years in the youngest cohort but decreased in the two older cohorts. The most marked increase with age was found for nocturia, which increased from 38% at 50 years to 76% at 75 years. Hesitancy likewise increased steadily from 43% at 50 years to 55% at 75 years, but a marked cohort increase took place only in the two younger age groups. A conspicuous rising prevalence with age was characteristic of incomplete emptying in all age groups. For this symptom the baseline prevalence in 60- and 70-year-old men was clearly lower than the prevalence in the next youngest cohort after the follow-up period, representing the so-called cohort effect. The most constant symptom was dysuria, with a 20–25% prevalence in all cohorts throughout the follow-up period. Urge incontinence was reported in 10% of 50-year-olds. The prevalence of urge incontinence increased markedly with age, reaching 35% at age 75 years. Stress incontinence also increased with age, albeit slowly.

Symptom severity

Urinary symptoms were mostly mild or infrequent (Table II). The mildest symptom category (score 1) was reported by 83% of the 809 men with hesitancy, 75% of the 739 with incomplete emptying, 58% of the 1025 with post-micturition dribble, 91% of the 1007 with nocturia, 89% of the 378 with urge incontinence, 95% of the 354 with dysuria and 91% of the 160 with stress incontinence in the 1999 survey. Moderate (score 2) symptoms were found in 5–41% of the symptomatic men and severe (score 3) in 0–4%.

Symptom alteration

In the follow-up of initially mildly or moderately symptomatic men (scores 1 or 2), 2–19% had progressed and 16–52% had improved; however, most (46–77% for each symptom) reported no change in urinary function. Progression was commonest for incomplete emptying and post-micturition dribble

Table II. *Distribution of DAN-PSS-1 symptom scores at baseline and 5-year follow-up*

			DAN-PSS-1 symptom score; *n* (%)					
Urinary symptom	Survey	*n*	0	1	2	3	>0	*p*[a]
Hesitancy	Baseline	1616	865 (53.5)	655 (40.5)	69 (4.3)	27 (1.7)	751 (46.5)	0.01
	5 years	1616	807 (49.9)	670 (41.5)	126 (7.8)	13 (0.8)	809 (50.1)	
Incomplete emptying	Baseline	1616	1145 (70.9)	325 (20.1)	114 (7.1)	32 (2.0)	471 (29.1)	<0.001
	5 years	1616	877 (54.3)	554 (34.3)	155 (9.6)	30 (1.9)	739 (45.7)	
Post-micturition dribble	Baseline	1606	589 (36.7)	779 (48.5)	225 (14.0)	13 (0.8)	1017 (63.3)	0.73
	5 years	1606	581 (36.2)	596 (37.1)	422 (26.3)	7 (0.4)	1025 (63.8)	
Nocturia	Baseline	1633	745 (45.6)	835 (51.1)	49 (3.0)	4 (0.2)	888 (53.4)	<0.001
	5 years	1633	626 (38.3)	911 (55.8)	94 (5.8)	2 (0.1)	1007 (61.7)	
Urge incontinence	Baseline	1619	1375 (84.9)	240 (14.8)	4 (0.2)	–	244 (15.1)	<0.001
	5 years	1619	1241 (76.7)	336 (20.8)	41 (2.5)	1 (0.1)	378 (23.3)	
Dysuria	Baseline	1613	1258 (78.0)	334 (20.7)	14 (0.9)	7 (0.4)	355 (22.0)	1.00
	5 years	1613	1259 (78.1)	335 (20.8)	18 (1.1)	1 (0.1)	354 (21.9)	
Stress incontinence	Baseline	1619	1486 (91.8)	129 (8.0)	3 (0.2)	1 (0.1)	133 (8.2)	0.04
	5 years	1619	1459 (90.1)	146 (9.0)	12 (0.7)	2 (0.1)	160 (9.9)	

[a] McNemar's test for all symptoms (score > 0) between baseline and follow-up.

(19%), and improvement for stress incontinence (52%) and dysuria (47%) (Fig. 3). For all symptom entities the proportion of men whose symptoms had improved was greater than that of men whose symptoms had worsened. At follow-up, 6–34% of initially healthy men had symptoms (scores 1–3).

Symptom interference

The mean interference index increased twofold from 2.3 (2.1–2.5) in 1994 to 4.4 (4.1–4.7) in 1999 for the three age groups as a whole (mean increase 2.1; 1.76–2.44; $p < 0.01$). The age-specific mean

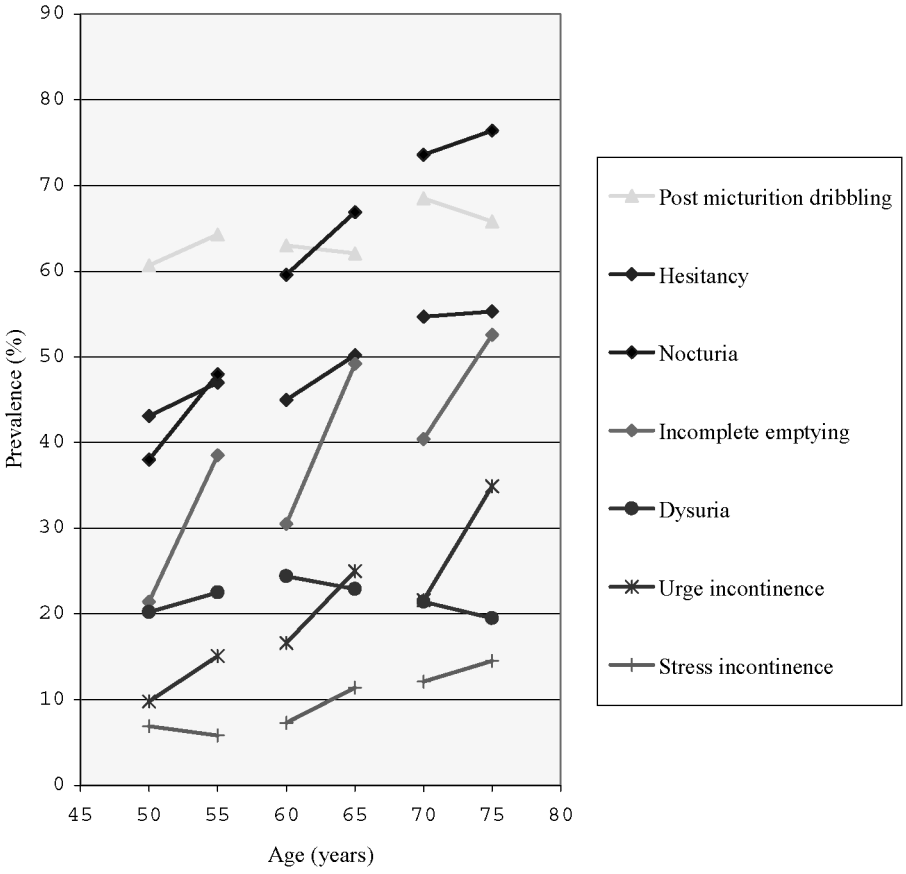

Fig. 2. Prevalence of urinary symptoms at baseline and at the 5-year follow-up by age.

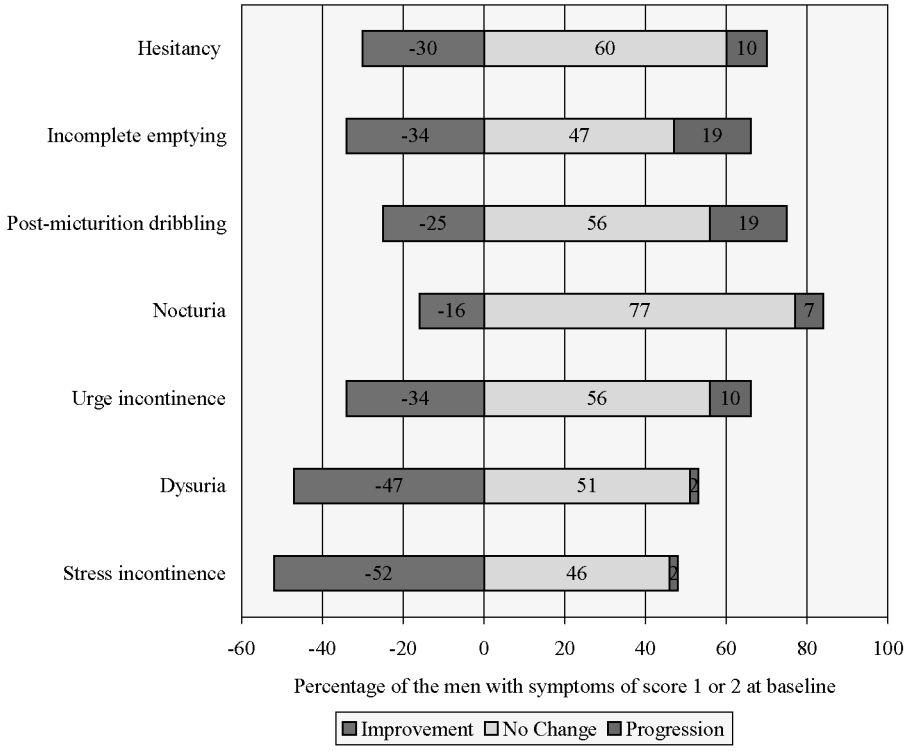

Fig. 3. Alteration in symptom severity at the 5-year follow-up.

interference indexes were 1.6, 2.7 and 3.3 for men aged 50, 60 and 70 years at baseline, respectively and the corresponding values 5 years later were 3.3, 4.8 and 6.3. The cross-sectional differences between the age groups were statistically significant except between 60- and 70-year-old men in the 1994 survey. At baseline, 73%, 19% and 8% of the men reported mild, moderate and severe interference in daily life due to urinary symptoms, respectively. After 5 years, the corresponding values were 52%, 30% and 18% ($p < 0.01$).

DISCUSSION

In this study there was a clear tendency towards an increase in the prevalence of all typical voiding and storage symptoms with age. Aggravation of interference in men's daily life was also clear. Another distinct finding was that most of the symptoms reported were mild and that there was a marked tendency for symptoms to improve during the follow-up period. The response rate in this survey was 58%, which is similar to that in previous studies (15–17). Non-responders were younger than responders and, especially in the youngest cohort, the non-responder rate was high. A greater proportion of the responders than non-responders were retired and, conversely, unemployment was more common among non-responders. In other respects the groups were similar and non-response bias is not significant in this material. Over-representation of older men among responders may have influenced the prevalence rates of urinary symptoms, but this effect is probably subtle. The basic source of information in this study was the DAN-PSS-1 questionnaire. Instead of total scores or bother scores we used only symptom scores and analyzed each symptom separately (12) for two reasons: (i) in the baseline survey two of the original DAN-PSS-1 questions were not used; and (ii) the presence of probably marked differences between the two translations. After linguistic re-evaluation the questions used in the analysis were comparable and were also equivalent to those in the original English version.

Aging has been shown to be the most important risk factor for LUTS in previous longitudinal (15, 17) and cross-sectional studies (18). Overall our findings were in accordance with this, but there were also some interesting differences between symptoms. Dysuria and post-micturition dribble showed a constant prevalence throughout the follow-up period. The causes of dysuria are diverse and are often related to infections of the lower urinary tract, which occur fairly evenly throughout men's lives. Post-micturition dribble was a very common symptom: it started probably early in middle age and then remained fairly constant, resulting in a high, unchanging prevalence in the study population. The prevalence of post-micturition dribble in our study

(64%) was much higher compared with previous reports: 40% in the Olmsted study (2), 45% in a Scottish study (1) and only 25% in a French study (9). Also, the prevalences of both hesitancy and incomplete emptying were higher in our study than in previous studies (1, 2, 6, 9). As in the French study (9), our study population excluded men aged <50 years. Other studies included younger men (aged ≥ 40 years). In the Olmsted study (2), the prevalence of post-micturition dribble was 37% for men aged 40–49 years and 42% for men aged ≥ 50 years. However, the differences in the prevalences reported in those surveys were probably dependent more on disparity in data collection methods and questionnaires than in the age distribution of the study populations.

A clear age-related increase was seen in the prevalence of nocturia, incomplete emptying, hesitancy and urge incontinence. In contrast to post-micturition dribble, the increases in hesitancy, incomplete emptying and urge incontinence reached statistical significance at the 5-year follow-up. The marked age dependence of these symptoms was further enhanced by the fact that there was also a prominent increase in prevalence within each age cohort. Only in the oldest age group did the prevalence of nocturia and hesitancy increase very little with age, indicating that the prevalence of these symptoms reached a plateau in the elderly. A clear cohort effect was seen in the incomplete emptying symptom, in which the prevalences after 5 years exceeded baseline in the next oldest cohort. One possible explanation for this might be that during the follow-up period the men learnt to recognize their symptoms better than at baseline because of repetition of the survey or, more probably, because of the substantial increase in the information available relating to benign prostatic hyperplasia (BPH) and men's diseases in general in the community between the survey years. Why the phenomenon was this outstanding only for incomplete emptying remains unclear.

The prevalence of nocturia, defined as urinating once or more per night, varies in the literature from 59% to 74% (1, 6, 9, 10, 19). Our prevalence was 54% at baseline and 62% at follow-up. Both age-related and cohort increases were very clear. More than 90% of subjects with this symptom reported only one or two voidings per night. In current clinical practice, solitary nocturia is often considered normal for an aging male. However, in the DAN-PSS-1 questionnaire, nocturia is graded as none, one to two, three to four and five or more voidings during sleeping time and therefore the weakest symptom level of solitary nocturia cannot be distinguished as a separate category. In any case, although mild symptoms predominated, almost 10% of men with nocturia reported three or more voidings per night. This group suffers from a disturbing symptom calling for further investigation, both clinical and aetiological, to identify risk factors and comorbidities which can be treated.

Urinary incontinence, especially urge-type incontinence, increased almost threefold in the population as age increased from 50 to 75 years. It is possible that our figures, which are quite high compared with those reported previously, were influenced by the fact that our population was totally unselected. We did not exclude patients with BPH or other diseases known to affect voiding, or men with poor general health. The study population also included a marked proportion of individuals with chronic constipation (6%), faecal incontinence (2%), arthrosis (23%) and neurological disorders (11%), which have been found to be connected with an increased prevalence of LUTS (20). The prevalence of male stress incontinence has not been well studied and it is not included in widely used LUTS questionnaires other than the DAN-PSS-1. Many men obviously had difficulties in differentiating between true stress incontinence and post-micturition dribble when engaging in physical activity immediately after voiding. This diminishes the reliability of the symptom scores but obviously not the trend, which was similar for both types of incontinence.

Changes in the severity of the urinary symptoms have previously been evaluated only in the Scottish and Olmsted studies (15, 17). In our study, symptom improvement was much more common and symptom worsening more uncommon than in those previous studies. However, in the Olmsted study all men with a history of prostatectomy, prostate cancer or other medical conditions (other than BPH) known to interfere with voiding function were excluded, whereas in the Scottish study only patients with a diagnosis of BPH but who had not received treatment for it were followed. In view of these differences and the fact that the questionnaires used to collecting the LUTS data were dissimilar, it is difficult to compare our study directly with the other two. In any case, spontaneous improvement or fluctuation in urinary symptoms probably explains a large proportion of the symptom improvement seen in our material, because only 10% of the men reported having any prostate or urinary symptom-specific treatment during the follow-up period. There is also a possibility that subjects implicitly compared themselves to other men of the same age, and not to themselves 5 years previously, and so considered themselves to have fewer symptoms. Furthermore, although there was an increase in the prevalence of most symptoms, improvement was, nonetheless, more frequent than progression. This means that initially symptom-free men contributed substantially to the prevalences.

The degree of interference increased significantly between baseline and follow-up for all daily life

activities and the cohort increase was also clear in cross-sectional analysis. These changes were somewhat more prominent here than in the Scottish study (15), which is in accordance with our higher prevalences for most symptoms as well as the older study population.

CONCLUSIONS

First, urinary symptoms in the elderly male population are very prevalent in Finland, as elsewhere, and their prevalence increases clearly with age. Second, the interference of urinary symptoms in men's daily activities increases in a community, although most men report only mild symptoms and there is also a tendency for spontaneous improvement. Third, for most of the symptoms there was a clear increase with age but no evidence of an increasing trend with time. Only incomplete emptying showed a cohort-type increase which was also consistent with an increase with time. This, together with the almost uniformly higher prevalences in our study compared to those in previous reports, may indicate that the DAN-PSS-1 symptom questions are very sensitive at detecting LUTS.

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REFERENCES

1. Garraway WM, Collins GN, Lee RJ. High prevalence of benign prostatic hypertrophy in the community. Lancet 1991; 338: 469–71.
2. Chute CG, Panser LA, Girman CJ, Oesterling JE, Guess HA, Jacobsen SJ, et al. The prevalence of prostatism: a population-based survey of urinary symptoms. J Urol 1993; 150: 85–9.
3. Homma Y, Kawabe K, Tsukamoto T, Yamanaka H, Okada K, Okajima E, et al. Epidemiologic survey of lower urinary tract symptoms in Asia and Australia using International Prostate Symptoms Score. Int J Urol 1997; 4: 40–6.
4. Koskimäki J, Hakama M, Huhtala H, Tammela TLJ. Prevalence of lower urinary tract symptoms in Finnish men: a population-based study. Br J Urol 1998; 81: 364–9.
5. Berges RR, Pientka L, Höfner K, Senge T, Jonas U. Male lower urinary tract symptoms and related health care seeking in Germany. Eur Urol 2001; 39: 682–7.
6. Norman RW, Nickel JC, Fish D, 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.
7. Britton JP, Dowell AC, Whelan P. Prevalence of urinary symptoms in men aged over 60. Br J Urol 1990; 66: 175–6.
8. Jensen KM-E, Jorgensen JB, Mogensen P, Brille-Brahe NE. Some clinical aspects of uroflowmetry in elderly males. A population survey. Scand J Urol Nephrol 1986; 20: 93–9.
9. Sagnier P-P, MacFarlane G, Richard F, Botto H, Teillac P, Boyle P. 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.
10. Bosch JLHR, Hop WCJ, Kirkels WJ, 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.
11. Koskimäki J. Lower urinary tract symptoms in men [Dissertation]. Tampere, Finland: University of Tampere; 1997.
12. Hald T, Nordling J, Andersen JT, Bilde T, Meyhoff HH, Walter SA. A patient weighted symptom score system in the evaluation of uncomplicated benign prostatic hyperplasia. Scand J Urol Nephrol 1991; 138: 59–62.
13. Epstein RS, Deverka PA, Chute CG, Panser LA, Oesterling JE, Lieber MM, et al. Validation of a new quality of life questionnaire for benign prostatic hyperplasia. J Clin Epidemiol 1992; 45: 1431–45.
14. Jacobsen SJ, Guess HA, Panser LA, Girman CJ, Chute CG, Oesterling JE, 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.
15. Lee AJ, Garraway WM, Simpson RJ, Fisher W, 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.
16. Diokno AC, Brown MB, Goldstein N, Herzog AR. Epidemiology of bladder emptying symptoms in elderly men. J Urol 1992; 148: 1817–21.
17. Jacobsen SJ, Girman CJ, Guess HA, Rhodes T, Oesterling JE, Lieber MM. Natural history of prostatism: longitudinal changes in voiding symptoms in community dwelling men. J Urol 1996; 155: 595–600.
18. Haidinger G, Temml C, Schatzl G, Brössner C, Roehlich M, Schmidbauer CP, et al. Risk factors for lower urinary tract symptoms in elderly men. Eur Urol 2000; 37: 413–20.
19. Wolfs GGMC, Knotterus JA, Janknegt RA. Prevalence and detection of micturition problems among 2,734 elderly men. J Urol 1994; 152: 1467–70.
20. Koskimäki J, Hakama M, Huhtala H, Tammela TLJ. Association of non-urological diseases with lower urinary tract symptoms. Scand J Urol Nephrol 2001; 35: 377–81.