KARI A. O. TIKKINEN

Epidemiology of Nocturia

Results from the FINNO Study

ACADEMIC DISSERTATION
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the Faculty of Medicine of the University of Tampere,
for public discussion in the Small Auditorium of Building M,
Pirkanmaa Hospital District, Teiskontie 35,
Tampere, on March 5th, 2010, at 12 o'clock.

UNIVERSITY OF TAMPERE

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Dedicated to the FINNO Study participants

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Abbreviations

AHI	apnea-hypopnea index
AUA-SI	American Urological Association Symptom Index
BMI	body mass index
BPE	benign prostatic enlargement
BPH	benign prostatic hyperplasia
BPO	benign prostatic obstruction
CAD	coronary artery disease
CI	confidence interval
DAN-PSS	Danish Prostatic Symptom Score
FINNO	Finnish National Nocturia and Overactive Bladder
FVC	frequency-volume chart
HRQL	health-related quality of life
ICS	International Continence Society
LUTS	lower urinary tract symptoms
MHT	menopausal hormone therapy
NCS	Nocturia Confounder Score
NP	nocturnal polyuria
OAB	overactive bladder (syndrome)
OR	odds ratio
OSA	obstructive sleep apnea
RCT	randomised controlled trial
RLS	restless legs syndrome
SD	standard deviation
SSRI	selective serotonine reuptake inhibitor
SUI	stress urinary incontinence
TURP	trans-urethral resection of prostate
UCS	Urgency Confounder Score
UUI	urgency urinary incontinence

Abstract

Background: Nocturia (waking at night to urinate) is one of the most common and bothersome lower urinary tract symptoms. Nocturia is associated with impaired quality of life, and increased morbidity and even mortality. Given the poor state of knowledge about nocturia, treatment is frequently inadequte.

Objectives: To describe the prevalence of nocturia and overactive bladder by age and sex, formulate a clinically meaningful definition for nocturia based on bother and quality of life impact of nocturia, and identify risk factors (conditions, medications, lifestyle and female reproductive factors) of nocturia and evaluate their impact at population level.

Material and methods: The Finnish National Nocturia and Overactive Bladder (FINNO) Study was initiated in early 2003. In 2003-2004, questionnaires were mailed to 6,000 subjects (aged 18-79 years) randomly identified from the Finnish Population Register Centre. Questionnaires contained items on medical conditions, medications, lifestyle, socio-demographic and reproductive factors, health-related quality of life (HRQL), urinary symptoms, and sleep disorders using validated instruments.

European standard population and Finnish population structure were used for age-standardisation. HRQL and bother from nocturia were examined in relation to self-reported nocturia frequency (using the American Urological Association Symptom Index and the Danish Prostatic Symptom Score). Bother from nocturia was assessed on a four-point scale (none-small-moderate-major). HRQL was measured by the 15D instrument which can be used as a profile measure or for a single index score (15D Score). 15D Score is a 0-1 scale with a minimum clinically important difference of 0.03.

To assess risk factors for nocturia, factors associated with nocturia in age-adjusted analyses were entered into a multivariate model. Backward elimination was used to select variables for the final model with adjustment for confounding. Furthermore, propensity scores were used

for adjustment of confounding in some analyses. To assess the population-level impact, population fraction in the exposed, attributable fraction and attributable number were calculated. In addition, positive predictive value and sensitivity were calculated for the identified risk factors.

Results: Of the 6,000 subjects, 3,727 participants (1,725 men and 2,002 women) returned the questionnaires. The response proportion was approximately 32% after the 1st round, 50% after the 2nd round, and finally 62.4% after the 3rd round.

After age-standardisation (to the Finnish population structure), 26%, 9%, 2% and 1% of men and 32%, 10%, 2% and 1% of women reported one, two, three or at least four void(s)/night. Nocturia was more common among women at younger ages, but the sex differences disappeared by middle age. In the elderly, nocturia was more frequent among men. Nocturia increased at a constant rate with age. It increased twice as rapidly in men than women. Degree of bother increased with nocturia frequency ($p<0.01$). The most commonly reported degree of bother for those with 1, 2 and 3 nightly voids was no bother, "small" bother and "moderate" bother respectively. The mean age-adjusted 15D Score for men (women) without nocturia was 0.953 (0.950), 0.925 (0.927) with 1 void per night, 0.898 (0.890) with 2 voids per night, and 0.833 (0.840) with ≥3 voids per night. Nocturia was associated with statistically significant decrease on 15D Score and all dimensions of 15D except eating.

While numerous risk factors for nocturia were identified, none affected ≥50% of nocturia cases in both sexes. The factors with the greatest impact at the population level were overactive bladder/urinary urgency (attributable number/1,000 subjects, AN 24), benign prostatic hyperplasia (AN 19) and snoring (AN 16) for men; and overweight and obesity (AN 40), overactive bladder (AN 24) and snoring (AN 17) for women. Moreover, risk factors included prostate cancer and antidepressant use for men; coronary artery disease and diabetes for women; and restless legs syndrome and obesity for both sexes. Among women, parity, postpartum and postmenopausal periods were associated with increased nocturia (but not with overactive bladder).

The prevalence of overactive bladder was 6.5% for men and 9.3% for women, i.e. approximately half of that reported in earlier studies. Possible overestimation in the earlier

literature could be due to numerous methodological reasons. Among subjects with overactive bladder, nocturia (defined as at least two voids per night) was reported by 56% of men and 40% of women. However, only 31% of subjects of both sexes with nocturia reported overactive bladder.

Limitations: The cross-sectional study design limits conclusions about causality. Although the response proportion was high, approximately one third of those contacted did not participate in the study. Regarding impact measures (which generally are context specific), these results from the Finnish population may not be directly generalisable to other ethnicities.

Conclusions: In the population-representative FINNO Study, approximately 28% of subjects reported one, 10% two, 2% three, and 1% four or more void(s)/night. Nocturia was more common among young women than young men, but more common among men than women in old age. Most subjects reported small bother from nocturia with two nocturia episodes, and moderate bother only from three nocturia episodes. Two nocturia episodes impaired HRQL compared to those with no nocturia.

Numerous risk factors for nocturia were identified. However, none of them accounted for ≥50% of the nocturia cases, highlighting its multifactorial etiology. The risk factors differed slightly by sex. At population level, overactive bladder, benign prostatic hyperplasia and snoring for men, and overweight/obesity, overactive bladder and snoring for women accounted for the largest proportion of nocturia. Among women, parity, postpartum year and postmenopausal period were associated with increased nocturia. Overall, the lower urinary tract, but also beyond it, should be considered when examining and treating nocturia.

Tiivistelmä

Tausta: Yövirtsaaminen (nokturia) on hyvin yleinen oire. Vanhimmissa ikäluokissa enemmistö väestöstä käy öisin virtsaamassa ja nokturian merkitys kasvaakin tulevaisuudessa väestön vanhetessa. Nokturia heikentää unen laatua, lisää sairastavuutta, ja on toisinaan yksinäänkin merkittävästi elämänlaatua heikentävä oire. Koska nokturian syyt tunnetaan huonosti, hoidolla ei saada useinkaan riittävää vastetta.

Tavoitteet: Väitöstutkimus on osa vuonna 2003 alkanutta kansallista virtsaamishäiriöitä kartoittavaa FINNOS-seurantatutkimusta. Väitöstutkimuksen tavoitteena oli selvittää nokturian ja yliaktiivisen rakon yleisyyttä eri sukupuolilla ja eri ikäryhmissä, esittää nokturialle määritelmä haitan ja elämänlaatuvaikutusten perusteella, sekä selvittää nokturian syytekijät (sairaudet, lääkitykset, elintavat ja lisääntymistekijät) ja arvioida niiden vaikutusta väestötasolla.

Menetelmät: Vuosina 2003-2004 lähetettiin kirjekysely kuudelle tuhannelle 18-79 -vuotiaalle satunnaisotannalla väestörekisteristä valitulle suomalaiselle. Lomake sisälsi virtsaamisoirekyselyt (DAN-PSS ja AUA-SI), geneerisen elämänlaatumittarin ja unikyselyt. Lisäksi selvitettiin laajasti muita sairauksia ja niiden hoitoja. Myös elintavat, lisääntymistekijät ja sosiodemografiset tekijät otettiin huomioon.

Ikävakioinnissa käytettiin Euroopan standardiväestöä ja Suomen väestörakennetta. Elämänlaatua ja nokturiasta koettua haittaa verrattiin yövirtsaamiskertoihin. Elämänlaatua mitattiin 15D-mittarilla. 15D:tä voi käyttää sekä viidentoista profiilin (elämänlaadun eri ulottuvuuksia) että yhden indeksiluvun mittarina. 15D-indeksiluvun (asteikko: 0-1) pienin kliinisesti merkittävä ero on 0,03.

Riskitekijöitä selvitettäessä otettiin monimuuttuja-analyyseihin mukaan tekijät, jotka olivat yhteydessä nokturiaan ikävakioiduissa analyyseissa. Poistavaa valintaa (taaksepäin elimininointi) käytettiin lopullisessa mallinnuksessa ottaen huomioon sekoittavat tekijät.

Joissakin analyyseissa käytettiin lisäksi propensiteettipistemäärämenetelmiä. Väestötason vaikutusta arvioitaessa laskettiin ylimääräosuus altistuneilla, ylimääräosuus väestössä ja tapausylimäärä. Lisäksi havaittujen riskitekijöiden positiivinen ennustearvo ja herkkyys selvitettiin.

Tulokset: Kutsutuista 6000 suomalaisesta 3727 (62,4 %) osallistui (1725 miestä ja 2002 naista). Miehistä 26 %, 9 %, 2 % ja 1 % sekä naisista 32 %, 10 %, 2 % ja 1 % raportoi käyvänsä kerran, kahdesti, kolmesti ja vähintään neljästi yössä virtsaamassa. Nokturia lisääntyi voimakkaasti ikääntyessä ($p < 0.001$), miehillä kaksinkertaisella nopeudella naisiin verrattuna. Nuorten keskuudessa nokturia oli yleisempää naisilla, kun taas ikäihmisistä miehet kävivät yövirtsalla useammin. Koettu haitta lisääntyi nokturian vaikeutuessa ($p < 0.01$). Enemmistölle yksi yövirtsaamiskerta ei ollut haitallinen, kaksi kertaa yössä oli pieni haitta, kun taas kolme ja vähintään neljä virtsaamiskertaa yössä oli suurimmalle osalle kohtalainen tai hyvin suuri haitta. Ikävakioitu 15D-indeksiluku oli 0,953 (0,950) miehillä (naisilla), joilla ei ollut nokturiaa; 0,925 (0,927) miehillä (naisilla), jotka virtsasivat kerran yössä; 0,898 (0,890) miehillä (naisilla), jotka virtsasivat kahdesti yössä, ja 0,833 (0,840) miehillä (naisilla), jotka virtsasivat vähintään kolmesti yössä. Nokturia oli sekä miehillä että naisilla tilastollisesti merkitsevästi yhteydessä heikentyneeseen elämänlaatuun sekä tarkasteltaessa 15D-indeksilukua että 15D-mittarin osa-alueita (yhtä lukuun ottamatta: syöminen).

Monimuuttuja-analyysissa havaittiin lukuisia nokturian riskitekijöitä, mutta yksikään tekijä ei ollut enemmistöllä yövirtsaamista raportoineista. Väestötasolla yövirtsaamista selittivät eniten miehillä yliaktiivinen rakko (tapausylimäärä tuhatta kohden (TY) 24), eturauhasen hyvänlaatuinen liikakasvu (TY 19) ja kuorsaus (TY 16) sekä naisilla ylipaino ja lihavuus (TY 40), yliaktiivinen rakko (TY 24) ja kuorsaus (TY 17). Riskitekijöitä, joilla oli tosin pienempi väestötason vaikutus, olivat myös eturauhassyöpä ja masennuslääkkeiden käyttö miehillä, sepelvaltimotauti ja diabetes naisilla, sekä levottomat jalat -oireyhtymä ja lihavuus molemmilla sukupuolilla. Naisilla lisäksi lapsiluku, synnytyksen jälkeinen vuosi ja vaihdevuosien jälkeinen aika (postmenopaussi) liittyivät lisääntyneeseen yövirtsaamiseen.

Yliaktiivisen rakon vallitsevuus oli miehillä 6,5 %:a ja naisilla 9,3 %:a vastaten noin puolta aiemmin esitetystä. Aiempien tutkimusten suuremmat esiintyvyysluvut johtuivat pääosin metodologisista puutteista tai epäedustavien otosten käyttämisestä väestöpohjaisten sijasta.

Johtopäätökset: Noin 28 % suomalaisista raportoi yhden, 10 % kaksi, 2 % kolme ja 1 % vähintään neljä virtsaamiskertaa yössä. Nuoruudessa yövirtsaaminen on yleisempää naisten kuin miesten keskuudessa; vanhoilla miehillä taas on enemmän nokturiaa kuin vanhoilla naisilla. Suurin osa ihmisistä raportoi yövirtsaamisesta haittaa, kun virtsaamiskertoja on kaksi yössä, ja vähintään kohtalaista haittaa, kun kertoja on kolme yössä. Yövirtsaaminen vähintään kahdesti yössä on yhteydessä heikentyneeseen elämänlaatuun.

Nokturialle ei löytynyt yhtä pääsyytä – yövirtsaaminen onkin usein monen tekijän summa. Väestötasolla miesten yövirtsaamista selittävät eniten yliaktiivinen rakko, eturauhasen hyvänlaatuinen liikakasvu ja kuorsaus. Naisilla vastaavia syitä ovat ylipaino ja lihavuus, yliaktiivinen rakko ja kuorsaus. Alempien virtsateiden sairaudet, mutta myös monet virtsateiden ulkopuoliset tekijät tulee ottaa huomioon tutkittaessa ja hoidettaessa yövirtsaamista.

Introduction

Nocturia (waking at night to urinate) is a common cause of nocturnal awakenings, and may lead to sleep maintenance insomnia (Middelkoop et al. 1996, van Kerrebroeck et al. 2002, Bing et al. 2006, Bliwise et al. 2009). Nocturia can be bothersome, is associated with impaired mental and somatic health (Asplund et al. 2005a) and even increased mortality (Asplund 1999).

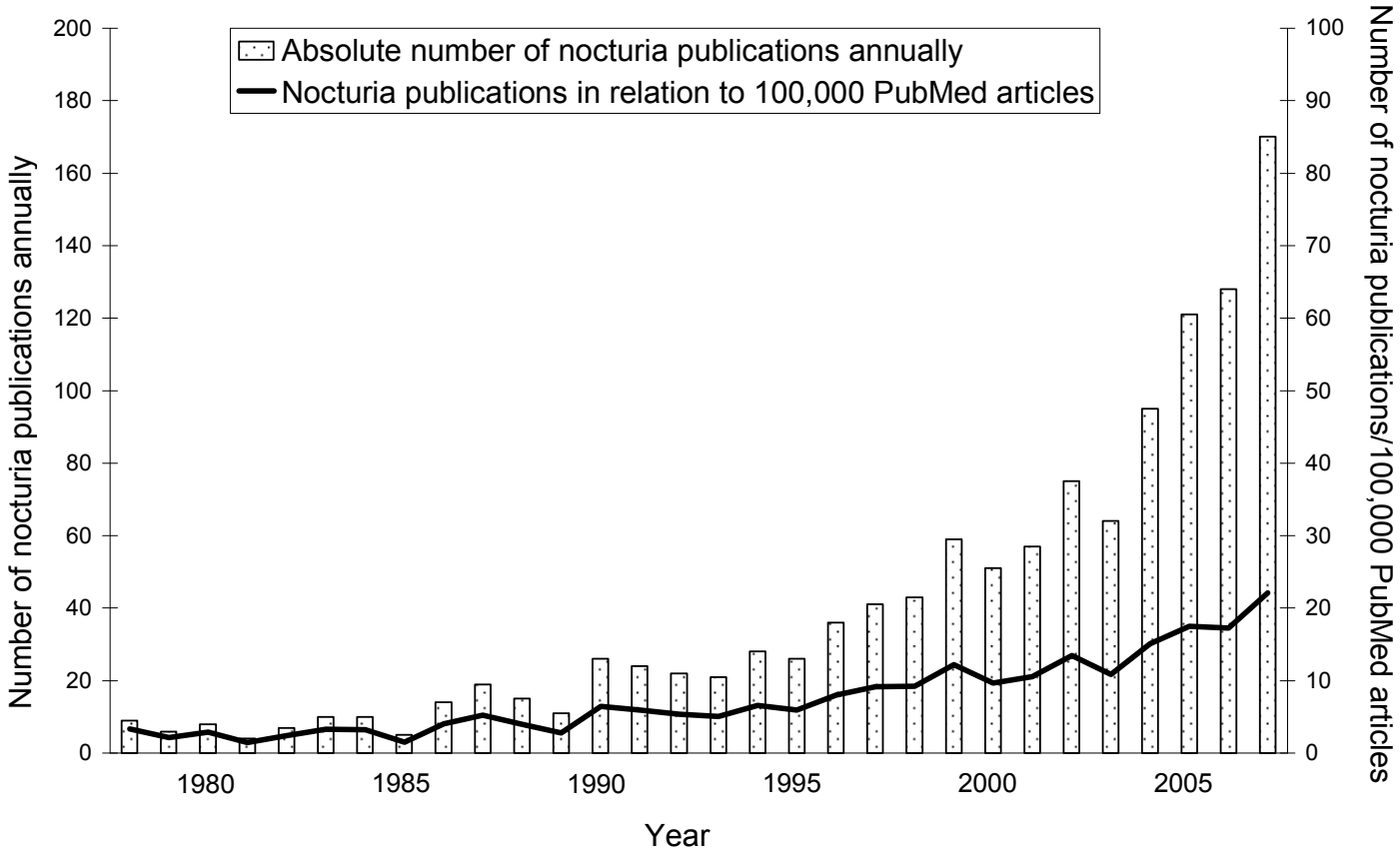
Traditionally, urologists have defined nocturia as frequency of urination at night without reference to urine amount, whereas internists have assumed that nocturnal frequency results from an excessive amount of urine produced with less focus on other lower urinary tract symptoms (LUTS) (Rubin & Nagel 1951). For a long time, there has been evidence that among healthy people urine flow is lower during the night than during the day (Roberts 1860), and that electrolyte excretion is reduced at night (Norn 1929). Furthermore, healthy elderly people have been shown to excrete a higher proportion of urinary water, sodium, potassium, and solute output at night than young people (Kirkland et al. 1983).

The International Continence Society (ICS) defines *nocturia* as waking at night one or more times to void and *nocturnal polyuria* (NP) as the production of an abnormally large volume of urine during sleep (van Kerrebroeck et al. 2002). Nocturnal urinary incontinence or nighttime bed wetting (enuresis) differs from nocturia. According to the ICS, nocturia is also a part of a symptom complex called *overactive bladder syndrome*. Overactive bladder (OAB) is a symptom-defined condition characterised by urinary urgency, with or without urgency urinary incontinence (UUI), usually with increased daytime frequency and nocturia (Abrams et al. 2002, Abrams et al. 2009). The term OAB is appropriate if there is no proven infection or other obvious pathology (Abrams et al. 2002). By definition, urinary urgency refers to sudden compelling desire to pass urine (Abrams et al. 2002). However, there is an on-going debate on the definitions, especially regarding urinary urgency and OAB (Madersbacher 2005, Blaivas 2007, Yamaguchi et al. 2007, Homma 2008).

The etiology of nocturia is not well understood. In women, nocturia is often attributed to aging or childbirth, and in men, the symptoms are frequently attributed to obstruction due to benign prostatic hyperplasia (BPH) / benign prostatic enlargement (BPE) (Harvard Health Letter 1999). Other conditions believed to cause nocturia include OAB, NP, obstructive sleep apnea (OSA), behavioural factors, and awakening for other reasons like anxiety or primary sleep disorders. Behavioural and environmental factors thought to contribute to nocturia include diuretics, likewise caffeine, alcohol or excessive fluid intake shortly before bedtime. (Weiss & Blaivas 2000, Lose et al. 2001, Hunskaar 2005)

Despite growing research interest in nocturia (Figure 1), its treatment is still problematic. Nocturia is the most persistent lower urinary tract symptom (LUTS) following prostatectomy (Abrams et al. 1979). In a US study, 38% reported ≥2 voids per night three years after trans-urethral resection of prostate (TURP) (Bruskewitz et al. 1986). Parallel results were also reported in a recent study: nocturia was the most common LUTS among men who had experienced prostate surgery (Norby et al. 2005). Among patients with OAB/detrusor overactivity, nocturia is also probably the most persistent OAB symptom following neuromodulation or botulinum toxin injections (Bosch 2006, Flynn et al. 2009). Bedtime fluid intake patterns likely have little to do with frequency of nocturia in most individuals (Johnson et al. 2005b). Continuous positive airway pressure treatment has been shown in non-randomised studies to relieve nocturia among patients with OSA (Fitzgerald et al. 2006, Margel et al. 2006). Many pharmacological approaches to nocturia have been tested, including single and combined drug therapy with alpha-blockers, 5-alpha-reductase inhibitors, and antimuscarinic bladder relaxants in men; menopausal hormone therapy (MHT) in women; and in either gender, diuretics, vasopressin analogues, antimuscarinics, and non-steroidal anti-inflammatory drugs. However, treatment is often ineffective or involves side-effects. (Abrams et al. 1979, Bruskewitz et al. 1986, Cardozo et al. 1993, Reynard et al. 1998, Weiss & Blaivas 2000, Homma et al. 2002, Mattiasson et al. 2002, Johnson et al. 2003, Lose et al. 2003, Araki et al. 2004, Addla et al. 2006, Kaplan et al. 2006, Rackley et al. 2006, Rembratt et al. 2006, Swanson et al. 2006, Bae et al. 2007, Brubaker & Fitzgerald 2007, Johnson et al. 2007, Robinson et al. 2007)

Figure 1. Absolute and relative number of annual nocturia articles between 1978 and 2007. Separately for each time period (e.g. from Jan 1st, 1978 to Dec 31st, 1978), PubMed search was performed using word ´nocturia´ as search key. Number of annual publications was examined for the same time period.



Overall, earlier research on urinary symptoms has focused mainly on stress urinary incontinence (SUI) in women and on LUTS suggestive benign prostatic obstruction (BPO) in men (Hunskaar 2005). Since nocturia increases very strongly with age, its importance increases as the population ages (Weiss & Blaivas 2000). There is a paucity of epidemiological investigations on nocturia, especially using samples of both sexes and all adult ages. It has been proposed that further studies on nocturia - using population-based sample of both sexes and wide age range - should be performed to assess bother, its impact on quality of life, and risk factors and comorbidity of nocturia (Hunskaar 2005).

The Finnish National Nocturia and Overactive Bladder (FINNO) Study was initiated in 2003 to explore the prevalence, natural history, impact and risk factors of urinary storage symptoms (especially nocturia and urinary urgency) using population-based sample of both sexes and all adult ages.

1. Literature review

1.1 Terms and definitions

"*Epidemiology is so beautiful and provides such an important perspective on human life and death, but an incredible amount of rubbish is published.*" (Taubes 2007)

Sir Richard Peto, Professor of Medical Statistics & Epidemiology

1.1.1 Epidemiology

The origin of the word epidemiology is unknown, but it is derived from the Greek words meaning ´study upon populations´ (*epi* = upon, *demos* = people, *ology* = study). Although few excellent epidemiological investigations were conducted earlier, most principles of epidemiology began to form only in the second half of the 20th century. The latter part of the 20th century was an era of rapid growth in terms of epidemiological concepts (Rothman et al. 2008). MacMahon and Pugh (MacMahon & Pugh 1970) defined *epidemiology as the study of the distribution and determinants of disease in man*, whereas Miettinen *as the principles of studying the occurrence of illness and related states and events, including those of health care* ("occurrence research") (Miettinen 1985).

Nowadays, the scope of epidemiology has widened substantially. Epidemiology includes 1) the methods for measuring the health of groups and for determining the attributes and exposures that influence health; 2) the study of the occurrence of disease in its natural habitat (rather than in the controlled laboratory environment); and 3) the methods for the quantitative study of the distribution, variation, and determinants of health-related outcomes in specific groups (populations) of individuals, and the application of this study to the diagnosis, treatment, and prevention of these states or events. Epidemiology can be divided into 1) *descriptive (observational) epidemiology*, 2) *analytical epidemiology*, and 3) *clinical epidemiology*. Clinical epidemiology (evidence-based medicine) serves as *´a basic science for*

clinical medicine´ and encompasses diagnosis and treatment in patient care, including evaluation of various approaches in terms of techniques and methods, algorithms and decision rules as well as the organisation and provision of services (Sackett et al. 1991).

Epidemiology is characterised by an empirical, quantitative and stochastic approach to the study of health-related phenomena. Empirical approach means that observations are systematically collected. Quantitative and stochastic nature means that observations are treated numerically and occurrence and effects can be presented as probabilities. These characteristics form the basis for the epidemiological concept of cause. Generally, a cause in epidemiology is defined as a factor that alters the probability of occurrence of the consequence. Causal relations investigated in epidemiology are typically complex, multifactorial networks and their elucidation is demanding due to limitations in easily applicable concepts and measurements. A risk factor (when used in the wide sense on not necessarily implying causality as in this study) can be defined as an antecedent event, condition, or characteristic associated with an outcome. Sometimes a distinction is made between causal factors (with well established etiological role), correlates (without a causal effects), risk factors (incompletely understood possible causal factors) and risk indicators (predictive factors regardless of possible causal involvement). (Rothman et al. 2008)

Epidemiology is closely related to several other disciplines including (clinical) medicine, statistics and demographics. Both medicine and epidemiology cover health and disease. The focus in clinical medicine is an individual (patient), whereas epidemiology looks at the population level. Clinical epidemiology (evidence-based medicine) is in between. Statistics has provided tools for epidemiological research, whereas many study designs used in epidemiology are originally from demographical research.

This dissertation covers prevalence, impact and risk factors of nocturia. The natural history of nocturia will be assessed in our future work. Despite lacking the prospective aspect of nocturia here, this dissertation covers the other most important viewpoints of epidemiology, thereby justifying the title *´Epidemiology of nocturia´*.

1.1.2 Lower urinary tract symptoms and nocturia

Earlier research on urinary symptoms has focused on LUTS on men and on SUI in women. Traditionally, nocturia has often been attributed to aging or childbirth in women, and to LUTS suggestive of benign prostatic hyperplasia (BPH) in men. In recent years ´overactive bladder symptoms´ and their treatment in both sexes has commanded attention worldwide (Ouslander 2004, Cartwright et al. 2008). Nocturia was for a long time a neglected topic in the medical literature (Barker & Mitteness 1988). However, it has recently been recognised as a clinical entity in its own right (Weiss & Blaivas 2000, van Kerrebroeck et al. 2002), and currently there is a growing interest in nocturia (Figure 1).

Generally, the definition of a disease/condition/symptom is a critical factor in evaluating its epidemiology; nocturia is no exception to this rule (Hunskaar 2005). To facilitate discussion and research related to LUTS, the ICS has produced standardisation reports. The ICS revised its Standardisation Report of lower urinary tract function terminology in 2002 (Abrams et al. 2002). The Report has been already revised further and the discussion/debate is ongoing (Abrams et al. 2009).

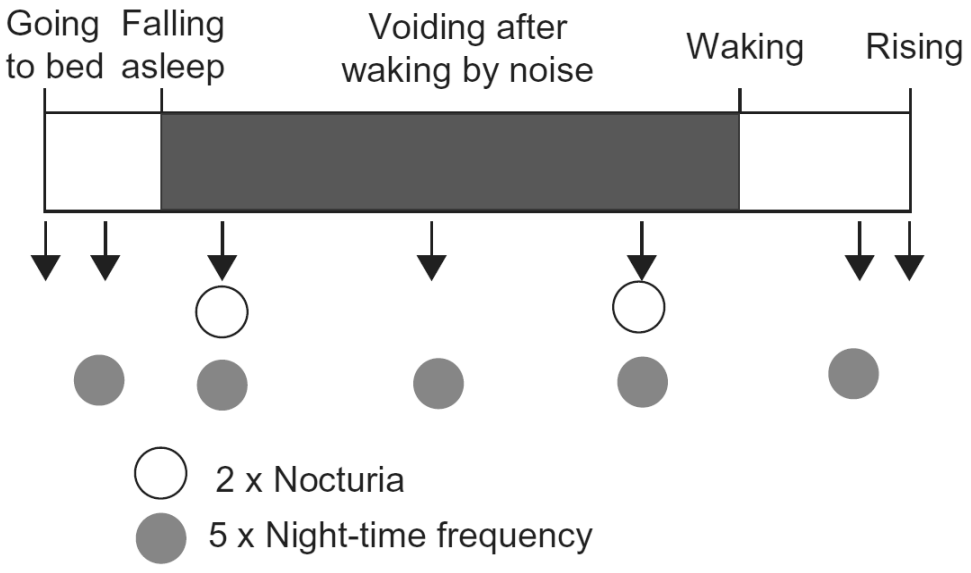
In the 2002 Standardisation Report (Abrams et al. 2002), LUTS were divided into three major groups (storage, voiding and post-micturation symptoms), while related symptoms were further divided into four groups (symptoms associated with sexual intercourse, symptoms associated with pelvic organ prolapse, genital and lower urinary tract pain, and genitor-urinary pain syndromes and symptom syndromes suggestive of lower urinary tract dysfunction).

Voiding symptoms include slow stream, splitting/spraying, intermittent stream, hesitancy, straining and terminal dribble, whereas post micturition symptoms include feeling of incomplete emptying and post micturition dribble (Abrams et al. 2002). The FINNO Study aims to evaluate especially urinary storage symptoms such as nocturia and urinary urgency. The ICS recognises four kinds of ´urinary storage symptoms´, (formerly ´irritative´ symptoms):

1. ***Increased daytime frequency*** (formerly urinary frequency, *pollakisuria*) defined as the complaint by the patient who considers that he/she voids too often by day.
2. ***Nocturia*** defined as the complaint that the individual has to wake at night one or more times to void
3. ***Urgency*** defined as the complaint of a sudden compelling desire to pass urine which is difficult to defer.
4. ***Urinary incontinence*** is the complaint of any involuntary leakage of urine.

It has been proposed that the difference between nocturia and night-time frequency should be clarified as shown in Figure 2 (Homma 2008).

Figure 2. Newly defined nocturia does not include voiding from the time of going to bed until the time of falling asleep, waking-and-voiding not due to a desire to void, or voiding from the time of waking until the time of rising from bed. (Figure including figure legend reprinted with permission from Homma. Lower urinary tract symptomatology: Its definition and confusion. Int J Urol 2008;15:35-43).



1.2 Prevalence of nocturia

Prevalence is a measure of the total number of cases of a condition in a population, whereas incidence is the rate of occurrence of new cases. Thus, prevalence indicates how widespread a condition is whereas incidence conveys information about the risk of condition. As nocturia is a fluctuating symptom, not ´irreversible´ such as a cancer diagnosis, the incidence figures do not represent incidences in the traditional sense. Hence, prevalence estimates may be more relevant when estimating how common nocturia is.

Most earlier studies on nocturia prevalence have been conducted among elderly men (Britton et al. 1990, Sommer et al. 1990, Garraway et al. 1991, Chute et al. 1993, Homma et al. 1994, Sagnier et al. 1994, Malmsten et al. 1997, Moller et al. 2000b). Generally, nocturia is a very common symptom among both sexes. The estimated prevalence of nocturia has varied, largely due to differences in symptom assessment, study population, data collection, and definitions used (Hunskaar 2005).

According to questionnaire studies, most elderly people void at least once per night (Weiss & Blaivas 2000). In the Krimpen study (Blanker et al. 2000a), nocturia was assessed by frequency-volume charts (FVCs). At least 1.5 voids per night (calculated based on information on two or three nights) was present in 30% of men aged 50-54 and in 60% of men aged 70-78 years, whereas at least 2.5 voids per night was present in 4% and 20%, respectively. This concurs with other studies (Britton et al. 1990, Sommer et al. 1990, Garraway et al. 1991, Chute et al. 1993, Homma et al. 1994, Sagnier et al. 1994, Malmsten et al. 1997, Schatzl et al. 2000, van Dijk et al. 2002, Coyne et al. 2003, Rembratt et al. 2003, Yoshimura et al. 2004), the prevalence of nocturia increases with age.

There is a paucity of studies assessing and comparing LUTS in both sexes (of all ages), especially at population level. Recently, a few comparative studies have been published (Schatzl et al. 2000, van Dijk et al. 2002, Coyne et al. 2003, Rembratt et al. 2003, Yoshimura et al. 2004). Among subjects aged 65 or more, slightly more nocturia was found among men (31% reported at least two voids per night) than women (26%) in a Swedish study (Rembratt et al. 2003). A Dutch study (using a random sample from a telephone company database)

concluded that nocturia is more common among women. This was due to higher nocturia prevalence among young women than young men - differences disappeared among the elderly (van Dijk et al. 2002). Other studies did not report any difference in nocturia prevalence between genders (Schatzl et al. 2000, Coyne et al. 2003, Yoshimura et al. 2004).

1.3 Bother and impact of nocturia

Urinary storage ("irritative") symptoms, such as urinary frequency, urgency and nocturia, have been reported to be more bothersome than voiding ("obstructive") symptoms, such as weak stream or incomplete emptying (DuBeau et al. 1995, Eckhardt et al. 2001). Earlier results suggest that nocturia may impair well-being more than generally recognised. Nocturia causes bother (DuBeau et al. 1995, Swithinbank et al. 1999, Coyne et al. 2003, Fiske et al. 2004) and entails sleep loss, daytime fatigue, missed work, perceived health, and depression (Asplund & Åberg 1992, Asplund & Åberg 1996, Samuelsson et al. 1997). In several studies, among men with LUTS suggestive of BPH, nocturia has been regarded as more bothersome than other LUTS (Jolleys et al. 1994, DuBeau et al. 1995). Bother has been suggested as a common denominator that brings patients to the doctor (Barry 1997).

There is a growing body of evidence regarding the negative effects of disturbed sleep on health, mood, morbidity and ultimately also on mortality (Hublin et al. 2007, King et al. 2008, Paunio et al. 2009). Nocturnal micturition is associated with sleep disorders and increased daytime fatigue (Asplund & Åberg 1992). It is suggested that bothersomeness of nocturia is primarily related to sleep, however, there is still a paucity of evidence for this in the literature (Hetta 1999, Wagg et al. 2005, Endeshaw 2009). In some studies, nocturia was the most important reason for nocturnal awakenings leading possibly to sleep maintenance insomnia (Middelkoop et al. 1996, Bing et al. 2006). On the contrary, in a US sleep centre study, OSA and other sleep disorders were responsible for the majority of nocturia (Pressman et al. 1996).

Nocturia has also been associated with an increased risk of falling (Stewart et al. 1992, Brown et al. 2000). Falls are the greatest single risk factor for fractures in elderly people (Järvinen et al. 2008). However, whether falls are due to nocturnal visits to the lavatory, due to daytime fatigue, or due to other comorbidities is not clear. It is also possible that nocturia does not cause falls but is associated with factors causing falls – being an indicator of frailty. There is

no randomised controlled trial (RCT) assessing the impact of nocturia treatment in prevention of falls and fractures. Generally, there is a paucity of studies examining bother and impact of nocturia, especially at population level (Hunskaar 2005).

1.4 Risk factors of nocturia

The causes and risk factors of nocturia are not well understood (Hunskaar 2005). Despite increasing recent research interest in nocturia (Figure 1), our understanding of nocturia (Table 1) is based mainly on *expert opinions* rather than *scientific evidence*. However, these lists (Table 1) are beneficial especially for future research as hypothesis-generating (Resnick 1990, Abrams et al. 2002, Weiss 2006, Appell & Sand 2008, Kujubu & Aboseif 2008, Schneider et al. 2009).

Table 1. Factors proposed as involved in etiology and pathogenesis of nocturia (many conditions are mutually related – fundamental etiology of a condition is often unclear).

Urological conditions (in alphabetical order)		
Bladder outlet obstruction (caused by e.g. BPH)	Detrusor overactivity	Painful bladder syndrome
Bladder hypersensitivity	Interstitial cystitis	Pelvic floor laxity (cystocele, uterine prolapse, etc)
Calculi of bladder or ureter	Learned voiding dysfunction	Sensory urgency
Cancer of bladder/prostate/urethra	Neurogenic bladder	Urine tract infection
Decreased bladder capacity	Overactive bladder (syndrome)	
Non-urological conditions (in alphabetical order)		
Ageing	Excessive fluid intake	Peripheral edema
Anxiety	Hypercalcemia	Pharmacological agents: alcohol, β-blockers, caffeine, calcium-channel blockers, diuretics, lithium, selective serotonine reuptake inhibitors, theophylline, etc
Autonomic dysfunction	Hypoalbuminemia	
Chronic kidney disease	Hypokalemia	
Chronic obstructive lung disease	Insomnia	
Chronic pain	Multiple sclerosis	
Congestive heart failure	Nephrosis	
Defect in secretion or action of antidiuretic hormone	Neurodegenerative conditions (Parkinsonism or Alzheimer´s)	Periodic limb movement
		Pruritus
Depression	Nocturnal polyuria	Restless legs syndrome
Diabetes mellitus/insipidus	Nocturnal epileptic seizures	Sleep apnea
Dyspnea	Oestrogen deficiency	Venous insufficiency

Modified from Resnick 1990, Abrams et al. 2002, Weiss 2006, Appell & Sand 2008, Kujubu & Aboseif 2008, Schneider et al. 2009.

In the earlier literature on nocturia (before the FINNO Study), the following conditions (in alphabetical order) have been reported as the main underlying factors behind or risk factor for nocturia.

Ageing. There have been numerous studies showing that elderly subjects have more nocturia than younger people (Sommer et al. 1990, Chute et al. 1993, Homma et al. 1994, Sagnier et al. 1994, Malmsten et al. 1997, Blanker et al. 2000a, Kawauchi et al. 2000, Schatzl et al. 2000, van Dijk et al. 2002, Coyne et al. 2003, Rembratt et al. 2003, Yoshimura et al. 2004).

For instance, in a community-based US study, less than 5% of those aged 18-24 reported two voids per night while the corresponding figures were approximately 15% and 25% for those aged 45-54 and 65-74 respectively (Coyne et al. 2003). Overall, age is one of the most important correlates of nocturia (Malmsten et al. 1997, Blanker et al. 2000a, Schatzl et al. 2000, van Dijk et al. 2002, Coyne et al. 2003, Yoshimura et al. 2004).

Benign prostatic hyperplasia. Many individuals with nocturia, particularly elderly men, have other LUTS (such as urinary frequency, weak stream, urgency) and these symptoms are most often attributed to BPH/BPE/benign prostatic obstruction (BPO) in men (Weiss & Blaivas 2000). BPH/BPE/BPO constitute a very well-recognised risk factor for nocturia (Blanker et al. 2000a, Yu et al. 2005). Its impact may have been overemphasised, especially in clinical practice. This is supported by Japanese studies, where nocturia was the least specific LUTS associated with benign prostatic obstruction and treatment to relieve benign prostatic obstruction had less effect on nocturia than on other symptoms (Homma et al. 2002, Yoshimura et al. 2003). Rate of nocturia improvement was 13.9% in tamsulosin group and 19.6% in the TURP group (Yoshimura et al. 2003). Other six LUTS assessed were each improved in 18.2% - 28.5% of patients in the tamsulosin and in 37.0% - 63.0% of patients in the TURP group respectively. In the earlier studies, nocturia had been reported as one of the most (if not the single most) persistent LUTS following prostate surgery (Abrams et al. 1979, Bruskewitz et al. 1986).

Depression. In a Swedish population-based study (Asplund et al. 2004), subjects with major depression (assessed by the Major Depression Inventory (Bech et al. 2001)) reported substantially more nocturia than those without. The association was especially strong among men (OR 6.5, 95% CI 2.6-15.6 for men, and OR 2.8, 95% CI 1.3-6.3 for women, adjusted for age and ´somatic health´). However, in a subsequent analysis from the same database (Asplund et al. 2005b), the authors reported that both major depression (OR 4.6, 95% CI 2.8-7.5) and taking an SSRI (OR 2.2; 95% CI 1.1-4.5) were associated with increased prevalence of nocturia (gender was deleted by the logistic regression model).

Female reproductive and gynaecological factors. The relation of nocturia to reproductive factors, such as pregnancy, parity, menopause, MHT and hysterectomy, has received little attention (Lose et al. 2001). Nocturia is a common symptom during pregnancy (Parboosingh & Doig 1973, Aslan et al. 2003). In a British study more than 60% of pregnant women (mean

age 24.3, SD 4.9, range 19-40 years) reported at least three nocturnal voids per week, with highest prevalence of nocturia (66%) in the third trimester (Parboosingh & Doig 1973). Increased prevalence of nocturia among post-menopausal women has earlier been reported (in the Danish study: OR 2.4, 95% CI 1.1-5.2; and in the Swedish study OR 1.8, 95% CI 1.3-2.5, <5 years after menopause versus before) (Rekers et al. 1992, Alling Moller et al. 2000, Asplund & Åberg 2005). However, MHT was not related with either increased or decreased nocturia in an RCT (Cardozo et al. 1993) or population-based study (Asplund & Åberg 2005). Earlier results are inconsistent regarding hysterectomy and nocturia: hysterectomy being associated with decreased (Vervest et al. 1988, Virtanen et al. 1993, Thakar et al. 2002) or increased prevalence of nocturia (Alling Moller et al. 2000), or not associated with nocturia (Prasad et al. 2002, Altman et al. 2003).

Hypertension and coronary disease. It has been proposed that NP and essential hypertension are manifestations of the same pathophysiological process (McKeigue & Reynard 2000). However, the connection between nocturia and hypertension is not clear. In a Japanese health screening study and a population-based study among elderly in the US (Yoshimura et al. 2004, Johnson et al. 2005b), hypertension was associated with nocturia (OR 1.64, 95% CI 1.45-1.87 in the Japanese study; OR 1.52, 95% CI 1.19-1.94 in the US study), but, in the Dutch study (Blanker et al. 2000a) and in a Swedish study (Rembratt et al. 2003) NP/nocturia was not associated with hypertension. Appropriate research methodology is of particular importance when assessing the impact of hypertension on nocturia: the treatment for hypertension may cause (Bulpitt et al. 2000, Weiss & Blaivas 2000) or alleviate nocturia (Reynard et al. 1998), with calcium-blockers and poorly-timed vs. ´properly´ timed diuretics as examples. Cardiac disease, coronary disease and congestive heart failure have been proposed as causal or risk factors for nocturia in most review articles (Table 1). However, this was not supported in studies conducted mainly among men (Blanker et al. 2000a, Rembratt et al. 2003, Yoshimura et al. 2004). However, in all these studies (Blanker et al. 2000a, Rembratt et al. 2003, Yoshimura et al. 2004), an association between cardiac symptoms/disease and nocturia was found in the preliminary analyses before multivariate models.

Lifestyle factors. Both coffee and alcohol are diuretic liquids with the potential to increase urine volumes. Treatment guidelines usually recommend decreasing (bedtime) fluid intake,

especially coffee and alcohol (Table 1). However, earlier research did not find any relation between nocturia and coffee (Samuelsson et al. 1997, Asplund & Åberg 2004) or alcohol (Schatzl et al. 2000, Yoshimura et al. 2004). Earlier results are very inconsistent regarding smoking and nocturia: smoking being a risk factor (Asplund & Åberg 2004), a protective factor (Schatzl et al. 2000, Yoshimura et al. 2004), or not associated with nocturia (Samuelsson et al. 1997). In the population-based Krimpen study (Blanker et al. 2002a), smoking was associated with increased day-to-night ratio of urine production. In the Austrian health-screening study (Schatzl et al. 2000), no relation was found between physical activity and nocturia.

Neurological diseases. Several neurological conditions are potentially causal factors for OAB (Compston & Coles 2002, Ouslander 2004, Winge & Fowler 2006). Much less is known about the impact of neurological diseases on nocturia. Most patients with multiple sclerosis (approximately 75%) have bladder dysfunction leading to urinary storage symptoms (Compston & Coles 2002, DasGupta & Fowler 2003), and potentially to nocturia. In Swedish and Dutch studies on elderly people, nocturia was associated with stroke (OR 2.0, 95% CI 1.1-3.6) and cerebrovascular disease (OR 1.8, 1.2-2.7) respectively (Asplund 2002, Gourova et al. 2006). Sleeping problems and nocturia are common among Parkinson´s patients (Partinen 1997). In a study among Parkinson´s patients, severity of disease was also associated with increased nocturia (mean of nocturia episodes was 1.8 in the mild, and 2.9 in the severe Parkinson groups) (Young et al. 2002).

Nocturnal polyuria. According to the ICS (Abrams et al. 2002), NP is present when an increased proportion of the 24-hour output occurs at night. According to the Report, the normal range of nocturnal urine production differs with age and the normal ranges remain to be defined. The report also states that NP is present when more than 20% (young adults) to 33% (aged over 65) of the daily urine volume is produced at night. Furthermore, the ICS defines polyuria as the measured production of more than 2.8 L of urine per 24hr in adults. However, these definitions are not based on large-scale population based studies. In the population-based Krimpen study, nocturia was strongly associated with NP (Blanker et al. 2000a). However, it was difficult to separate men with and without increased voiding frequency on the basis of nocturnal urine production (Blanker et al. 2000a, Blanker et al. 2002b). Among these men, nocturnal urine production was slightly more than 60 ml/hr. The authors suggested that nocturnal urine production exceeding 90 ml/hr is abnormal. However,

they concluded that "nocturnal urine production as an explanatory variable for nocturnal voiding frequency is of little value." (Blanker et al. 2002b) Overall, the fundamental pathogenesis of NP is difficult to assess. Congestive heart failure, "third spacing" (venous insufficiency, nephrosis), or late-night diuretic administration are potential underlying causes. Possible pathways also include diminished renal concentrating capacity, diminished sodium conserving ability, loss of the circadian rhythm of antidiuretic hormone secretion, decreased secretion of renin-angiotensin-aldosterone, increased secretion of atrial natriuretic hormone (e.g. due to OSA) leading to increased nighttime urine production. (Asplund 1995, Miller 2000, Weiss & Blaivas 2002)

Obesity and diabetes. Obesity (but not overweight) was associated with nocturia among women (aged 40-64) in a population-based study (BMI ≥30: OR 3.5, 95% CI 2.6-4.7; BMI <20 as reference) (Asplund & Åberg 2004). No association of BMI and nocturia (defined as at least two voids per night) was reported in a study among urogynaecology patients (Elia et al. 2001). In this study, women were classified by BMI as low (19.8), normal (19.8-26.0), high (26.1-29.0), and obese (>29.0). In these groups, nocturia was reported by 47.1%, 41.4%, 47.1%, and 55.0%. Even though there was no linear relation between nocturia and BMI, actually, there was a potential U-shape relation between BMI and nocturia. Diabetes and OSA patients with nocturia have been shown to have higher BMI than diabetes and OSA patients without nocturia (Bulpitt et al. 1998, Hajduk et al. 2003, Guilleminault et al. 2004). An association between diabetes and nocturia has been reported in some (Asplund 2002, Yoshimura et al. 2004; OR 1.5, 95% CI 1.1-2.3; OR 1.7, 95% CI 1.3-2.2 respectively) but not in other studies (Blanker et al. 2000a, Rembratt et al. 2003).

Overactive bladder and detrusor overactivity. According to the ICS, OAB is a symptom-defined condition characterised by urinary urgency, with or without UUI, usually with increased daytime frequency and nocturia (Abrams et al. 2002, Abrams et al. 2009). It is commonly proposed that urinary urgency/OAB is the primary driver of all symptoms of OAB also leading to increased nocturia (Wein & Rackley 2006). However, there is a paucity of evidence. In a British study among women aged 40 or more (Matharu et al. 2005), self-reported nocturia predicted detrusor overactivity in urodynamics (OR 1.9, 95% CI 1.1-3.3, OR 2.0, 95% CI 1.1-3.8, and OR 3.1 95% CI 1.4-6.6 for women with one, two, and three or more void(s) per night respectively). (Urodynamic study is investigation of the (dys)function

of the lower urinary tract where the idea is to replicate the symptoms of the patient, and then examine them and determine their cause.) However, the treatment of nocturia with bladder relaxants (antimuscarinics) is often unsuccessful (Michel & de la Rosette 2005).

Painful bladder syndrome/interstitial cystitis. Nocturia is also part of a debilitating condition called painful bladder syndrome/interstitial cystitis (PBS/IC). PBS/IC is characterised by urinary frequency, urgency, nocturia and suprapubic pain. PBS/IC is a rare condition with unknown (multifactorial) etiology. (Leppilahti et al. 2002, Bouchelouche & Nordling 2003)

Sleep disorders. In a Swedish urology clinic study (Kinn & Harlid 2003), snoring was associated with increased nocturia (snorers: mean 2.3 voids/night, range 1-4; and controls 1.1, range 0-3, $p<0.01$). However, snorers also had higher BMI (snorers: mean 30.2, range 23.0–39.5; and controls 24.1, range 21.8–31.1, $p<0.001$; no multivariate analysis was reported). Snoring is closely related to OSA (Malhotra & White 2002). In a US sleep centre study, OSA and sleep disorders were responsible for most (79.3%) nocturia (Pressman et al. 1996). In a small sleep centre study (Krieger et al. 1993), an impact of OSA on nocturia was also found. The reported mean of controls (with mean BMI of 24.8) was 2.2 voids per night compared to 3.9 among OSA patients with apnea hypopnea index (AHI) >50 (with mean BMI of 31.8). In US studies conducted among community-dwelling older adults, subjects with increased AHI had greater mean nocturia episodes, nighttime urine production and atrial natriutretic peptide excretion (Endeshaw et al. 2004, Umlauf et al. 2004). In the Georgian study (Endeshaw et al. 2004), mean of nocturia episodes were 1.7 (SD 1.1), 1.6 (SD 0.9), and 2.6 (SD 1.4) for subjects in AHI groups of <10, 10-24, and ≥25 per hour of sleep. In the Alabamian study (Umlauf et al. 2004), nocturnal urine output was associated with increasing AHI index: 707 ml (SD 263), 844 ml (SD 359), and 977 ml (SD 327) in the groups of AHI indices <5, 5-14.9, and >15 respectively.

2. Aims of the study

The aim of the FINNO Study is to assess the prevalence, natural history, impact and risk factors of urinary (storage) symptoms using population-based sample of both sexes and all adult ages. The specific aims of this dissertation are:

1. To describe and compare the prevalence of nocturia and overactive bladder among men and women of all adult ages (Studies I-II)

2. To examine the bother and impact of nocturia on quality of life (Study III) in order to distinguish those forms of nocturia which disturb normal life

3. To identify the risk factors for nocturia and assess their population-level impact (Studies IV-VI)

3. Materials and methods

3.1 Design

Data collection for the first stage of the FINNO Study was by postal questionnaires to a sample of 6,000 Finns aged 18-79 randomly identified from the Finnish Population Register Centre (Table 3). Questionnaires were first mailed in late November 2003, with reminders a month later. To those who did not respond, a final round of questionnaires was mailed in February 2004. To ensure responder-friendliness and intelligibility, the questionnaire was pretested in a pilot study.

Equal numbers of men and women were recruited from the general population. Stratification by age was used in subject selection, with oversampling of the younger age groups to achieve a similar number of subjects with nocturia or urinary urgency in all age groups regardless of the prevalence of these symptoms (Table 2). We selected the target level of accuracy so that, given a true prevalence of 15%, we could exclude a prevalence of 10% or lower. The response proportion was approximately 32% after the first round, 50% after the second round, and finally 62.4% after the third round (Table 2).

The FINNO Study complies with the Declaration of Helsinki. Under the Finnish regulations on questionnaire surveys, exemption from ethical review was granted by the ethics committee of the Pirkanmaa Hospital District (R06072) (Tampere, Finland). STROBE recommendations for the reporting of observational studies were followed (von Elm et al. 2007).

Table 2. Number of subjects and response proportions by age and sex in the FINNO Study, Finland, 2003-2004.

Men					
Age groups (years)	**Target sample**	**Ineligible**	**Eligible sample**	**Participants**	**Response proportion (%)**
18 - 29	800	4	796	388	48.7
30 - 39	800	2	798	428	53.6
40 - 49	600	0	600	335	55.8
50 - 59	300	0	300	197	65.7
60 - 69	300	2	298	226	75.8
70 - 79	200	4	196	151	77.0
Men overall	3,000	12	2,988	1,725	57.7
Women					
Age group (years)	**Target sample**	**Ineligible**	**Eligible sample**	**Participants**	**Response proportion (%)**
18 - 29	800	3	797	510	64.0
30 - 39	800	2	798	495	62.0
40 - 49	600	3	597	408	68.3
50 - 59	300	1	299	213	71.2
60 - 69	300	1	299	237	79.3
70 - 79	200	1	199	139	69.8
Women overall	3,000	11	2,989	2,002	67.0
Both genders	**6,000**	**23**	**5,977**	**3,727**	**62.4**

3.2 Exclusions

In Studies I and IV, we made no exclusions. In Studies II-III and V-VI, subjects who were pregnant, in the immediate postpartum period (puerperium defined as six weeks after delivery), or experiencing a urinary tract infection were excluded. Furthermore, in Study II, we conducted analyses with different exclusions (Appendix 1). Information on pregnancy was based on both data from the Finnish Population Register Centre and the questionnaire (Appendix 2). Puerperium information was based on data on delivery dates from the Finnish Population Register Centre, which also provided urbanity data.

3.3 Assessment of urinary symptoms, their impact and potential risk and confounding factors

3.3.1 Measures of lower urinary tract symptoms and bother

The main outcome of the study was nocturia, with its impact on well-being and occurrence of other urinary symptoms also evaluated in some analyses. Information on LUTS was collected using the Danish Prostatic Symptom Score (DAN-PSS) questionnaire (Schou et al. 1993), with an additional frequency question and a nocturia question from the American Urological Association Symptom Index (AUA-SI) (Barry et al. 1992). DAN-PSS was elicited for the past two weeks, and the AUA-SI question pertained to the past month (Table 3). In the validation studies (Hansen et al. 1995, Barry et al. 1992), both the DAN-PSS and the AUA-SI nocturia question had excellent test-retest reliabilities (r = 0.84 for both). Furthermore, the DAN-PSS and the AUA-SI nocturia question have also been validated using a Finnish translation (Koskimäki, personal communication regarding unpublished data).

Responses to nocturia questions from the DAN-PSS and the AUA-SI were combined to assess occurrence and bother of nocturia (as the AUA-SI does not elicit bother and DAN-PSS does not elicit precise nocturia information). The DAN-PSS has four response options for nocturia, whereas the AUA-SI has six (Table 3). Subjects who did not respond to the AUA-SI were not included in the analyses because of the lack of precise information on the number of nocturnal voids. In the case of discrepancy between the responses to the two questions, the DAN-PSS was regarded as the gold standard so that the DAN-PSS response nearer to the AUA-SI response was chosen. Consistency between the two nocturia questions was excellent; for instance Kappa for being classified as a nocturia case (using definition of at least two voids per night) by the AUA-SI or the combination of the DAN-PSS and AUA-SI nocturia responses was 0.97 (95% confidence interval (CI) 0.95-0.99; $p < 0.001$) in men and 0.98 (95% CI 0.96-0.99, $p<0.001$) in women.

Both the current ICS definition of nocturia (one or more voids per night) and the traditional definition of at least two voids per night were used in Studies I and IV. We aimed to assess the clinically meaningful definition for nocturia in the Study III. In that particular study (Study III), nocturia was defined as either one, two, three or at least four voids per night. In the HRQL analyses, subjects were classified by reported nocturia: those reporting no nocturia

(reference group), with 1 void per night, with 2 voids per night, and with at least 3 voids per night. On the basis of results of the Study III, we only used the definition of at least two voids per night in most analyses (Studies II and V-VI). Two or more episodes was used as a cut-off point because this degree of nocturia was typically viewed as bothersome and was associated with clinically important deterioration in HRQL whereas 1 void per night was not (Study III).

For bother assessment of nocturia the DAN-PSS question “If you have to urinate during the night, is this a bother for you?” was used with answer options: “No”, “Small”, “Moderate”, or “Major” (Schou et al. 1993).

Table 3. Questions related to the presence of nocturia and other OAB symptoms in the FINNO Study, Finland, 2003-2004.

Symptom	Defining questions	Response options
Nocturia	How many times do you have to void per night? (Schou et al. 1993) Over the last month, how many times did you most typically get up to urinate from the time you went to bed at night until you got up in the morning? (Barry et al. 1992)	None / 1-2 times / 3-4 times / 5 times or more Never / 1 time / 2 times / 3 times / 4 times / 5 times or more
Increased daytime frequency	What is the longest interval between each urination, from when you wake up until you go to bed? (Schou et al. 1993) How many times did you usually urinate per day during the last month?	>3 h / 2–3 h / 1–2 h / <1 h _____ voids per day
Urinary urgency	Do you experience an imperative (strong) urge to urinate? (Schou et al. 1993)	Never / Rarely / Often / Always
Urgency urinary incontinence	Is the urge so strong that urine starts to flow before you reach the toilet? (Schou et al. 1993)	Never / Rarely / Often / Always

3.3.2 Measures of health-related quality of life

HRQL was measured by the generic 15D instrument (Sintonen 2001). It includes 15 dimensions: moving, vision, hearing, breathing, sleeping, eating, speech, eliminating, vitality, mental functions, discomfort and symptoms, depression, distress, energy and sexual activity. Each dimension has a single question with five response options. The 15D can be used as a profile measure or for a single index score (15D Score) by means of population-based preference weights. They generate the dimension level values on a scale 0-1 for profiles and the index score on a scale 0-1 (0 = being dead, 1 = full health); 0.03 is regarded as the minimum clinically important difference in the 15D Score which corresponds to the minimum generally distinguishable difference (i.e. a practically important change in the 15D Score in the sense that people can on average notice the difference) (Sintonen 2001). Missing values on one to three dimensions were imputed using linear regression analysis using the other 15D dimensions, age and sex, as explanatory variables/predictors (Sintonen 1994). The responsiveness, reliability and validity of 15D have been thoroughly established and it has been used extensively in clinical and health care research (Bowling 2004, Moock & Kohlmann 2008).

3.3.3 Assessment of potential risk and confounding factors

Questions modified from the National FINRISK Studies conducted by the National Public Health Institute were used to assess information on self-reported physician-diagnosed conditions, prescribed medications and other treatments, likewise the use of alternative treatments (Table 4 and Appendix 2). These questions - while not validated - have been extensively used (Vartiainen et al. 1998, Laatikainen et al. 2003, Peltonen et al. 2008). Comorbidity indicators were formulated for conditions deemed common or previously identified or hypothesised as risk factors of LUTS (Appendix 3). Medication use was based on self-reported medication lists and classified into 27 groups using the Anatomical Therapeutic Chemical classification (WHO Collaborating Centre for Drug Statistics Methodology 2004) (Appendix 4).

Lifestyle factors, including body mass index (BMI), smoking, coffee and alcohol consumption were assessed by questionnaire (Table 4 and Appendix 2). Information on sociodemographic factors (marital status, education, employment, *not* urbanity) was also assessed by questionnaire (Appendix 2). Information on urbanity, parity (no information on delivery mode) and postpartum period (six weeks to one year after delivery; based on delivery dates) was derived from the Finnish Population Register Centre. Information on menstrual history in past year, MHT, hysterectomy and surgery for SUI (no detail on surgical procedures) was assessed by questionnaire. Women were classified as premenopausal, postmenopausal, hysterectomised, or MHT users (Table 5).

The questionnaire also included a modified version of the Basic Nordic Sleep Questionnaire (Partinen & Gislason 1995) to assess sleep disorders, such as snoring. We used 11 items of the original 21-item questionnaire. The Basic Nordic Sleep Questionnaire uses a five-point scale (with a basic scale of response options such as: 1, "never or less than once per month"; 2, "less than once per week"; 3, "on 1-2 nights per week"; 4, "on 3-5 nights per week"; and 5, "every night or almost every night"). We used snoring information here based on responses to Basic Nordic Sleep Questionnaire (Table 4 and Appendix 5), which referred to the past two weeks.

Information on physician-diagnosed conditions, medications, specific symptoms, and lifestyle factors was available each for 97%-100% of men and 95%-100% of women. Only the question on alcohol consumption (which was not significantly associated with nocturia) had relatively low response (86% of men, 76% of women). Information on age, socio-demographic and female reproductive/gynaecological factors was available for at least 99% of both sexes.

Table 4. Terms and definitions used regarding potential risk and confounding factors of nocturia in the FINNO Study, Finland, 2003-2004.

Term	Defining Questions	Response Categorisation		
Physician-diagnosed conditions	"Have you ever been diagnosed by a physician with any of the following conditions?" with numerous response options (Appendix 3).	(No)	Yes	
Regular use of prescribed medication	Regular use of medication was based on self-reported medication lists assessing drug "names, dosages, and frequency of usage (not at all; "when needed" or "course way"; regularly) (Appendix 4).	No, "When needed" or "Course way" users	Regular users	
Lifestyle factors				
Alcohol	"How many units of alcohol do you typically drink per week?" unit of alcohol corresponds bottle of beer (33 cl), glass of wine (12 cl), or restaurant portion of spirit (4 cl)	Units per week		
Coffee	"How many cups of coffee do you typically drink per day?"	Cups per day		
Body mass index	"How tall are you?" and "How much do you weigh?" were used to calculate body mass index (BMI).	BMI <25 (reference[a])	BMI 25-30 (overweight)	BMI ≥30 (obesity)
Smoking	"Have you ever smoked?" (yes/no) and "Do you still smoke?" (yes/no) were combined.	Never smoker (reference)	Former smoker	Current smoker

Sociodemographic factors			
Marital status	"What is your current marital status?"	Married/Living together, Widowed, Divorced/Separated, Never married	
Education	"Which of the following describes your education?"	Basic level, Vocational school, College, University	
Employment	"In the last three months, have you been mainly?"	Student, Employed, Unemployed, Retired	
Urbanity	Based on data from the Finnish Population Register Centre	Small community (less than 50,000 inhabitants), Large community (at least 50,000 inhabitants)	
Specific symptoms[b]			
Snoring	"How often do you snore while sleeping (ask other people if you are not sure)?" (Partinen & Gislason 1995)[c]	Never or less than once per month; Less than once per week; or On 1-2 nights per week	On 3-5 nights per week; or Every night or almost every night
Stress urinary incontinence	"Do you experience leakage of urine when physically active (e.g. coughing, sneezing, lifting)?" (Schou et al. 1993)	Never or Rarely	Often or Always
Urinary urgency (overactive bladder)	"Do you experience an imperative (strong) urge to urinate?" (Schou et al. 1993)[d]	Never or Rarely	Often or Always

Female reproductive/gynaecological factors			
Parity	Based on data from the Finnish Population Register Centre	Number of delivered children	
Postpartum period	Based on delivery date data from the Finnish Population Register Centre	Defined as more than 6 weeks but not more than 1 year after delivery	
Menopausal status (Classification in Table 5)	"Did you have periods during the last 12 months?"	No	Yes
	"Have you had a hysterectomy?"	No	Yes
	"Do you use hormone therapy for menopausal symptoms?"	No	Yes
	"If you answered yes, do you use vaginal, oral or transdermal?"	(No)	Yes
Surgery for stress urinary incontinence	"Have you had surgery for stress urinary incontinence?"	No	Yes

[a] Only 0.3% of male and 3% of female respondents were underweight (BMI <18.5). The prevalence of nocturia was similar in underweight and normal-weight women by either nocturia criterion (≥1 void/night or ≥2 voids/night). Hence, we used non-overweight (BMI <25) persons as the reference group.

[b] These specific symptoms have been shown to be risk factors for nocturia (Samuelsson et al. 1997, Weiss et al. 1998, Kinn & Harlid 2003).

[c] We also used another snoring question for a small minority of subjects (for 1% of men and 6% of women of final study population in the Study VI; for subjects who did not provide answer to this but provided answer to another snoring question); details in Appendix 5.

[d] Having "often" urinary urgency was used as a cut-off point because this degree of urgency was typically viewed as bothersome and was associated with clinically important deterioration in HRQL whereas having "rarely" was not (Tikkinen et al. 2008, Tikkinen et al. 2009).

Table 5. Classification of women by menopausal status in the FINNO Study, Finland, 2003-2004.

Characteristic	**Definition**
Premenopausal	Non-hysterectomised women without MHT who menstruated during the previous year and non-hysterectomised women under 40 years old
Postmenopausal	Non-hysterectomised women without MHT who did not menstruate during last year (and at least 40 years old)
Women with MHT[a]	Non-hysterectomised women with MHT (and at least 40 years old)
Hysterectomised	Women who reported prior hysterectomy

[a] Menopausal hormone therapy (MHT) included women who reported current use of vaginal or systemic MHT. The prevalence of nocturia was similar between women reporting using vaginal or systemic MHT (age-standardised 15.9% of vaginal and 15.5% of systemic MHT users, p=0.51). Hence, we combined these.

3.4 Statistical analysis

Subjects were stratified into six age groups: 18–29, 30–39, 40–49, 50–59, 60–69 and 70–79 years. Prevalence of nocturia and OAB were calculated for these age groups, and the groups were used for age standardisation. European standard population (Ahmad et al. 2001) was used in Studies I and IV, population structure of Finland (Population Register Centre 2004) in Studies III and V-VI, and both population structures (Ahmad et al. 2001, Population Register Centre 2004) in Study II. The age-adjusted mean 15D Score and dimension level values for the 15D dimensions were calculated by frequency of nocturia (Study V).

The effect of nocturia frequency (1, 2, 3, or ≥4 voids per night) on perceived bother was assessed using Fisher´s exact test for grouped data. To assess the effect of age on perceived bother, linear-by-linear association test was used separately for both sexes (Study III).

In Studies I and IV, unconditional logistic regression was used (for multivariate analysis) with nocturia as outcome. Similarly, logistic regression was used in Studies V-VI. Binomial regression with identity link and OAB as outcome was used for extrapolation of age-specific prevalence of OAB among people aged 80 years or more in Study II.

In Study IV, tests for trend were computed with logistic regression by including tritomous BMI as a continuous variable in the models. Departure from linearity was assessed by adding a continuous BMI term to a model already containing a categorical BMI variable and assessing the improvement in the fit of the model (likelihood ratio test).

In Study III, the effect of nocturia on HRQL (15D Score and dimension level values) was assessed using analysis of covariance with adjustment for age (by sex; sex was significantly associated ($p < 0.05$) with seven dimensions). Tests for trend were conducted by including nocturia in four categories (0, 1, 2 or ≥3 voids per night) as a linear term in the model.

In the analysis of association of major comorbidity (coronary artery disease (CAD), mood disorder, obstructive lung disease, OSA, osteoarthrosis) with HRQL and (bother from) nocturia, the subjects were classified into three groups with cut-off points defined as 15D Scores corresponding to the minimum clinically important difference (0.03 points) and twice the minimum clinically important difference (0.06 points) below the average of subjects without nocturia (separately for both sexes). By nocturia and bother, subjects were classified as free of nocturia, nocturia with not more than small (”no” or ”small”) bother and nocturia with at least moderate (”moderate” or ”major”) bother. Separately for each major comorbidity (used as outcomes), test for trend was obtained with logistic regression by including HRQL/nocturia in three categories as a linear term in the age-adjusted model. (Study III)

In Study VI, the final analysis included subjects providing information on nocturia, risk and confounding factors. For the risk factors identified, age-standardised sensitivity, positive predictive value, attributable fraction in the exposed, population attributable fraction and attributable number were calculated according to *A Dictionary of Epidemiology* (Last 2001) (Table 6). These indicators are commonly used to evaluate the validity of diagnostic tests, but here they were applied as indicators of the ability of the determinant to identify subjects with and without nocturia, in a sense similar to that of impact measures (attributable fraction and number). Attributable fraction in the exposed, population attributable fraction and attributable number were also calculated in Study IV.

Table 6. Definitions and formulae for sensitivity, positive predictive value, attributable fractions and attributable number (Last 2001).

Measure	**Definition**	**Formula**[a]
Sensitivity (Sn)	Proportion of persons with the condition (nocturia) who are correctly identified by a test (risk factor).	$Sn = Pr[T+|C+] / Pr[C+]$
Positive predictive value (PPV)	Proportion of persons with the positive test (risk factor) who have the condition (nocturia).	$PPV = Pr[C+|T+] / Pr[T+]$
Attributable fraction in the exposed (AF_e)	Proportion by which the prevalence of the condition (nocturia) among the exposed persons (with risk factor) would be reduced if the exposure (risk factor) were eliminated.	$AF_e = (P_e – P_u)/P_e$
Population attributable fraction (PAF)	Proportion by which the prevalence of the condition (nocturia) in the entire population would be reduced if the exposure (risk factor) were eliminated.	$PAF = (P_t – P_u)/P_t$
Attributable number (AN)	Number of prevalent cases of the condition (nocturia) attributable to the exposure (risk factor).	$AN = N_e \times (P_e – P_u)$

Abbreviations: C+, those with the condition (nocturia); N_e, number of persons in the exposed population (with risk factor); P_e, prevalence of the condition (nocturia) among the exposed (with risk factor); Pr, probability; P_t, prevalence of the condition (nocturia) in the total population; P_u, prevalence of the condition (nocturia) among the unexposed (without risk factor); T+, test positive (those with the risk factor).

[a] Regarding formulae of attributable fractions and attributable number, it is assumed that causes other than the one under investigation have similar effects on the exposed and unexposed groups. Sensitivity, positive predictive value, attributable fraction in the exposed and population attributable fraction were calculated as percentages, whereas attributable number was calculated as number of cases per 1,000 subjects.

3.5 Controlling for confounding

Using external clinical judgment for choosing the potential confounders was not justifiable due to inconsistencies in the literature. Thus, due to the exploratory nature of these analyses, we used stepwise backward elimination methods for model building (Sun et al. 1996). In Study VI, potential risk factors of nocturia included conditions, medications, specific symptoms and lifestyle factors, whereas age, socio-demographic and female reproductive and gynaecological factors were treated as potential confounders. Conversely, age, conditions, medications, specific symptoms, lifestyle and socio-demographic factors served as potential confounders for the female reproductive and gynaecological factors in Study V.

First, we calculated ORs for variables with adjustment for age (Studies IV-VI). Then multivariate analyses with all variables and confounders were performed. All reproductive factors and potential confounders associated ($p < 0.10$) with nocturia (or urgency/OAB) in the age-adjusted analysis were entered into multivariate model (Studies V-VI). Finally, backward elimination techniques were used to select variables for the final model of nocturia (and urgency), separately, with likelihood ratio tests used to determine significance. At least 10% change in the estimate due to the elimination of a potential confounder was deemed confounding.

In Study V, propensity scores (Nocturia Confounder Score (NCS) and Urgency Confounder Score (UCS)) were calculated on the basis of comorbidity and medication among women responding on both symptoms. For each comorbidity and medication factor (reported by at least ten women), we calculated age-adjusted odds ratios (with confidence intervals). All factors respectively associated with nocturia or urgency (Appendix 6) were used to construct the NCS and UCS formulae:

$$\text{Score} = \sum_{i=1}^{n} (\text{OR}_{\text{rf}} - 1)_{\text{n}} \qquad \text{AND} \quad \text{only if } p < 0.10 \text{ for } \text{OR}_{\text{rf}}$$

where OR_{rf} is the odds ratio for a risk factor. Nagelkerke R^2 was 15% for NCS, and 13% for UCS; $p < 0.001$ for both.

Finally, confounders emerging were NCS and age for nocturia, and UCS, age, smoking, and education for OAB in Study V; and age for men, menopausal status for women, and employment for both sexes in Study VI.

3.6 Effect modification

Effect modification (heterogeneity of effect) was assessed on the basis of the statistical significance of the interaction term (e.g. BMI × age) in a model containing the main effects (in the previous case: BMI, age) in Studies III-V.

3.7 Estimating bias due to selective participation

In Studies I and II, adjustment to correct for selection bias due to selective participation (drop-out related to nocturia/OAB) was applied using modified methods originally proposed by Drane (linear or exponential extrapolation of trends in prevalence) (Drane 1991, Drane et al. 1993).

In Study I, prevalence of nocturia by mailing round was calculated (by age and sex). As the prevalence decreased from the first to the second and third round responses, the mean decrease per round was calculated. The prevalence of nocturia among non-participants was assumed to be lower than among participants by a similar difference (Δp) as had been observed between the first rounds, using the formula: $p_{\text{non-respondents}} = p_{\text{participants}} + \Delta p$ (where p is prevalence of nocturia).

In Study II, adjustment was made separately for each symptom and combination of symptoms (urgency, OAB with or without UUI, frequency and nocturia) after possible exclusions. First, prevalence of symptoms was calculated by mailing round. As the prevalence of symptoms was lower in the subsequent than in the first round responses, the prevalence among non-participants (of the eligible study population) was assumed to be similar to that of the late responders, using the formula: $p_{\text{non-participants}} = (p_{\text{2nd round participants}} + p_{\text{3rd round participants}})/2$ where p is prevalence of symptom (urgency, OAB with or without UUI, frequency or nocturia). Hence, based on the number of non-participants and prevalence of symptoms, we calculated

the number of subjects with each symptom (and combinations). The corrected prevalence of symptom was calculated using the formula: $p_{corrected} = (N_{participants} \times p_{participants} + N_{non\text{-}participants} \times p_{non\text{-}participants)} / (N_{participants} + N_{non\text{-}participants})$ where p is the prevalence of symptom (or combination of symptoms) and N is the number of subjects. Concerning analyses for corrected prevalence of symptoms, we also performed an analysis excluding the same proportion of subjects among non-participants as we had done among participants, but the results did not materially change.

In Study III, age-standardised bother from nocturia and age-adjusted mean 15D Score and dimension level values were compared between mailing rounds. Similarly, in Study IV, the mean BMIs for all mailing rounds were calculated by sex and age group to estimate possible selection bias due to selective participation. The differences between rounds were small and nonsystematic in terms of bother/HRQL (Appendices 7-8) and BMI (mean BMIs by round among men: 26.10, 26.39, and 26.31; mean BMIs by round among women: 24.67, 25.37, and 25.36). Furthermore, no differences were found in prevalence of sociodemographic (Study I), reproductive and gynaecological (Study V) and identified risk factors (Study VI) (Appendices 9-11). However, four exceptions emerged (age-adjustedly) (Appendix 11). More nocturia and OAB was reported by first round responders than among responders in subsequent rounds in both sexes (p for trend = 0.01 for both nocturia and OAB; combined for both sexes). Moreover, men responding in the first round reported more antidepressant use than second and third round responders (p for trend = 0.04). Among women slightly less obesity was found among first round responders than in subsequent rounds (p for trend = 0.05). However, we found no trend in the magnitude of the estimates (ORs) of risk factors for nocturia by response round, suggesting an absence of systematic error (Appendix 11).

4. Results

4.1 Participation in the FINNO Study

Of the 6,000 subjects, 3,727 (62.4%) returned the questionnaire in the survey and 23 (0.4%) were ineligible (Figure 3). Of the respondents, 3,651 (98%) responded to all the nocturia questions. Of the participants, 51% (1,891 subjects) responded at the first, 28% (1,036 subjects) at the second and 15 % (562 subjects) at the third round. In addition, 240 respondents (6%) did not give the date of questionnaire completion, and therefore the mailing round could not be defined. The mean age of the respondents was 44.0 years (SD 16.5) and median 42 years for men, and 42.5 years (SD 16.0) and median 40 years for women. Based on socio-demographics, the most typical FINNO Study participant was married or living together, from a small community, and employed; education background varied very widely among participants (Table 7).

Figure 3. Flow chart of the FINNO Study, Finland, 2003-2004.
These exclusions (below) were used in all studies except the first two.

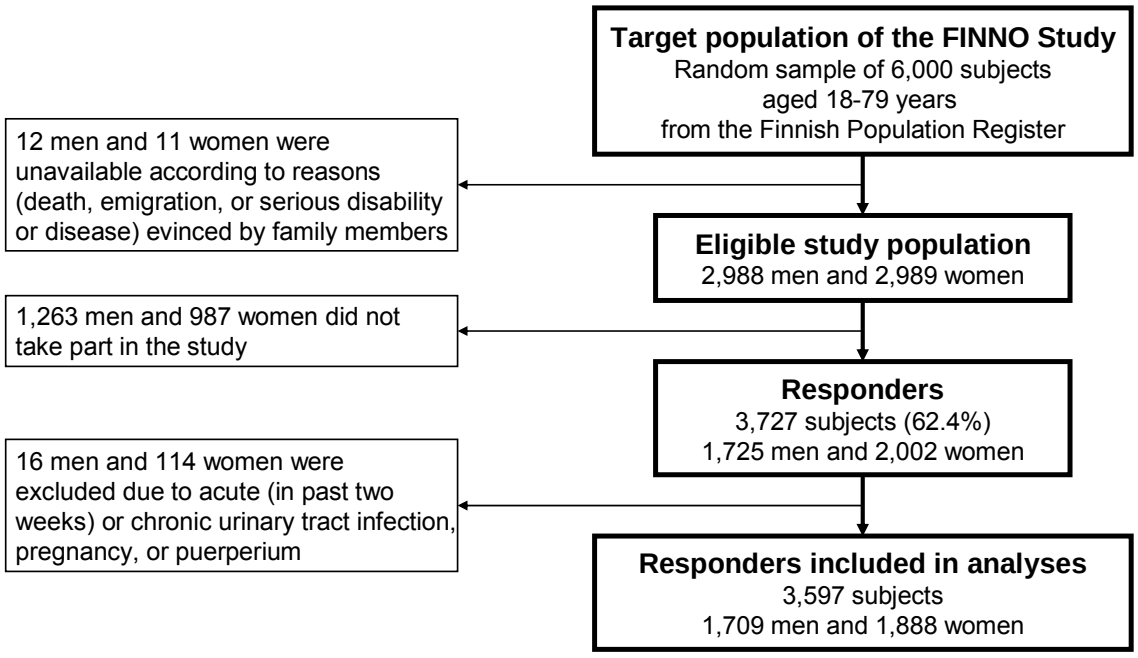


Table 7. Number of subjects by sex and socio-demographic characteristics in the FINNO Study, Finland, 2003-2004.

Characteristics	Men		Women	
	n	%	n	%
Marital status				
Married/living together	1227	71.1	1345	67.2
Widowed	24	1.4	112	5.6
Divorced/separated	80	4.6	150	7.5
Never married	383	22.2	381	19.0
No response	11	0.6	14	0.7
Education				
Basic level	477	27.7	489	24.4
Vocational school	583	33.8	608	30.4
College	326	18.9	480	24.0
University	330	19.1	400	20.0
No response	9	0.5	25	1.2
Employment				
Student	173	10.0	270	13.5
Employed	1018	59.0	1170	58.4
Unemployed	110	6.4	143	7.1
Retired	399	23.1	393	19.6
No response	25	1.4	26	1.3
Urbanity				
Small community	1060	61.4	1186	59.2
Large community	654	37.9	806	40.3
Unknown	11	0.6	10	0.5

4.2 Prevalence of nocturia

Nocturia (defined as at least one void per night) was more common among young women than among young men. The prevalence among men started to approach that in women in the age group 40-49 years and reached it at ages 50-59 years, when half of both men and women reported nocturia. In older age groups, nocturia was more common among men, though the prevalence was very high in both sexes. (Figure 4A)

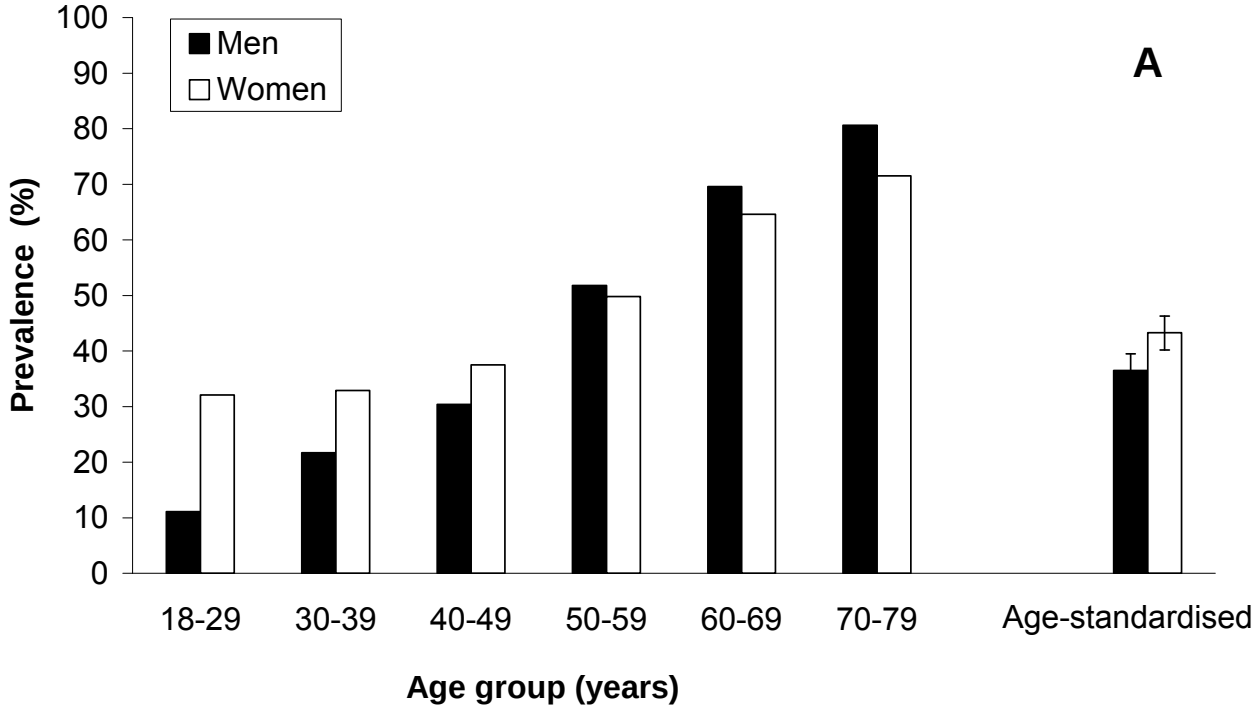
When nocturia was defined as at at least two voids per night (Figure 4B), it increased strongly with age in both genders. Young women (18-29 years) reported over ten times more nocturia than young men. Men reached women in their fifties to sixties. At the age of 50-59 years, approximately 12% of men and 16% of women voided at least twice per night. In older age groups men had more nocturia than women. Among those aged 60-69, approximately two out of five men and every fourth women voided at least two times per night. At ages 70-79 years, approximately 45 % of men and 37 % of women voided at least twice per night. (Figure 4B)

Using European standard population, the age-standardised prevalence of nocturia (≥1 void/night) was 37% (95% confidence interval, CI 34%-40%) for men and 43% (95% CI 40%-46%) for women (Figure 4A). With the criterion (≥2 voids/night) prevalence was 12% (95% CI 10%-14%) for men and 13% (95% CI 11%-14%) for women (Figure 4B). Prevalence of nocturia by number of episodes is shown in Figure 5.

The prevalence of nocturia increased at a constant rate with age. Mean increases in ORs were 7.3% (6.5%-8.2%) per year for men and 3.5% (2.9%-4.1%) per year for women. Thus the increase in OR was over two times higher in men than in women. There was no statistically significant departure from linearity in either sex ($p < 0.001$). The trend was also similar defined as at least two voids per night. (Table 8)

Figure 4. Prevalence of A) at least 1 void per night, and B) at least 2 voids per night in the FINNO Study, Finland, 2003-2004.

Age-standardisation was performed using European standard population (Ahmad et al. 2001).



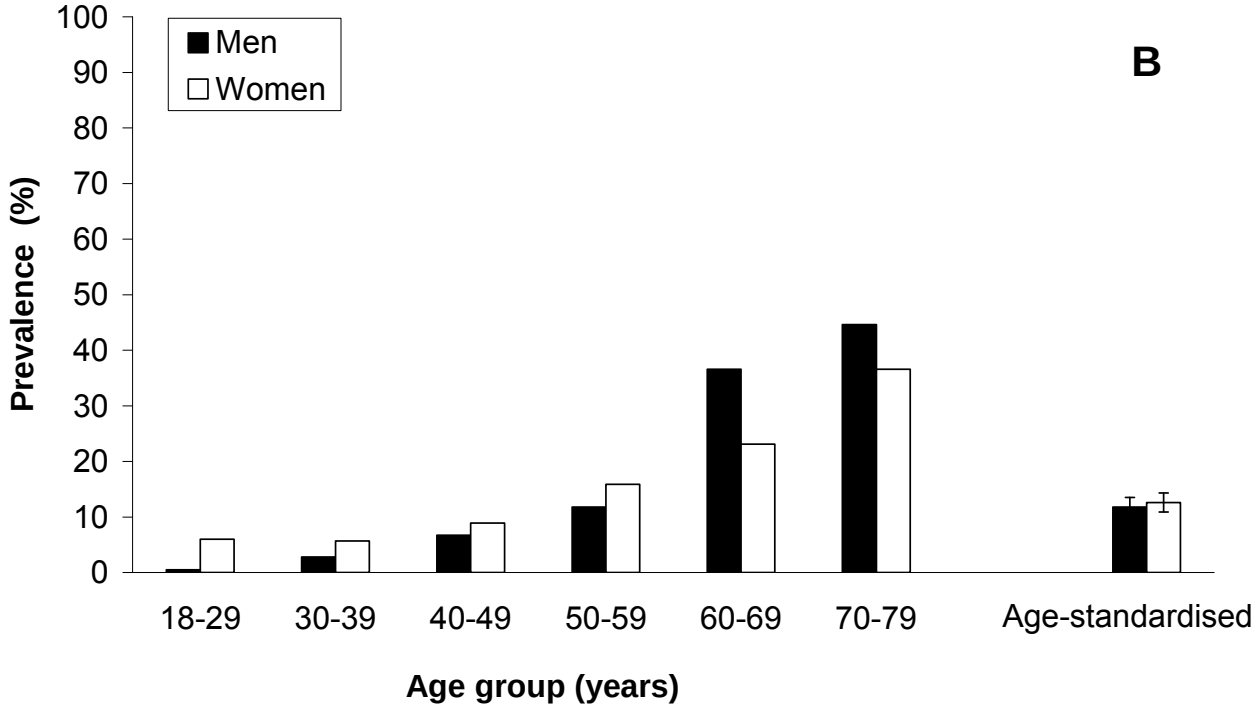
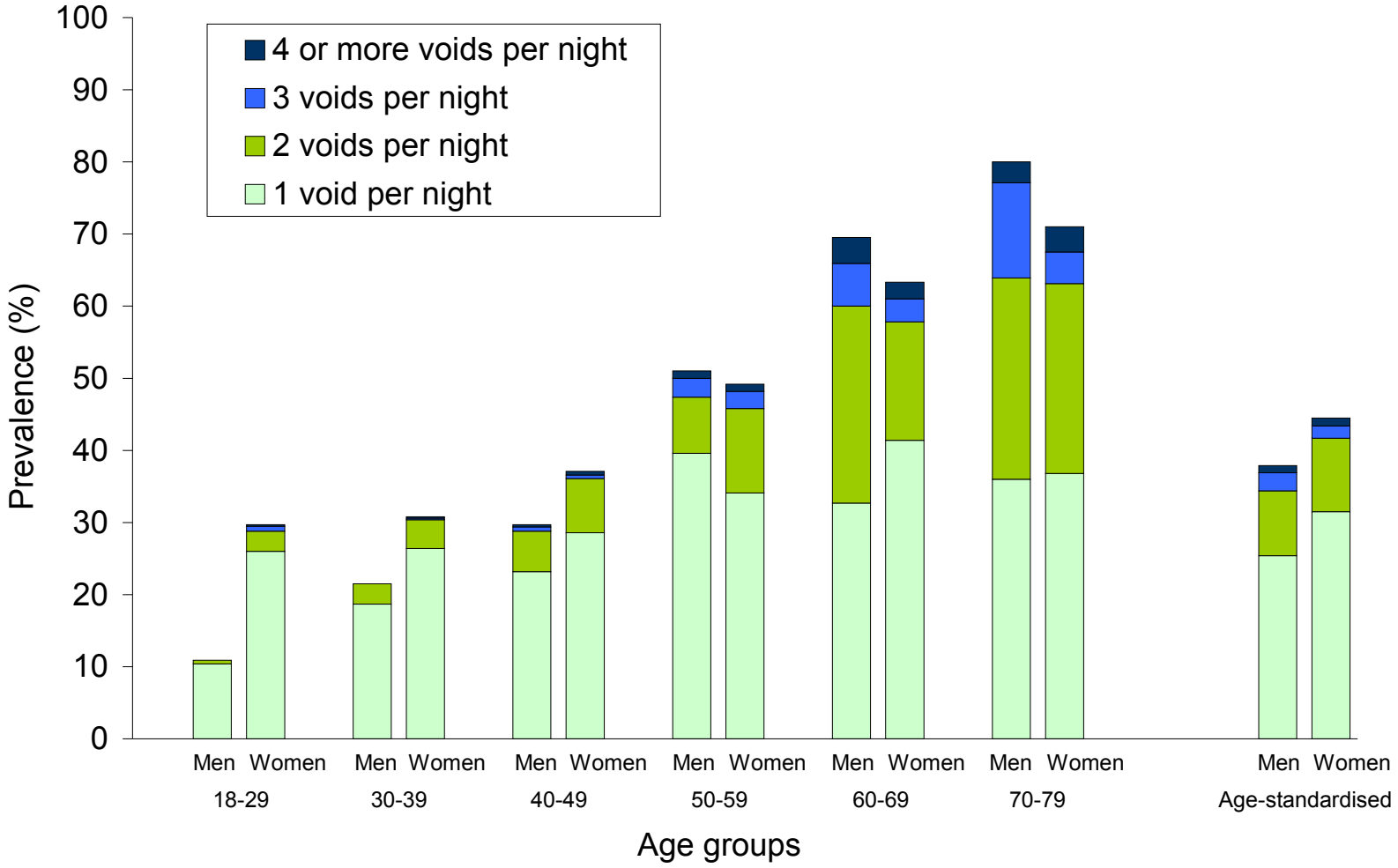


Table 8. Odds ratios of nocturia defined as at least 1 void/night or at least 2 voids/night by age groups (years) and per year of age for both sexes in the FINNO Study, Finland, 2003-2004.

Age groups	At least one void per night			At least two voids per night		
	OR	**95 % CI**	***p***	**OR**	**95 % CI**	***p***
Men						
18 – 29	1.0	(reference)		1.0	(reference)	
30 – 39	2.2	1.5 - 3.3		5.6	1.2 - 25.2	
40 – 49	3.5	2.3 - 5.2		13.9	3.2 - 59.6	
50 – 59	8.6	5.6 - 13.1		25.7	6.0 - 110.1	
60 – 69	18.3	11.9 - 28.0		110.9	26.9 - 456.8	
70 – 79	33.1	19.5 - 56.0		154.6	37.0 - 645.5	
Age (per year)	1.073	1.065 - 1.082	< 0.001	1.096	1.082 - 1.109	< 0.001
Women						
18 – 29	1.0	(reference)		1.0	(reference)	
30 – 39	1.0	0.8 - 1.3		1.0	0.6 - 1.6	
40 – 49	1.3	0.9 - 1.7		1.5	0.9 - 2.6	
50 – 59	2.1	1.5 - 2.9		3.0	1.8 - 5.1	
60 – 69	3.9	2.8 - 5.4		4.8	2.9 - 7.7	
70 – 79	5.3	3.4 - 8.2		9.1	5.4 - 15.3	
Age (per year)	1.035	1.029 - 1.041	< 0.001	1.051	1.041 - 1.060	< 0.001

After non-respondent analysis the corrected nocturia prevalences of men (at least one void per night) were from the youngest age groups to the oldest: 6.8-16.6-23.5-44.6-67.3-76.0%. The corresponding figures among women were: 27.4-30.2-30.7-40.8-57.2-71.7%. Corrected age-standardised prevalence of nocturia was 31.3% for men and 37.8% for women.

Figure 5. Prevalence (%) of nocturia episodes by age group and gender in the FINNO Study, Finland, 2003-2004.
Pregnant and puerperal women and those subjects reporting urinary tract infection were excluded. Age-standardisation was performed using the age structure of Finland (Population Register Centre 2004).



4.3 Bother, health-related quality of life and nocturia

Of the 3,597 subjects included (Figure 3), 97% answered both the frequency of nocturia and degree of bother questions, and completed 15D. (Of the final analysis population, 94% answered all 15 questions of 15D, 5% answered 14, and 1% 13 questions.)

Overall, there was no gender difference in prevalence of bothersome nocturia or degree of bother among those with bothersome nocturia. (Figure 6). The degree of bother increased with frequency of nocturia in both sexes ($p < 0.01$ for each age group) (Figure 6). Moreover, comparing two adjacent categories at a time, the increase was statistically significant with each increment in number of nightly voids.

Slightly over half of respondents with 1 void/night reported no bother, and a similar proportion of subjects with 2 voids/night reported “small” bother. Of those with 3 voids/night and ≥4 voids/night slightly more than 40% reported ”moderate” bother, with 14% and 36% reporting ”major” bother respectively (Figure 6). Age did not affect perceived bother among men but among women, bother from nocturia decreased with increasing age ($p < 0.001$, $p < 0.01$, $p = 0.02$, and $p = 0.08$ for women with 1, 2, 3, or ≥4 void(s)/night respectively) (Figure 7). Interaction was found between age and sex for any bother among subjects with 1 void/night ($p < 0.01$) and for at least moderate bother among subjects with 2 voids/night ($p = 0.02$), indicating effect modification (different effect of age on bother by gender).

Figure 6. Age-standardised prevalence of bother by frequency of nocturia among men and women in the FINNO Study, Finland, 2003-2004. Error bars represent 95% confidence intervals. The age structure of Finland was used for age-standardisation (Population Register Centre 2004).

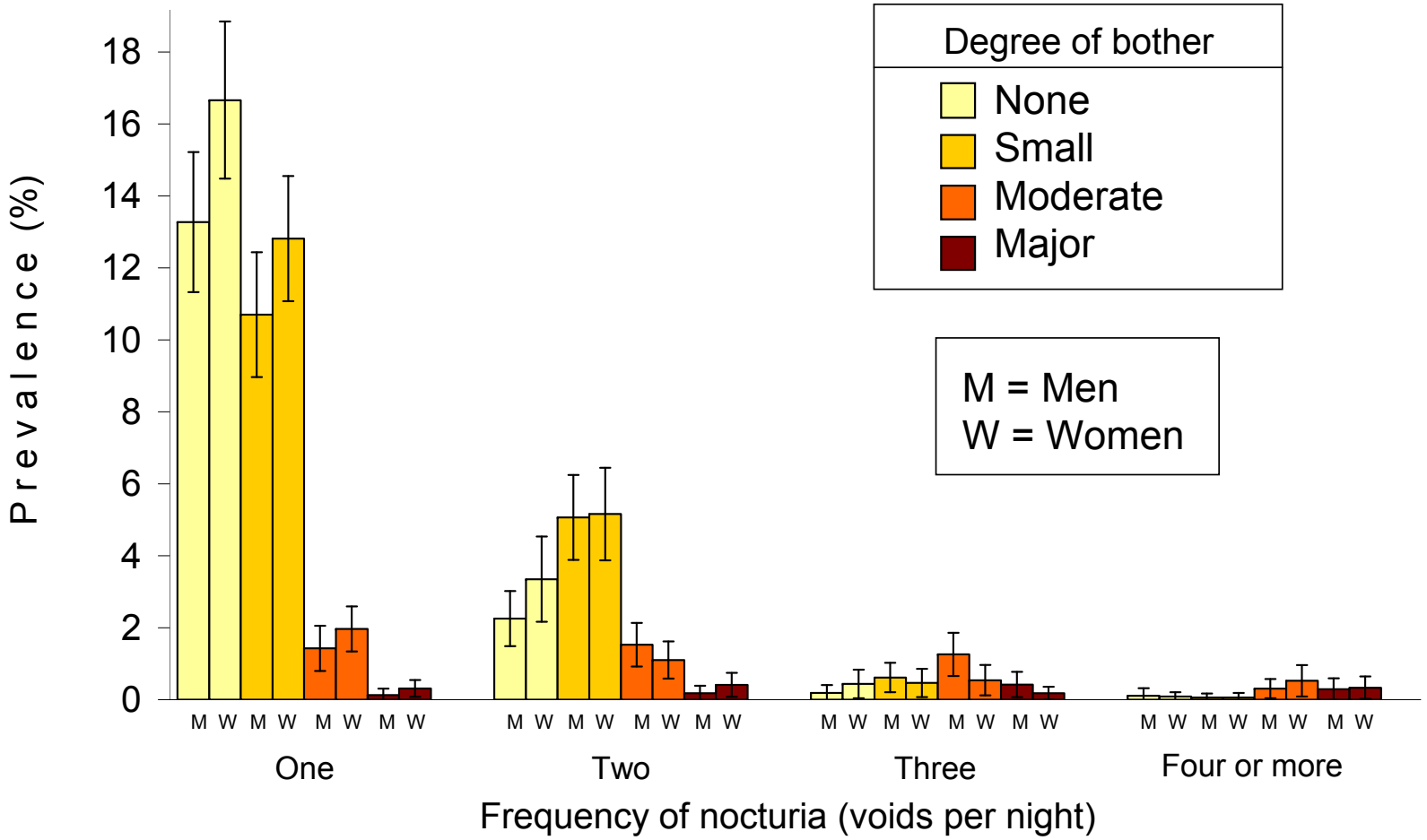
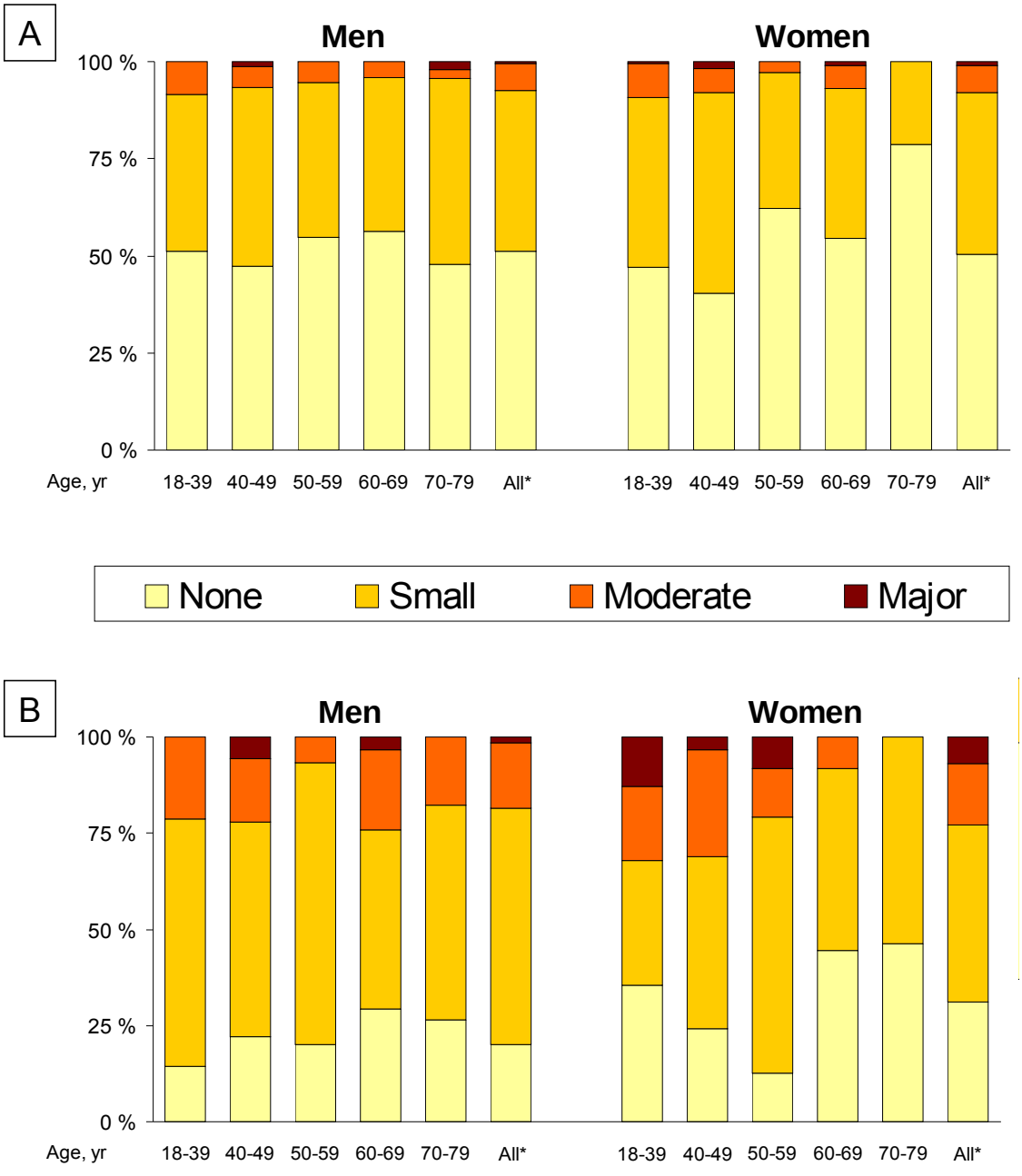


Figure 7. Degree of bother from nocturia by age group among men and women with 1 void per night (A); and with 2 voids per night (B) in the FINNO Study, Finland, 2003-2004.

"All" refers to the age-standardised proportions. Age-standardisation was performed using the age structure of Finland (Population Register Centre 2004).



The 15D Score did not differ between the sexes ($p = 0.79$). Furthermore, no difference was found in impact of nocturia on HRQL between sexes ($p = 0.38$ for interaction term). (Figure 8) In both sexes, nocturia was associated with statistically significant ($p < 0.05$) decrease on all dimensions of HRQL except eating (Figure 9).

Figure 8. The age-adjusted means for 15D Score by nocturia in both sexes in the FINNO Study, Finland, 2003-2004.
Error bars represent 95% confidence intervals. Age-standardisation was performed using the age structure of Finland (Population Register Centre 2004).

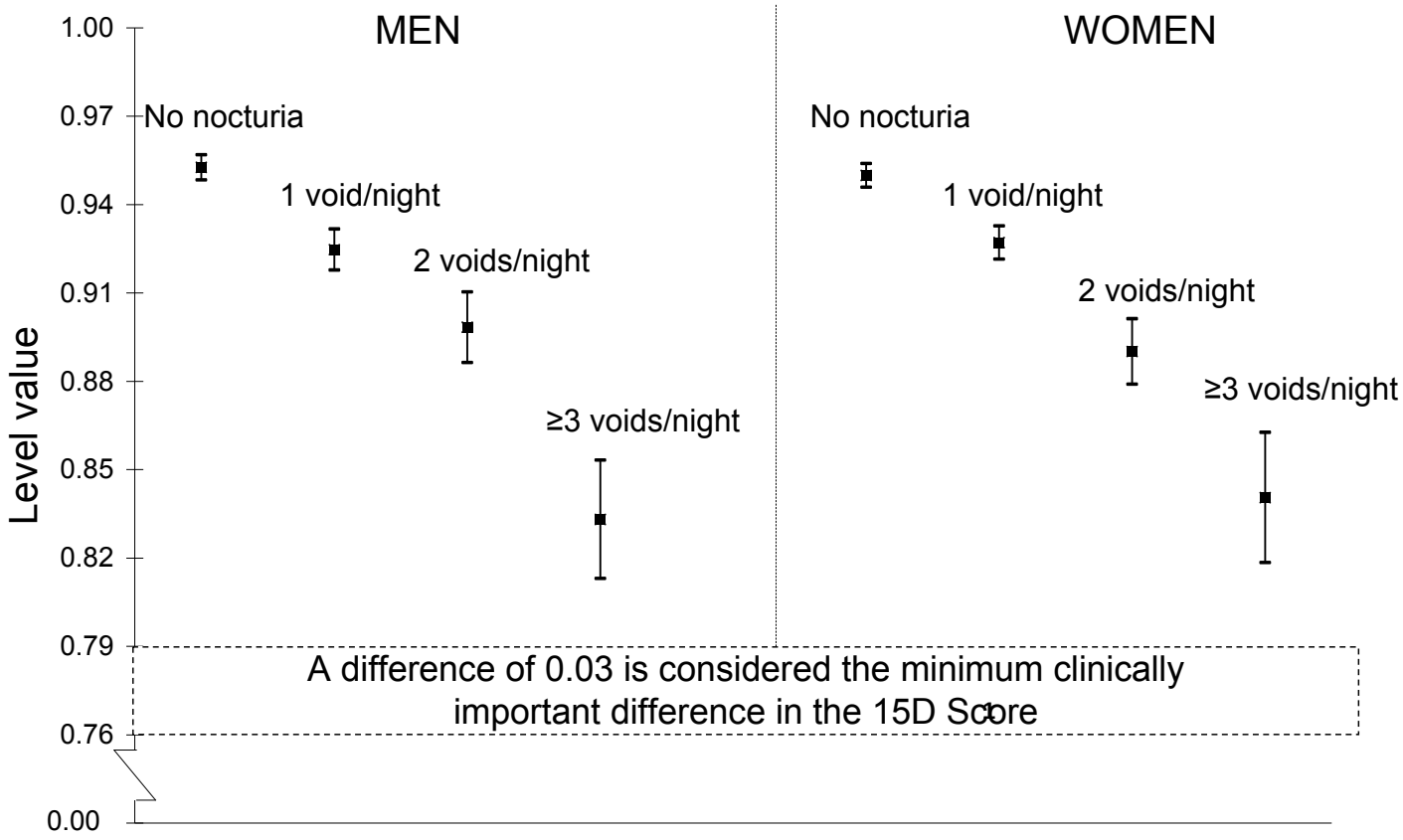
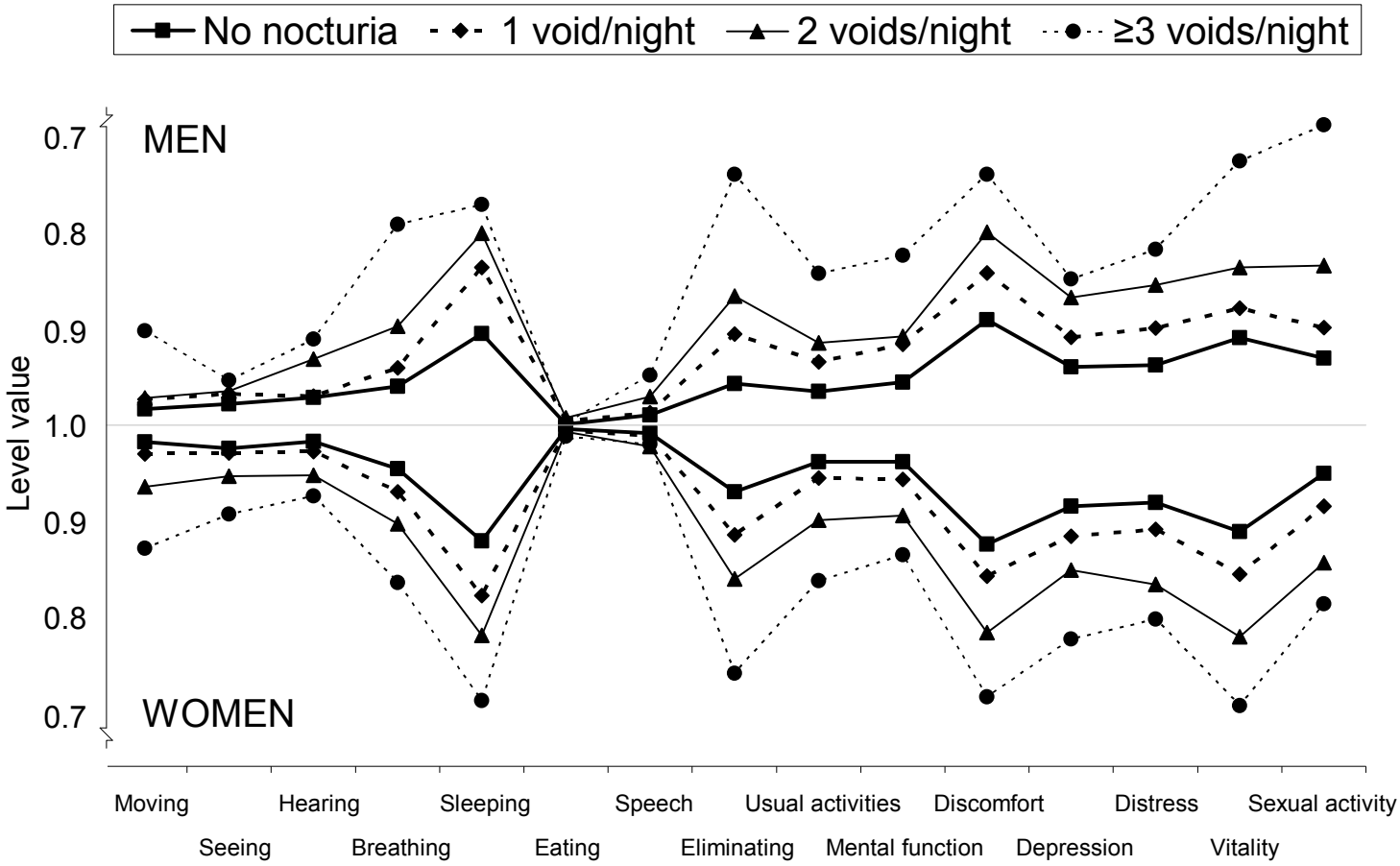


Figure 9. Age-adjusted means for dimension level values of 15D by frequency of nocturia in both sexes in the FINNO Study, Finland, 2003-2004.



Major comorbidities assessed were more common among those with impaired HRQL (p for trend < 0.001 for each comorbidity) (Appendix 12). Parallel results were also observed for most of the major comorbidities assessed by increasing nocturia ($p < 0.05$ for all except obstructive lung disease and osteoarthrosis in men). Furthermore, calculating the age-adjusted 15D dimension level values and 15D Score for both sexes without imputation for missing values yielded similar results (for instance, 15D Scores were 0.953, 0.928, 0.899, 0.835 for men and 0.952, 0.929, 0.895, 0.863 for women with 0, 1, 2, ≥3 void(s)/night respectively).

4.4 Prevalence of overactive bladder and its relation with nocturia

For the assessment of OAB prevalence (Overactive bladder analysis), we excluded 210 participants out of 3,727 FINNO Study respondents (Figure 3). Of the 3,517 subjects included (Figure 3), 99% (n = 3,467) provided information on urgency, and were included in the ´Overactive bladder analysis´ (Appendix 1). More detailed information regarding participation and exclusions in Appendices 13-15.

The age-standardised prevalence of OAB was 6.5% for men and 9.3% for women (Figure 11). Exclusion of men with BPH decreased the prevalence of OAB among men to 5.6%. The effect of BPH on the prevalence of OAB was strongest in elderly respondents with the prevalence decreasing from 17.5% to 13.5% at age 60-69 years and from 17.6% to 14.0% at age 70-79 years after further exclusion of men with BPH. Age-standardised prevalence of urgency (calculated without any exclusion) was 7.0% for men and 10.3% for women.

Without corrections for non-response, urgency was reported by 7.9% (95% CI, 6.5% to 9.3%) of men and 10.7% (95% CI, 9.0% to 12.3%) of women after age-standardisation. The corresponding figures for OAB were 7.3% (95% CI, 5.9% to 8.7%) for men and 9.7% (95% CI, 8.0% to 11.3%) for women. Further exclusion of men with BPH decreased the non-corrected prevalence of OAB to 6.3% (95% CI, 4.8% to 7.7%) among men aged 18-79 years.

In the ´All OAB symptoms analysis´ (Figure 12 and Appendix 1), UUI was reported by 11% of men and 27% of women among those with OAB. Increased daytime frequency (defined as more than eight voids per day) was reported by 23% of men and 38% of women with OAB whereas the corresponding figures for nocturia (defined as at least two voids per night) were 56% and 40%. On the other hand, even though subjects with OAB reported more frequency and nocturia than subjects without OAB, only 31% of men and 35% of women with frequency, and 31% of subjects among both sexes with nocturia reported OAB (Figure 12).

Figure 11. Prevalence of OAB in the FINNO Study, Finland, 2003-2004.

Age-standardisation was performed using the age structure of Finland (Population Register Centre 2004).

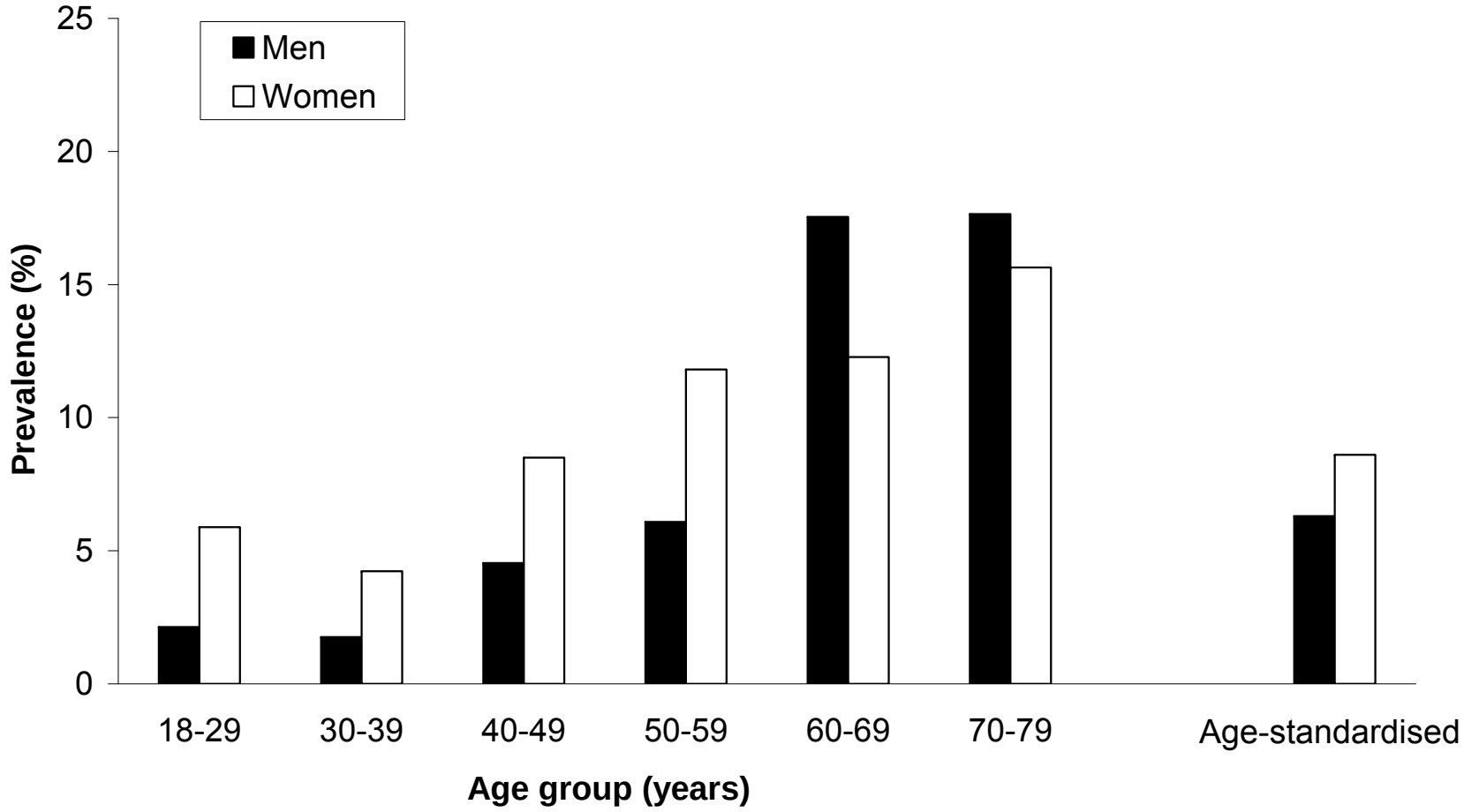
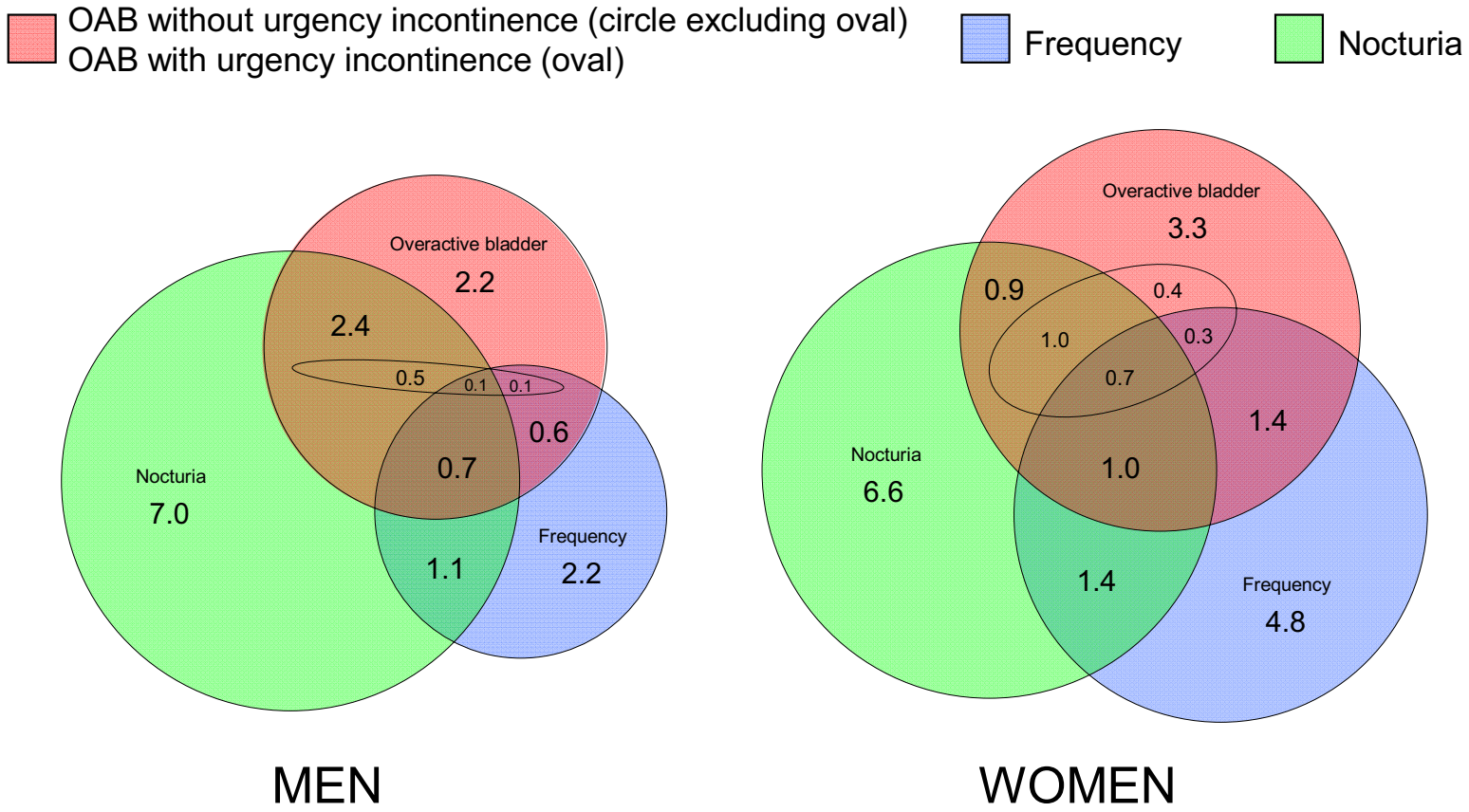


Figure 12. Age-standardised prevalence (%) of OAB symptoms in the FINNO Study, Finland, 2003-2004.

The topmost circle represents subjects with OAB without UUI excluding the area of the oval representing subjects with OAB with UUI. The rightmost circle represents subjects with increased daytime frequency (defined as more than eight voids/day) and the leftmost circle nocturia (defined as at least two voids/night). Age-standardisation was performed using the age structure of Finland (Population Register Centre 2004).



4.5 Risk factors of nocturia

4.5.1 Conditions, medications, lifestyle and nocturia

Of the 3,597 subjects included, 98% provided information on nocturia (basic analysis population for age-adjusted analyses) (Figure 3). Finally, 3,307 subjects (92%) responded to every question on nocturia, risk and confounding factors (final analysis population for the final model of the multivariate analysis). In the final analysis population, age-standardised prevalence of nocturia was 12.5% for men and 12.9% for women. Excluding subjects with missing information on any risk or confounding factors (final analysis population) did not change these estimates (true also for other analyses, such as that of Study V). For details of (potential) risk factors see Table 11, and Appendices 3-5.

In the multivariate analysis, factors significantly associated with nocturia included: OAB/urinary urgency, snoring, restless legs syndrome (RLS) and obesity for both sexes; BPH, antidepressant use, and prostate cancer for men; and overweight, diabetes and CAD for women. (Table 9)

At population level (Table 10), OAB and snoring for both sexes, BPH for men and overweight/obesity for women accounted for the largest proportion of nocturia. At individual level, the strongest risk factor was OAB for both sexes. However, differences between risk factors were mainly statistically nonsignificant (Table 10).

None of the risk factors was reported by ≥50% of men with nocturia (Figure 13): BPH, OAB and snoring had the highest sensitivity for nocturia (31%-49%). Of the women with nocturia, 71% were overweight or obese (Figure 14). Snoring and OAB were reported by one third of symptomatic women, other factors more rarely. In both sexes, ≥1 risk factor was reported by 82.8% of those with nocturia, and by 42.4% of men and 47.9% of women without nocturia.

Table 9. Prevalences (%) and odds ratios of risk factors for nocturia in multivariate analyses[a] in the FINNO Study, Finland, 2003-2004.

	Age-standardised prevalence[b]	95% confidence interval	Odds ratio	95% confidence interval
Men				
Overactive bladder	7.5	6.1, 9.0	7.39	4.46, 12.23
Prostate cancer	1.2	0.7, 1.8	5.45	1.74, 17.08
Antidepressant use	2.5	1.7, 3.3	3.16	1.29, 7.73
Restless legs syndrome	3.0	2.1, 4.0	2.91	1.30, 6.52
Benign prostatic hyperplasia	7.8	6.3, 9.3	2.18	1.31, 3.65
Obesity[c]	13.2	11.2, 15.1	2.07	1.17, 3.67
Snoring	35.1	31.9, 38.2	1.49	1.00, 2.22
Women				
Overactive bladder	9.9	8.2, 11.6	4.92	3.15, 7.67
Coronary artery disease	4.5	3.1, 5.8	3.13	1.48, 6.64
Restless legs syndrome	3.6	2.5, 4.8	2.86	1.41, 5.83
Diabetes	4.7	3.4, 5.9	2.68	1.38, 5.20
Obesity[c]	13.3	11.4, 15.3	2.18	1.30, 3.66
Overweight[c]	32.3	29.2, 35.4	1.90	1.25, 2.88
Snoring	18.4	16.1, 20.7	1.76	1.17, 2.64

[a] Adjusted also for identified confounders (age and employment for men; employment and menopausal status for women).

[b] Age-standardisation was performed using the age structure of Finland (Population Register Centre 2004).

[c] Non-overweight (body mass index < 25 kg/m^2) subjects as a reference.

Table 10. Fraction of nocturia attributable to identified risk factors in the FINNO Study, Finland, 2003-2004.[a]

	Attributable fraction in the exposed (%)	Population attributable fraction (%)	Attributable number (per 1,000 subjects)
Men			
Overactive bladder	77.2	24.0	24
Benign prostatic hyperplasia	69.1	13.1	19
Snoring	30.3	14.4	16
Obesity	29.1	5.9	6
Antidepressant use	65.6	4.3	6
Restless legs syndrome	53.1	4.7	4
Prostate cancer	65.8	3.9	3
Women			
Overweight/Obesity[b]	51.5	35.4	40
Overactive bladder	71.0	21.3	24
Snoring	46.8	16.4	17
Diabetes	63.3	8.6	9
Restless legs syndrome	63.4	7.4	7
Coronary artery disease	44.9	7.4	4

[a] Age-standardisation was performed using the age structure of Finland (Population Register Centre 2004).

[b] Body mass index (BMI) was classified as a dichotomous variable when calculating attributable fractions due to the dichotomous nature of these measures. Hence, the reference groups were non-obese (BMI <30 kg/m^2) for men and normal weight (BMI <25 kg/m^2) for women because overweight (BMI 25-30) was associated with nocturia only in women.

The majority of men with prostate cancer or OAB reported nocturia yielding positive predictive values of 74% and 59% respectively, while half of the men with BPH (49%) reported nocturia (Figure 13) and a minority of men with other risk factors had nocturia. Among women, no risk factors were associated with ≥50% probability of nocturia (Figure 14).

Figure 13. Sensitivity and positive predictive value for risk factors of nocturia (risk factor with the greatest impact at population level first) among men in the FINNO Study, Finland, 2003-2004.
Age-standardisation was performed using the age structure of Finland (Population Register Centre 2004).

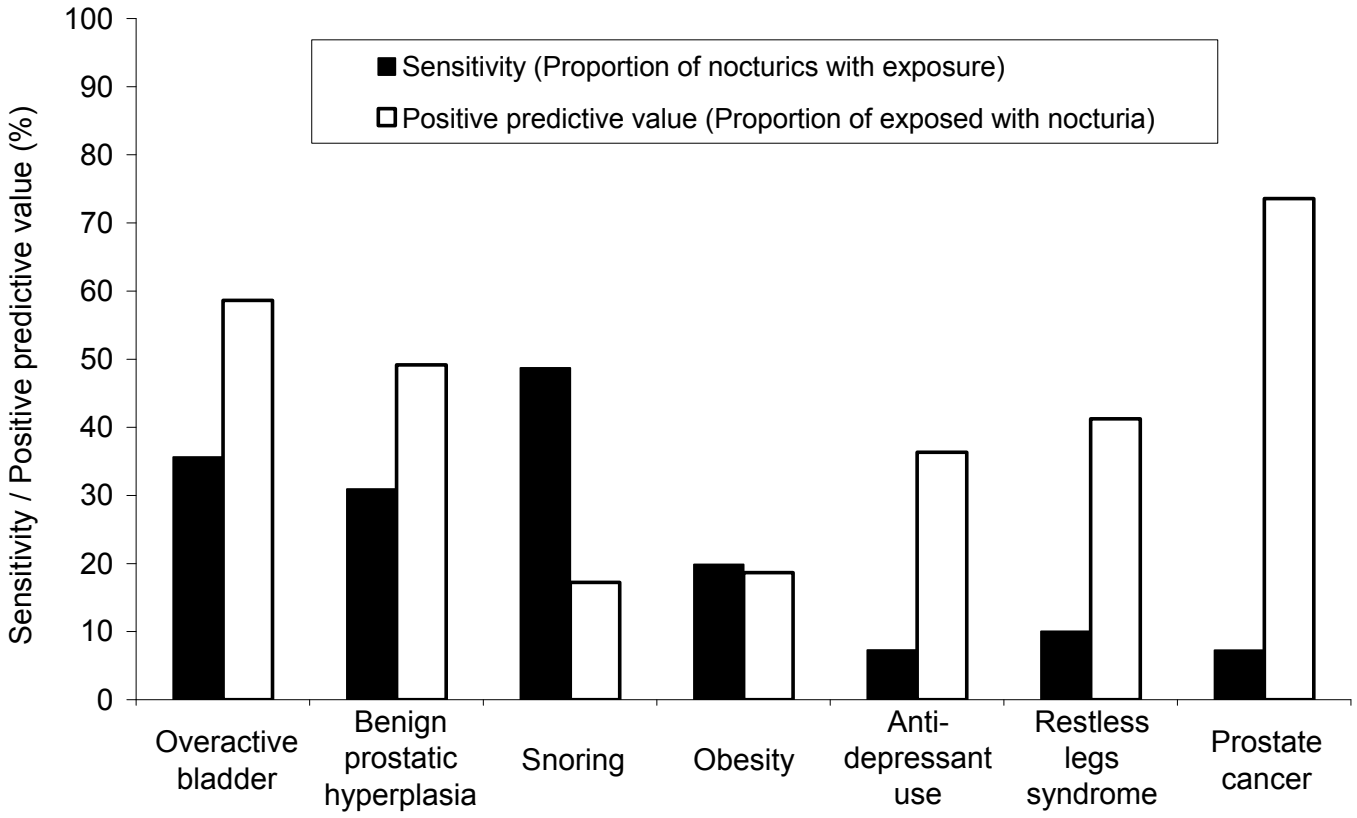
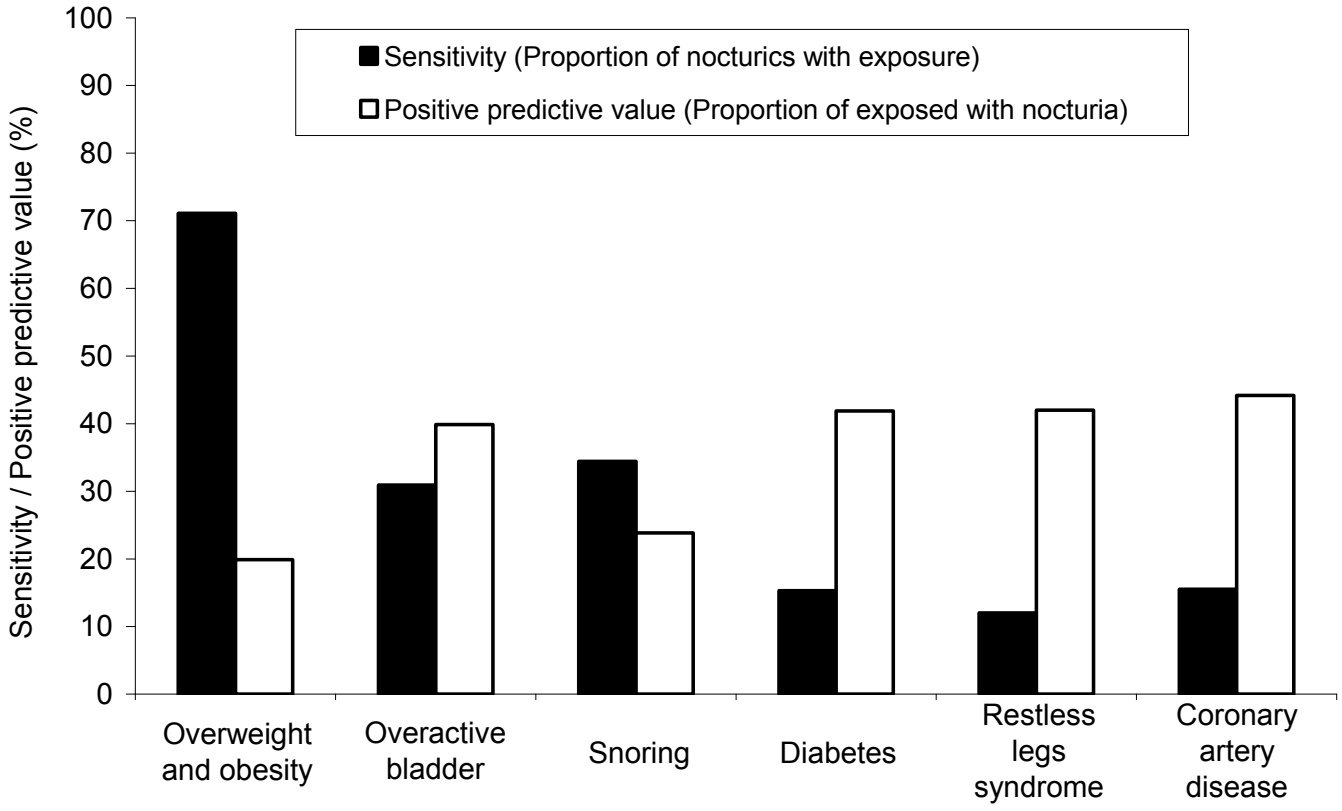


Figure 14. Sensitivity and positive predictive value for risk factors of nocturia (risk factor with the greatest impact at population level first) among women in the FINNO Study, Finland, 2003-2004.

Age-standardisation was performed using the age structure of Finland (Population Register Centre 2004).



4.5.2 Reproductive factors and nocturia

Of the 1,888 women included (Figure 3), 97% answered the nocturia and urgency/OAB questions. Finally, 1,728 women (92%) responded to every question on nocturia, urgency, reproductive and confounding factors (final analysis population). For details of reproductive and gynaecological factors see Table 11.

Table 11. Reproductive factors among 1,728 women in the FINNO Study, Finland, 2003-2004.

Characteristic	N (%)	Age-standardised prevalence (%)[a]	95% confidence interval
Parity			
0	623 (36)	30.6	28.1-33.2
1	248 (14)	15.5	13.4-17.6
2	493 (29)	30.9	27.9-33.9
≥3	364 (21)	23.0	20.4-25.6
Postpartum period[b]	53 (3)	2.2	1.6-2.8
Menopausal status			
Premenopausal	1159 (67)	52.9	49.8-56.0
Postmenopausal	276 (16)	23.8	20.9-26.8
Women with MHT	123 (7)	9.8	8.0-11.6
Hysterectomised	170 (10)	13.4	11.3-15.6
Surgery for stress urinary incontinence	33 (2)	2.5	1.6-3.4

[a] Age-standardisation was performed using the age structure of Finland (Population Register Centre 2004).

[b] Postpartum was defined as at least six weeks but not more than one year after delivery.

In the multivariate analysis (MODEL 3), parity and postpartum period were associated with nocturia (defined as at least two voids per night) (Table 12). Furthermore, postmenopausal women reported more nocturia than premenopausal but not more than hysterectomised women (OR 0.80; 95% CI 0.48-1.33); postmenopausal as reference)

or women on MHT (OR 0.78; 95% CI 0.44-1.40); postmenopausal as reference). However, there was no significant difference in nocturia between premenopausal, MHT, or hysterectomised women (Table 12). Furthermore, no difference between primi- and multiparous women was found in prevalence of nocturia (p = 0.91) or urgency/OAB (p = 0.65). Surgery for SUI was the only factor associated with urgency/OAB (age-adjusted OR 3.08; 95% CI 1.38-6.85; and in the multivariate analyses, OR 2.53; 1.04-6.13).

There was no statistically significant interaction between parity and age indicating lack of effect modification (nocturia p = 0.72, urgency/OAB p = 0.27). Effect modification analyses were unfeasible for other reproductive factors, given the small number of women in some strata. Finally, no difference was found in parity between participants and non-participants (70.5% (95% CI 64.1-77.0) of non-participants were parous).

Table 12. Odds ratios for nocturia by reproductive factors with and without adjustment for confounders and other reproductive factors among 1,728 women in the FINNO Study, Finland, 2003-2004.

Reproductive and gynaecological factors	**MODEL 1** (adjusted for age)			**MODEL 2** (adjusted for all confounders)			**MODEL 3** (adjusted for all confounders and mutually for other reproductive factors)		
	OR	**95% CI**	***p***	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***
Parity (continuous)	1.15	1.03-1.29	0.016	1.14	1.01-1.29	0.031	1.13	1.00-1.28	0.047
Postpartum period[a]	2.97	1.21-7.31	0.018	3.31	1.34-8.19	0.009	2.83	1.12-7.20	0.028
Menopausal status[b]									
Premenopausal	1.00			1.00			1.00		
Postmenopausal	2.49	1.33-4.67	0.004	2.18	1.14-4.18	0.018	2.31	1.20-4.42	0.012
Women with MHT	2.06	1.06-4.00	0.034	1.69	0.85-3.37	0.137	1.80	0.90-3.60	0.096
Hysterectomised	2.17	1.14-4.13	0.018	1.69	0.86-3.29	0.125	1.84	0.94-3.61	0.075
Surgery for SUI	1.29	0.54-3.12	0.568	1.02	0.40-2.60	0.963	0.93	0.36-2.45	0.889

[a] Postpartum period was defined as more than 6 weeks but not more than one year after giving birth.

[b] No other significant associations were found when other options (postmenopausal, women with MHT, or hysterectomised) were used as a reference (in any of the models (MODEL 1, 2 or 3)).

[c] MHT, menopausal hormone therapy; SUI, stress urinary incontinence.

4.5.3 Relation of nocturia to obesity

BMI was a risk factor for nocturia (Table 9 and Figures 13-14). Increasing BMI predicted nocturia overall for both men and women ($p < 0.001$ for both). There was no statistically significant interaction between BMI and age (with nocturia defined as ≥1 void per night, $p = 0.86$ for men and $p = 0.13$ for women; with nocturia defined as ≥2 voids per night, $p = 0.66$ and $p = 0.62$ respectively). Thus, there was no effect modification. There was no statistically significant departure from linearity in either sex.

Figure 13. Prevalence of nocturia (defined as ≥2 voids/night) among men in the FINNO Study, Finland, 2003-2004.
The white bars indicate non-overweight (BMI <25), the bars with diagonal lines overweight (BMI 25-29.9); and the black bars indicate obese (BMI ≥30) subjects.

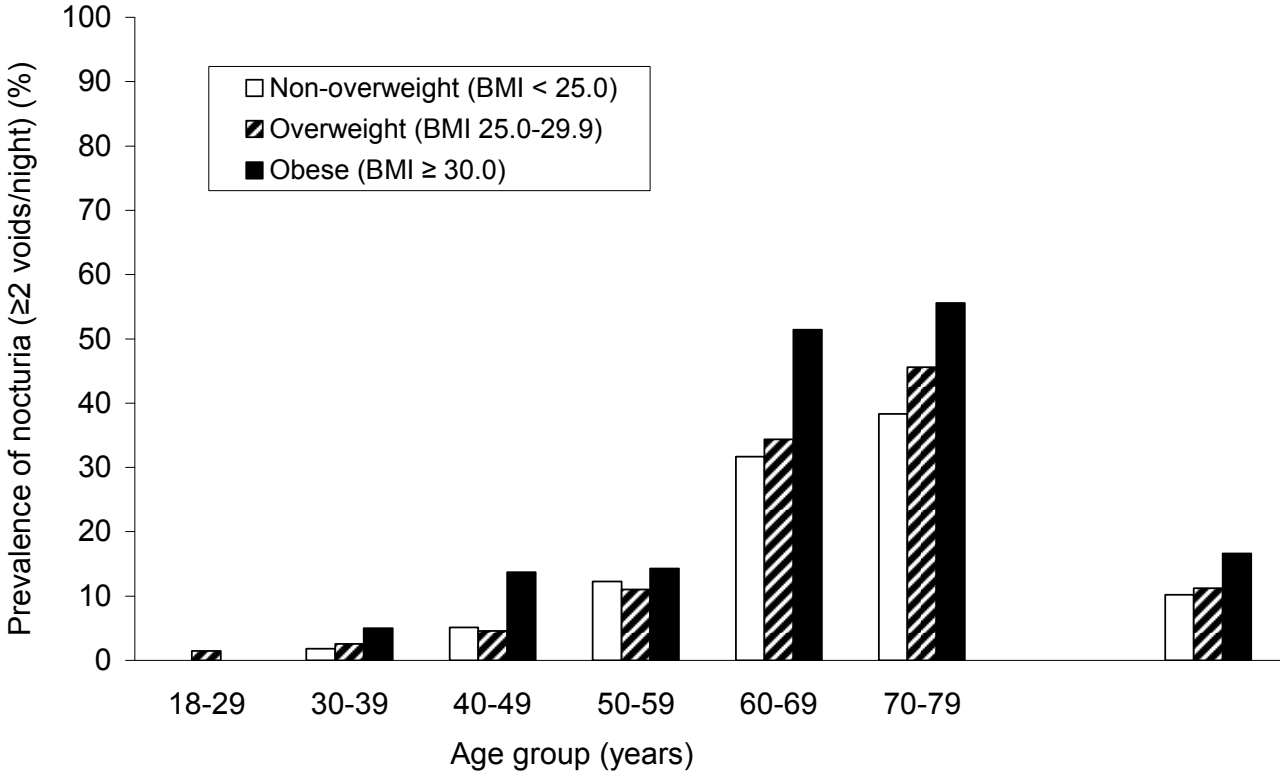
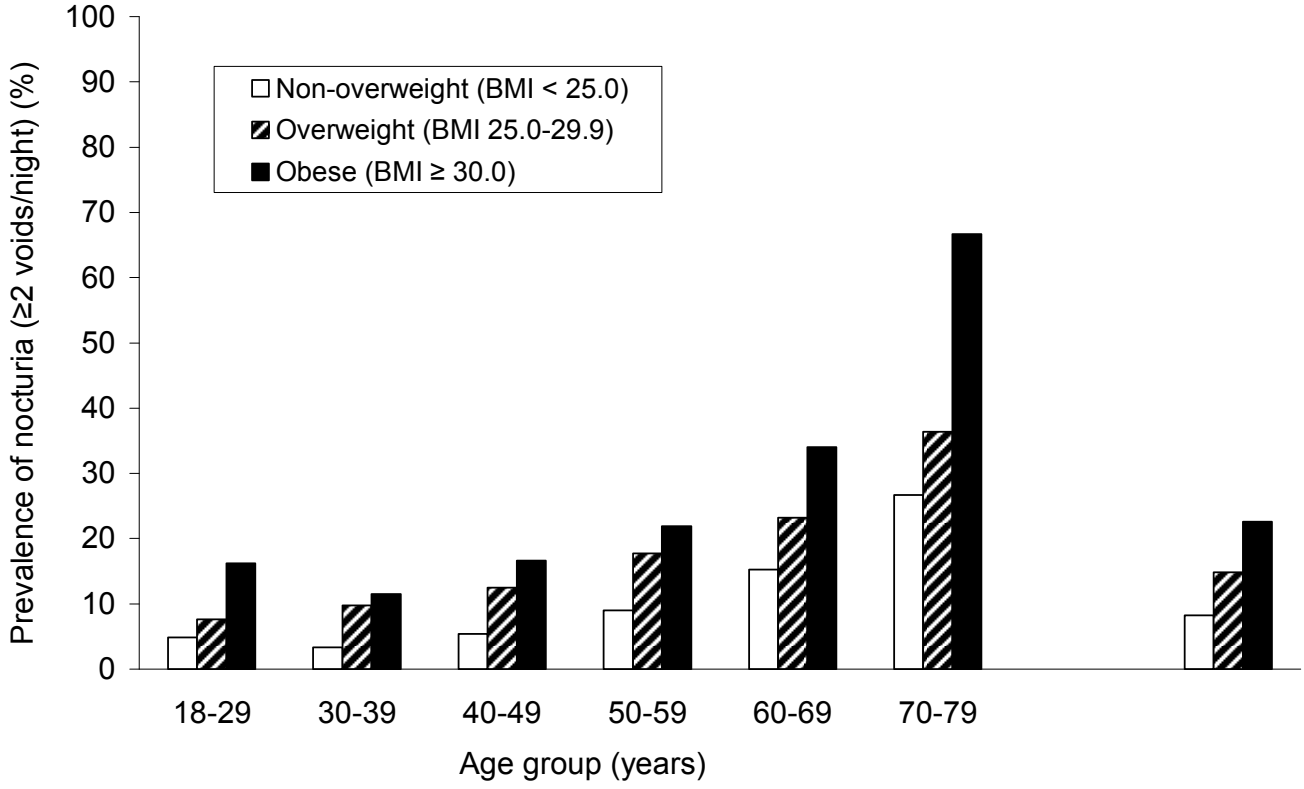


Figure 14. Prevalence of nocturia (defined as ≥2 voids/night) among women in the FINNO Study, Finland, 2003-2004.

The white bars indicate non-overweight (BMI < 25), the bars with diagonal lines overweight (BMI 25-29.9); and the black bars indicate obese (BMI ≥30) subjects.



5. Discussion

In the population-based FINNO Study, prevalence, impact and risk factors of nocturia were evaluated using a large, randomly selected study population of men and women aged 18-79, representative of Finnish adult population in numerous respects. Approximately 28% of subjects reported one, 10% two, 2% three, and 1% four or more voids per night. Nocturia was equally in among both sexes. However, in more detailed analyses clear differences between the sexes emerged. Nocturia was more frequent among women than men in the younger age groups, but more common among old men than old women. Most subjects reported small bother from nocturia with two nocturia episodes, and moderate bother only with three nocturia episodes. Two nocturia episodes distinctly impaired HRQL compared to those with no nocturia.

In the multivariate analyses, numerous risk factors for nocturia were identified. However, none of them accounted for more than half of the nocturia cases, highlighting its multifactorial etiology. The risk factors differed slightly by sex, suggesting differing contributions of various factors among men and women. At population level, OAB, BPH and snoring for men; overweight/obesity, OAB and snoring for women accounted for the largest proportion of nocturia. In addition, obesity and antidepressant use for men, diabetes and CAD for women, and RLS for both sexes were significantly associated with nocturia. However, these had less impact than the previously mentioned factors. Among women, parity, postpartum year and postmenopausal period were associated with increased prevalence of nocturia.

5.1 Prevalence of nocturia

Overall, approximately 40% of subjects reported voiding at least once per night. With nocturia defined as at least two voids per night, approximately one out of eight men and women had nocturia. Nocturia was more common in women in younger age groups. By the age of 50-59 years, men reached women in nocturia prevalence. In the older age groups, nocturia was more common in men. Prevalence of nocturia increased with age in men twice as rapidly as in women.

The findings of our study are comparable with those of a Swedish study (Rembratt et al. 2003), which reported elderly men having more nocturia than women. It was also a population-based survey with a high response proportion. However, it included only subjects at least 65 years of age and did not therefore provide information on the younger population. In a Dutch study (van Dijk et al. 2002), nocturia was more common in women than in men, whereas in Austrian and Japanese studies no gender difference was reported (Schatzl et al. 2000, Yoshimura et al. 2004). However, these studies were not population-based (Schatzl et al. 2000, van Dijk et al. 2002, Yoshimura et al. 2004).

In a population-based US telephone survey (Coyne et al. 2003), the age-standardised prevalence of nocturia was similar to our finding, but nocturia was reported almost equally commonly among men and women in all age groups. The explanation for the different kind of results may be methodological - questionnnaires may provide more reliable information than telephone surveys in several respects, including higher participation (Armstrong et al. 1992).

Recent studies have confirmed our findings: 1) higher prevalence of nocturia among young women than young men, and 2) difference in prevalence disappearing among the middle aged (Irwin et al. 2006, Parsons et al. 2007, Choo et al. 2008, Herschorn et al. 2008).

5.2 Prevalence of overactive bladder

In our study, the prevalence of OAB was 6.5% for men and 9.3% for women, i.e. one out of twelve adults aged 18-79 years had OAB. Subjects with OAB reported more frequency and nocturia than those without OAB, but the majority of subjects with frequency or nocturia did not report OAB.

The reported prevalence of OAB has varied widely in earlier studies due to differences in symptom assessment, study population, data collection procedures, and definition of OAB including exclusion criteria. Most studies have reported a greater prevalence of OAB than that found in our study (Lapitan et al. 2001, Milsom et al. 2001, Chen et al. 2003, Stewart et al. 2003, Corcos & Schick 2004, Moorthy et al. 2004, Homma et al. 2005, Temml et al. 2005, Irwin et al. 2006, Teloken et al. 2006, Yu et al. 2006a, Choo et al. 2008, Herschorn et al. 2008) (Appendix 16). Most studies (Milsom et al. 2001, Stewart et al. 2003, Temml et al. 2005, Irwin et al. 2006, Yu et al. 2006a, Zhang et al. 2006, Choo et al. 2008, Herschorn et al. 2008) have also reported more UUI among subjects with OAB than we found (probably mainly due to more selective participation).

The definition of a symptom-based disorder, such as OAB, has a major impact on the findings (Hunskaar 2005, Ioannidis 2005). We used the OAB definition of the ICS, with urinary urgency as a sufficient criterion for OAB (Abrams et al. 2002, Abrams et al. 2009). It does not define OAB in terms of severity or symptom bother. The classification of a symptom (including the time period for which occurrence of symptoms is elicited) has a marked/decisive influence on the result, due in part to the fluctuating nature and very high remission rates of LUTS, including urgency (Moller et al. 2000a, Wennberg et al. 2009). We asked about OAB in the last two weeks with four response options: if urgency was reported “never” or “rarely”, the subject was classified as normal, while “often” and “always” were regarded as abnormal. Having urinary urgency “often” was used as a cut-off point because this degree of urgency was typically viewed as bothersome and was associated with clinically meaningful deterioration in HRQL, whereas having urgency “rarely” was not (Tikkinen et al. 2008, Tikkinen et al. 2009).

Our OAB classification differed slightly from the Austrian study, where a five-point scale was used over the last four weeks and subjects who had urgency "occasionally" were also classified as abnormal (Temml et al. 2005). In the Chinese community-based study, women reporting urgency "occasionally" were deemed abnormal but only in the presence of other symptoms (frequency, nocturia, or urge incontinence) (Zhang et al. 2006). In the US study, those reporting ≥4 urgency episodes in the last four weeks and also reporting >8 voids per day, or ≥1 coping strategy were classified as pathological (Stewart et al. 2003). Some studies elicited symptoms over a very long or unspecified time (Milsom et al. 2001, Parazzini et al. 2002, Corcos & Schick 2004, Irwin et al. 2006, Teloken et al. 2006, Herschorn et al. 2008), whereas some did not exactly describe symptom classification and/or questions asked (Lapitan et al. 2001, Moorthy et al. 2004, Teloken et al. 2006). The crucial impact of definition on urological outcomes has earlier been shown regarding incontinence, potency and BPH prevalence (Blanker et al. 2000b, Krupski et al. 2003). Overall, in all symptom-defined disorders (such as OAB) including very mild or rare symptoms such as pathological symptoms blurs the distinction between mild and severe dysfunction, thereby causing a considerable risk of inducing healthy people to perceive themselves as sick (Moynihan & Henry 2006).

Unfavourable aspects of modern medical research are also perceptible in studies conducted on OAB (prevalence), ´herding´ and ´winner´s curse´ being examples (Table 13) (Young et al. 2008). Scientists may select methods to end up with similar estimates as previously published. In general, results stressing the importance of the topic (i.e. high prevalence estimates) are more likely to gain acceptance (publication bias) (Young et al. 2008). Overall, in actual studies, the observed relation varies with respect to the true one. Those studies which observe stronger than the true relationship are more likely to be written up and published. Subsequent replications will find in general less strong relations. However, exaggeration and overestimation of results and estimates may actually be of crucial importance in the evolution of new research topics. Urinary symptoms have traditionally been neglected areas of medicine (Stoddart et al. 2001). High prevalence estimates attract attention, and can, in theory, lead to increased disease awareness, and ultimately to earlier presentation and initiation of effective care. However, ´maximised´ prevalence estimates can also be used inappropriately for commercial purposes (to make the condition seem as widespread as possible to

maximise the magnitude of a medical problem) (Moynihan et al. 2002). Drug companies have recently identified lifestyle problems (especially self-diagnosed conditions) as a "growth market" (Almasi et al. 2006, Lexchin 2006). Hence, overestimation of prevalence estimates may also be part of *disease mongering* (Moynihan et al. 2002). Disease mongering (marketing disease, selling sickness) includes several steps such as 1) publicising large prevalence estimates, 2) highlighting doctors' ´failure´ to recognise ´disease´, and 3) suggesting that all ´disease´ should be treated. Furthermore, the benefits of the drug are often exaggerated, disadvantages minimised and concerns about the duration of clinical trials ignored (Moynihan et al. 2002, Woloshin & Schwartz 2006).

Table 13. Economic Terms and Analogies in Scientific Publication (Reprinted from Young et al. Why current publication practices may distort science. *PLoS Med* 2008;5(10):e201 under the Creative Commons Attribution License).

Economic Term	Meaning	Analogy in Scientific Publication
Winner's curse	The winner in an auction tends on average to have overpaid, especially when no participant is sure exactly how valuable the item is.	Scientific studies try to find true relationships, but none are certain of what these relationships are exactly. Published articles, especially in very competitive journals, have on average exaggerated results.
Oligopoly	A market where a few traders have the major share and each oligopolist has significant power to influence the market.	Very few journals with limited publication slots (compared with geometrically increasing scientific data that seek publication) determine highly visible science.
Herding	"Follow-the-leader" behaviour: the actions of the first or dominant player supersede the individual information and actions of all the players in a market.	Scientists may uncritically follow paths of investigation that are popularised in prestigious publications, neglecting novel ideas and truly independent investigative paths.
Artificial scarcity	Restrictions on the provision of a commodity above that expected from its production cost.	Print page limits are an obvious excuse for failure to accept articles, and further the small number of major "high-impact" journals have limited slots; extremely low acceptance rates provide status signals to successful publications and their authors.
Uncertainty	Situation where the real long-term value of a commodity is largely unpredictable.	For much (most?) scientific work, it is difficult or impossible to immediately predict future value, extensions, and practical applications.
Branding	Marking a product as valuable; of key importance when it is difficult to determine a product's value prior to consuming it.	Publishing in selective journals provides evidence of value of a research result and its authors, independent of the manuscript's content.

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In the standardisation report (Abrams et al. 2002, Abrams et al. 2009), the current definition of OAB includes also "…usually with increased daytime frequency and nocturia.", and those symptoms are defined as complaints without any severity assessment. In Study II, we defined frequency as more than 8 voids per day and nocturia as at least two voids per night – as in some earlier reports (Milsom et al. 2001, Parazzini et al. 2002, Stewart et al. 2003, Temml et al. 2005). Our definition of at least two voids per night for nocturia is justified by bother and HRQL impact. However, reported frequency may be inaccurate due to random error and recall bias (Stav et al. 2009). On the other hand, the definition of frequency or nocturia has *no* effect on the prevalence of OAB if the current definition is used.

According to the standardisation report (Abrams et al. 2002), for the diagnosis of OAB subjects with "urinary infection or other obvious pathology" should be excluded. Identification of OAB without excluding known reasons causing urinary urgency can result in overestimation of prevalence. Many studies did not report or use any exclusion criteria (Lapitan et al. 2001, Parazzini et al. 2002, Chen et al. 2003, Corcos & Schick 2004, Moorthy et al. 2004, Homma et al. 2005, Irwin et al. 2006, Zhang et al. 2006, Choo et al. 2008, Herschorn et al. 2008), or excluded only subjects with urinary tract infection (Milsom et al. 2001). In the Austrian and Brazilian studies (Temml et al. 2005, Teloken et al. 2006), exclusions were slightly broader (for example, diabetes) than in our study and in the US study (Stewart et al. 2003) even more extensive (including diabetes, congestive heart failure, and excessive fluid intake). In the Austrian study, exclusions were performed for subjects with urgency, not for the whole study sample (Temml et al. 2005). Those studies not applying any exclusions, such as the urinary tract infections, may have resulted in general overestimation of prevalence.

Several articles have been published on the prevalence of OAB. However, many of them have not been population-based (Lapitan et al. 2001, Parazzini et al. 2002, Moorthy et al. 2004, Temml et al. 2005), whereas the population-based studies (Milsom et al. 2001, Chen et al. 2003, Stewart et al. 2003, Corcos & Schick 2004, Homma et al. 2005, Irwin et al. 2006, Teloken et al. 2006, Yu et al. 2006a, Zhang et al. 2006, Choo et al. 2008, Herschorn et al. 2008) have failed: 1) to apply the current definition of OAB (Milsom et al. 2001, Chen et al. 2003, Stewart et al. 2003, Homma et al. 2005, Yu et al. 2006a, Zhang et al. 2006, Choo et al. 2008, Herschorn et al. 2008),

2) to report or use any exclusions (Corcos & Schick 2004, Homma et al. 2005, Irwin et al. 2006, Zhang et al. 2006, Choo et al. 2008, Herschorn et al. 2008), 3) to include all adult ages (Milsom et al. 2001, Corcos & Schick 2004, Homma et al. 2005, Teloken et al. 2006, Yu et al. 2006a, Choo et al. 2008), 4) to include both sexes (Zhang et al. 2006), 5) to report response proportion or non-responders (Milsom et al. 2001, Corcos & Schick 2004, Teloken et al. 2006, Herschorn et al. 2008), or 6) to achieve a satisfactory response proportion (Stewart et al. 2003, Corcos & Schick 2004, Homma et al. 2005, Irwin et al. 2006, Choo et al. 2008) (Appendix 16). However, as long as the symptom definition of OAB constitutes a description without any severity or bother assessment, a solid basis for assessing the prevalence of OAB is lacking.

"Claimed research findings may often be simply accurate measures of the prevailing bias." (Ioannidis 2005)

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Even though most studies have reported higher prevalence estimates than ours, the differences can be readily explained by discrepancies in study procedures (Appendix 16). For instance, the very first OAB prevalence study reported that "[t]he overall prevalence of overactive bladder symptoms in individuals aged ≥40 years was 16.6%" (Milsom et al. 2001). However, during their study period, the ´old OAB definition´ was used – besides urinary urgency and urgency incontinence, also reporting more than 8 voids per day was sufficient for ´OAB diagnosis´. Hence, only 54% of subjects classified as having OAB actually reported urinary urgency. Using the current OAB definition by the ICS, the prevalence of OAB would have been 9%. In the FINNO Study, OAB prevalence was 11% among subjects aged 40 or older. Hence, although our prevalence estimates for OAB are generally comparatively low, we may paradoxically have more OAB in Finland than in the countries of the first (Milsom et al. 2001) and recent (Irwin et al. 2006) international OAB studies (Appendix 16). This is also supported by the recent findings from the EPIC Study showing that among OAB cases "46% did not report symptom bother" (Irwin et al. 2008). This indicates that prevalence of clinically meaningful OAB was much lower than the reported 12% in the EPIC study (Irwin et al. 2006, Irwin et al. 2008).

Of the Finnish adult population, 5% are aged 80 years or more (Population Register Centre 2004). As our sample did not include this age group, we extrapolated the prevalence rates for people aged 80 years or more. Based on extrapolated prevalence rates of OAB among this age group (20.0% for men and 17.5% for women), we calculated age-standardised prevalence of OAB for men (6.9%) and women (9.8%). Adjustment for people aged 80 years or more did not materially change the prevalence rates indicating that one in twelve (8.4%) in the general population had OAB.

5.3 Bother, health-related quality of life and nocturia

In Study III, most respondents reported bother from nocturia with ≥2 episodes per night, and moderate bother only with ≥3 nocturia episodes. Of the FINNO Study respondents (regardless of nocturia frequency), 4% reported moderate bother from nocturia, while only 1% reported that waking up at night to urinate was a major bother. Overall, among those with any nocturia, approximately one in eight reported moderate or major bother, while both no and small bother was reported by slightly more than 40% of the subjects with nocturia. In general, degree of bother increased with nocturia frequency. Hence, of those with ≥4 voids per night, 36% regarded it as a major and 46% as a moderate bother.

Those with two nocturia episodes reported substantially impaired HRQL compared to those with no nocturia. At least three episodes of nocturia resulted in further impairment of similar magnitude. Using a standardised measure of a clinically important difference in 15D Score, those reporting a single nocturia episode were not notably different from those reporting none. In both sexes, subjects with ≥3 voids/night reported poorer HRQL than subjects without nocturia, or 1-2 voids/night.

Earlier results suggest that nocturia may impair well-being more than has been generally recognised. Nocturia can be bothersome (DuBeau et al. 1995, Swithinbank et al. 1999, Coyne et al. 2003, Fiske et al. 2004, Liew et al. 2006, Yu et al. 2006b, Lowenstein et al. 2007, Choo et al. 2008) entailing sleep loss, daytime fatigue, missed work, perceived health, and depression (Asplund & Åberg 1992, Asplund & Åberg 1996, Samuelsson et al. 1997, Mock et al. 2008). Among men with LUTS suggestive

of BPH/BPO, nocturia has been rated more bothersome than other LUTS (Jolleys et al. 1994, DuBeau et al. 1995, Batista-Miranda et al. 2007). In a Japanese clinical study, bother from nocturia predicted impaired quality of life more strongly than other LUTS (Ushijima et al. 2006).

Perceived bother from LUTS varies considerably between individuals (Andersson et al. 2004). Here, as in other studies (Schatzl et al. 2000, Coyne et al. 2003, Fiske et al. 2004, Liew et al. 2006, Yu et al. 2006b, Lowenstein et al. 2007, Choo et al. 2008) bother from nocturia depended upon its frequency. In Asian population-based studies and a Viennese health screening study, nocturia was no problem (Liew et al. 2006, Choo et al. 2008) or not more than "a bit of problem" (Schatzl et al. 2000) for most respondents. In a US urogynaecology clinic-based study (Lowenstein et al. 2007), the mean bother score ≥5 out of 10 was reported only with ≥3 nocturia episodes. These findings concur with our results: approximately half of subjects with one void per night reported no bother from nocturia, and of those with two voids per night, the most common response was "small" bother. Subjects with three voids per night most commonly reported "moderate" followed by "small" bother, while those with ≥4 voids per night, most commonly reported "moderate", followed by "major" bother. Nevertheless, number of nocturia episodes does not completely predict perceived bother (Sagnier et al. 1995). In our study, too, bother from nocturia varied widely. A very small proportion of individuals (0.7%) reporting one nightly episode of nocturia considered it a "major" bother and 18% of those with ≥4 nightly episodes of nocturia rated their bother as "none" or "small".

Overall, men and women reported similar bother from nocturia. However, older women were less bothered than younger women, but no such difference was observed among men. While the prevalence of nocturia increases with age, the prevalence of nocturia in men rises more steeply (Study I). A plausible explanation is that older women acquiesce, reporting less bother from nocturia as they are less likely to develop it as a "new" condition with increasing age, but these cross-sectional data cannot prove this. In contrast to other studies, a Viennese study reported no gender differences in bother from nocturia (Schatzl et al. 2000). A population-based study in Taiwan among adults over 40 years showed that men reported more bother and concern related to nocturia than women (Yu et al. 2006b). However, a Danish survey of adults aged 60-80

showed that women with ≥3 nocturia episodes were more bothered than men. In less severe nocturia, however, no gender difference was found (Bing et al. 2006). The Danish study also showed that nocturia caused more concern in younger age groups.

Our findings indicate that ≥2 episodes of nocturia differentiate those subjects reporting substantial bother from nocturia and impaired HRQL. These findings were consistent across age groups and unaffecetd by exclusion of those with missing values. A US study found that scores from OAB-q, an HRQL instrument designed specifically for OAB differed statistically significantly between subjects with one, two and three episodes of nocturia (as in our study). However, the clinical importance of the differences remained unclear (Coyne et al. 2003). Another US study (among female urology clinic patients) and a community-based study from Taiwan proposed that clinically significant nocturia (based on bother) is ≥2 voids per night (Fiske et al. 2004, Yu et al. 2006b).

While more frequent nocturia results in greater bother and poorer HRQL, not all bother from nocturia is explained by the number of nocturia episodes (Sagnier et al. 1995). Nocturia may also be associated with other factors causing impaired HRQL, rather than directly affecting self-rated health. This is supported by the association of nocturia with almost all dimensions of HRQL, not only those related to urination or sleep. Furthermore, comorbidities were strongly associated with impaired HRQL, and also with nocturia, indicating confounding. Treatment to reduce episodes of nocturia may therefore not relieve all impairment among subjects with nocturia. Indeed, nocturia may be a typical *geriatric syndrome* (i.e. one symptom or a complex of symptoms with high prevalence in old age, resulting from multiple diseases and multiple risk factors) (Olde Rikkert et al. 2003).

5.4 Risk factors of nocturia

Numerous risk factors for nocturia were identified in Study VI. However, none of them accounted for more than half of the nocturia cases, highlighting its multifactorial etiology. The risk factors differed slightly by sex, suggesting gender-specific etiologies. At population level, OAB, BPH and snoring for men; overweight/obesity,

OAB and snoring for women accounted for the largest proportion of nocturia. Although obesity and antidepressant use for men, diabetes and CAD for women, and RLS for both sexes were risk factors, these had less impact.

Concurring with earlier reports (Schatzl et al. 2000, Rembratt et al. 2003, Yoshimura et al. 2004, Weiss et al. 2007) OAB was strongly associated with nocturia among both sexes. While half of subjects with OAB also reported nocturia, only one in three with nocturia reported OAB. Among men, BPH had the second highest population attributable fraction of nocturia. Similarly, half of the subjects with BPH reported nocturia − yet only a third of the men with nocturia reported BPH. LUTS suggestive of BPE/BPH/BPO constitutes a well-recognised risk factor for nocturia (Blanker et al. 2000a, Yu et al. 2005). However, the impact of BPH may be overestimated (nocturic men are probably more likely to be BPH-diagnosed than men without nocturia, and women do not have less nocturia despite not having prostates). In Japanese studies, nocturia was the least specific LUTS associated with benign prostatic obstruction and treatment to relieve benign prostatic obstruction had less effect on nocturia than on other symptoms (Homma et al. 2002, Yoshimura et al. 2003). In a secondary analysis of the Veterans Affairs study on participants with LUTS/BPH receiving doxazosin had very modest (though statistically significant) reductions in nocturia, while finasteride had an effect indistinguishable from placebo (Johnson et al. 2007).

In the present analysis, nocturia was associated with obesity in both sexes; and also with overweight in women. Indeed, overweight/obesity had the greatest impact on nocturia at population level among women. Its effect at population level is likely stronger in countries with higher prevalence of overweight/obesity, such as the US (World Health Organization 2009). Among non-overweight subjects aged 30–39 years, only one out of 50 men and one out of 30 women reported voiding two or more times per night. Among obese subjects aged 30–39 years, the corresponding figures were one out of 20 for men and one out of nine for women. Among non-overweight subjects aged 70–79 years, slightly more than every third man and approximately every fourth woman reported having at least two voids per night. In this age group, more than half of obese men and two thirds of obese women reported voiding at least twice per night. The results were parallel with those obtained when nocturia was defined as at least one void per night. The etiology of nocturia is still unclear, and the factors between

nocturia and obesity are even more ambiguous. Nevertheless, the impact of obesity on nocturia has been confirmed in recent cross-sectional (Fitzgerald et al. 2007, Bing et al. 2008, Laven et al. 2008) and longitudinal (Shiri et al. 2008) studies. Potentially, preventing obesity may decrease nocturia, though establishing causality would ideally require an intervention study. Weight loss has already been shown to decrease urinary incontinence substantially among overweight and obese women (Subak et al. 2009).

At population level, snoring was one of the three most important nocturia risk factors for both sexes. Its strong impact at population level was due to a high prevalence (35% for men, 18% for women) - comparable to prevalences in other countries (Bearpark et al. 1995, Young et al. 2001). However, the strength of the association was relatively low (OR 1.5-1.8). In a Swedish urology clinic study (Kinn & Harlid 2003), snoring was associated with increased nocturia. Snoring is closely related to OSA. In a US sleep centre study, OSA and sleep disorders were responsible for the majority of nocturia (Pressman et al. 1996). In another US study, OSA severity predicted frequency of nocturia and continuous positive airway pressure treatment resulted in a significant decrease in nocturia (Fitzgerald et al. 2006). In a study among 31 urogynaecology patients participating in a home sleep study, prevalence of OSA was double among those with nocturia (81%) compared to those without (40%) (Lowenstein et al. 2008). In our study, OSA was not statistically significantly associated with nocturia after adjustment for other factors (despite associations in the age-adjusted analyses). This may be due to strong overlap with snoring (three-quarters of subjects with OSA reported snoring here) and ten times higher prevalence of snoring compared to OSA leading to more statistical power for snoring.

In our study, RLS was associated with nocturia. To the best of our knowledge, earlier epidemiological investigations have not demonstrated such a link. Increased risk of nocturia in patients with RLS may relate to disturbed sleep (Hornyak et al. 2005). Moreover, RLS patients use medications such as antidepressants, gastrointestinal medications and asthma/allergy drugs more frequently than subjects free of these (Pearson et al. 2008). Nocturia has previously been linked to (untreated) depression (Asplund et al. 2005b, Häkkinen et al. 2008) and to use of selective serotonin-reuptake inhibitors (Asplund et al. 2005b). In our study, nocturia was associated with

antidepressant use only in men. Depression itself was not associated with nocturia after adjustment for other factors despite associations in the age-adjusted analyses (OR 2.8, 95% CI: 1.6, 5.0 for men; and OR 2.0, 95% CI: 1.2, 3.3 for women).

Prostate cancer was associated with nocturia in our study. More than 70% of men with physician-diagnosed prostate cancer reported at least two voids per night, while 7% of men with nocturia reported prostate cancer. It remains unclear whether the subjects with nocturia are more prone to be diagnosed (due to use of prostate-specific antigen among men with LUTS), whether prostate cancer causes nocturia, or whether nocturia is a side-effect of (various) prostate cancer treatments. More SUI and less obstructive symptoms have been reported after radical prostatectomy whereas impact on nocturia has been neutral or negative (i.e. increased nocturia) (Namiki et al. 2005, Namiki et al. 2006, Sanda et al. 2008, Wolin et al. 2009). Side-effects of hormonal treatment of prostate cancer include hot flushes, cardiovascular toxic effects, increase in body fat and decrease in muscle wasting (side-effects of individual drugs differ) (Damber & Aus 2008). All these factors may ultimately lead to increased nocturia.

Diabetes and CAD were associated with nocturia in the age-adjusted analyses in both sexes, but after adjustment for other factors the association persisted only for women. An association between diabetes and nocturia has been reported in several (Asplund 2002, Lee et al. 2004, Yoshimura et al. 2004, Yu et al. 2005, Fitzgerald et al. 2006, Gourova et al. 2006, Fitzgerald et al. 2007, Bing et al. 2008, Sarma et al. 2008), but not all earlier reports (Blanker et al. 2000a, Rembratt et al. 2003, Johnson et al. 2005b). In the BACH Survey (Fitzgerald et al. 2007), factors associated with nocturia were increasing BMI, diabetes and cardiac disease. In a Danish study at ages 60-80 years (Bing et al. 2008), conditions associated with two nightly voids included increasing BMI, diabetes, urinary incontinence and recurrent cystitis. In both surveys (Fitzgerald et al. 2007, Bing et al. 2008), adjustment for sex was used, but it was not clear whether there were gender differences in risk factors. Some (Bursztyn et al. 2006, Gourova et al. 2006, Fitzgerald et al. 2007) but not other earlier reports (Blanker et al. 2000a, Rembratt et al. 2003, Yoshimura et al. 2004, Yu et al. 2005, Bing et al. 2008) found cardiac/coronary disease to be a risk factor for nocturia.

We found no association of coffee or alcohol consumption with nocturia. This concurs with earlier reports regarding both coffee (Samuelsson et al. 1997, Asplund & Åberg 2004, Johnson et al. 2005b) and alcohol (Schatzl et al. 2000, Yoshimura et al. 2004, Hsieh et al. 2007, Bing et al. 2008) except one clinic-based study (Gourova et al. 2006). We found no association of nocturia with smoking. The earlier results are inconsistent: in a Swedish study (Asplund & Åberg 2004) smoking was associated with increased nocturia but in Austrian (Schatzl et al. 2000) and Japanese (Yoshimura et al. 2004) studies with decreased nocturia. Several studies corroborated our results with no association of smoking with nocturia (two or more nightly voids) (Samuelsson et al. 1997, Bursztyn et al. 2006, Hsieh et al. 2007, Bing et al. 2008, Shiri et al. 2008).

Some results from Study VI contradict earlier findings. Generally, numerous factors explored in our study were not assessed in earlier studies, and many studies were not performed at population level (Pressman et al. 1996, Schatzl et al. 2000, Yoshimura et al. 2003, Yoshimura et al. 2004, Bursztyn et al. 2006, Fitzgerald et al. 2006, Gourova et al. 2006, Lowenstein et al. 2008). Hence, dissimilarities in study procedures and samples may well account for many of the contradictions among the findings (Ioannidis 2005). The fact that numerous factors were significantly associated with nocturia in the age-adjusted analyses, but not after further adjustment, highlights the importance of appropriate analysis including controlling for confounders. We assessed numerous factors including comorbidities, medications, and lifestyle, socio-demographic and reproductive factors. Due to inconsistencies in the literature, using pre-existing knowledge for in the choice of the potential confounders was not possible. Hence, due to the exploratory nature of this analysis, we used stepwise (backward elimination) methods for model building (Sun et al. 1996).

Nocturia has been classified as a symptom caused by a) NP b) low nocturnal bladder capacity, c) diminished global bladder capacity, d) a combination of NP and low bladder capacity, e) global polyuria, and/or f) sleep disorders (Weiss & Blaivas 2000). The risk factors we identified may well involve these pathways, and finally nocturia. However, the pathways are probably complex and there may also be numerous other underlying causes for the associations, such as autonomic nervous system hyperactivity and/or metabolic syndrome (McVary et al. 2005, Rohrmann et al. 2005). Identifying a

principal cause of nocturia has been difficult (Vaughan et al. 2009). In a recent non-randomised US study at a Veterans Affairs Medical Center, implementing a multicomponent behavioural intervention combined with drug(s) in older men reduced nocturia frequency, bother from nocturia, and time to initiate sleep. However, as the authors stated, an RCT should be performed (Vaughan et al. 2009).

In the FINNO Study (Study V), female reproductive factors associated with nocturia differed from those related to OAB (urinary urgency). Nocturia was associated with parity, postpartum and postmenopausal periods, while OAB was related to surgery for SUI (after adjustments for confounders). Hysterectomy and MHT use were not associated with nocturia or OAB.

Parous women reported more nocturia than nulliparous women, which contradicts earlier reports of no association between parity and nocturia (Alling Moller et al. 2000, Asplund & Åberg 2005). However, earlier studies included only perimenopausal women (Alling Moller et al. 2000, Asplund & Åberg 2005). Parallel with our findings, most earlier studies reported no association for parity with urgency (Handa et al. 2004) or OAB (Parazzini et al. 2003, McGrother et al. 2006), with two exceptions (Alling Moller et al. 2000, Zhang et al. 2006).

In our study, the postmenopausal period was associated with more nocturia, consistent with a Danish population-based study on 40 to 60 year-old women (Alling Moller et al. 2000). Two other studies have also reported increased nocturia in the postmenopausal period (Rekers et al. 1992, Asplund & Åberg 2005), whereas another attributed this to ageing rather than to menopausal transition (Lin et al. 2005). However, four studies demonstrated an association between postmenopausal period and increased urgency/OAB (Rekers et al. 1992, Prasad et al. 2002, Handa et al. 2004, Zhang et al. 2006). However, these were either not population-based (Prasad et al. 2002, Handa et al. 2004) or failed to control for age or comorbidities (Rekers et al. 1992, Zhang et al. 2006).

Surgery for SUI was strongly associated with increased OAB, as reported earlier (Kershen & Appell 2002). Furthermore, we found that postpartum period (as defined

here) was associated with increased nocturia but not with OAB. No reports of investigations into these relations could be found in the literature.

Hysterectomised women (with premenopausal status used as a reference) had an OR of 1.8 for nocturia, with borderline statistical significance. This association could be regarded as clinically meaningful, but because of the somewhat low level of precision, we could not exclude the possibility that it was due to chance. Six earlier studies have found no association of hysterectomy with nocturia and urgency and our results concur with these (Stanton et al. 1982, Weber et al. 1999, Altman et al. 2003, Parazzini et al. 2003, de Tayrac et al. 2007, Krogh et al. 2007). However, two studies reported less nocturia and urgency (Vervest et al. 1988, Thakar et al. 2002), and five studies reported a decrease of one or the other symptom after hysterectomy (most with follow-up of one year or less) (Virtanen et al. 1993, Carlson et al. 1994, Prasad et al. 2002, Learman et al. 2003, Gimbel et al. 2005). However, a Danish study reported more nocturia and urgency among hysterectomised women (Alling Moller et al. 2000). Most earlier studies were neither population-based surveys nor controlled trials (Stanton et al. 1982, Vervest et al. 1988, Virtanen et al. 1993, Carlson et al. 1994, Weber et al. 1999, Prasad et al. 2002, Altman et al. 2003, Parazzini et al. 2003, de Tayrac et al. 2007, Krogh et al. 2007).

We detected some indication of increased nocturia among women with MHT (compared to premenopausal women; OR, 1.8), but the finding was not statistically significant. An effect size this large could be considered clinically meaningful, but our result could also have been caused by chance. There are few studies evaluating the effect of MHT on nocturia and OAB/urgency. An RCT (Cardozo et al. 1993) and a population-based cross-sectional study (Asplund & Åberg 2005) did not find benefit from MHT for these symptoms. Other uncontrolled intervention studies have reported contradictory results.

Our results partly contradict earlier findings (Vervest et al. 1988, Rekers et al. 1992, Virtanen et al. 1993, Carlson et al. 1994, Alling Moller et al. 2000, Prasad et al. 2002, Thakar et al. 2002, Learman et al. 2003, Handa et al. 2004, Asplund & Åberg 2005, Gimbel et al. 2005, Lin et al. 2005, Zhang et al. 2006). However, many of the

differences are probably due to differences in study populations and methods. The fact that parity, postmenopausal period, hysterectomy and SUI surgery were significantly associated in unadjusted analyses with both nocturia and OAB highlights the importance of controlling for confounders. Given the numerous possible but unconfirmed risk factors, we assessed several potential confounders including comorbidities, medications, body mass index, and lifestyle, sociodemographic and reproductive factors. Earlier epidemiological studies have been limited by inadequate control of potential confounders (Rekers et al. 1992, Alling Moller et al. 2000, Handa et al. 2004, Asplund & Åberg 2005, Lin et al. 2005, McGrother et al. 2006, Zhang et al. 2006). While the results from earlier studies were known, confounder scores were constructed empirically (based on many comorbidities and medications) due to inconsistent results in previous studies. Using confounder score has the potential to improve statistical efficiency and may decrease residual confounding (Brenner & Blettner 1997), although perhaps with a risk of overadjustment by chance correlation.

In our study, increased nocturia was associated with parity, and postpartum and postmenopausal periods, also known to be associated with sleep disturbances (Lee et al. 2000, Moline et al. 2003). The association of nocturia with parity is more likely due to endocrinologic changes or changes in the nervous system associated with pregnancy than physical damage to the urinary tract during delivery (Lose et al. 2001). Our finding of no difference in nocturia between primi- and multiparous women is also consistent with this conjecture.

With age, the co-morbidities associated with increased nocturia increase (Weiss & Blaivas 2000). In our study, association of postmenopausal period with nocturia persisted after adjustment for confounders. This period is often associated with sleep disturbances for several reasons including hot flushes, mood disorders and increased sleep disordered breathing (Moline et al. 2003), and therefore the association with nocturia may be secondary. Similarly, increased nocturia during the postpartum period may be secondary to increased number of awakenings and impaired sleep quality. Most awakenings are for baby care, however, maternal depressed mood may also play a role (Moline et al. 2003).

In our study, SUI was related to both increased nocturia and OAB. However, only OAB was associated with surgery for SUI. It is known that SUI surgery may cause *de novo* OAB/urgency but the underlying mechanism remains unclear (Kershen & Appell 2002). It may be due to the obstructive effects of the procedures. However, bladder outlet obstruction is not the sole cause (Kershen & Appell 2002). Furthermore, people needing SUI surgery may already have more (bothersome) symptoms pre-operatively.

5.5 Strengths of the FINNO Study

The present study has several strengths. Through comprehensive and representative identification of cases, we avoided selection bias due to treatment seeking (reflecting both severity and health care service use). The FINNO Study benefits from 1) a large population-based sample of Finns randomly identified from the population register, 2) a wide age range of adults, 3) use of clinically relevant exclusion criteria, 4) validated questions about nocturia, other LUTS and sleeping disorders enabling outcomes consistent with standardised definitions, 5) a large number of relevant factors assessed, 6) use of a validated HRQL instrument, 7) adjustment for numerous potential confounders using sophisticated methodologies, 8) use of information from comprehensive national databases, and 9) an opportunity to compare, within the same study population, differences between men and women. Furthermore, a good response proportion, a high degree of completion of the items, and a representative study population were achieved. Finally, prevalence of several factors was similar among participants and non-participants, moreover numerous factors and indicators were largely similar by response round. These all indicate absence of selective participation. When needed, adjustment for selection bias was used.

5.6 Representativeness of the study population

The FINNO Study population is representative of Finnish adults in terms of socio-demographic, anthropometric, lifestyle and female reproductive factors as well as comorbidities and medication use.

Sociodemographic and anthropometic factors. The proportion of urban population was 40% among participants of the FINNO Study, compared with 39% in the entire population (Statistics Finland 2003). As for education, the proportion with university degrees was 22% in our study and 25% in Finland as a whole. The proportion of unemployed in our material was 7% while the official figure at the time of the study was 8%. Also, the marital status distribution corresponded well to the population data of Statistics Finland (Statistics Finland 2003). Our study population was similar in terms of BMI to that of the Health Behaviour and Health among the Finnish Adult Population Study carried out by the National Public Health Institute (Helakorpi et al. 2003). On the other hand, obesity was more common (age-standardised among subjects aged ≥30 years, 21% of men and 24% of women had measured BMI ≥30) in another population-based study of 8,000 persons (Aromaa & Koskinen 2004). The former study was comparable to ours in the sense that it was based on self-reported weight and height (Helakorpi et al. 2003). There are two possible explanations for the difference from latter population: 1) their study population was older (in our study, obesity prevalence was higher when the age group was restricted to persons aged 30 years or more: 16% of men and 15% of women) (Aromaa & Koskinen 2004), and 2) obese people tend to underestimate their weight in questionnaire surveys (Kuskowska-Wolk et al. 1989, Nieto-Garcia et al. 1990, Kuskowska-Wolk et al. 1992).

Conditions and medications. The frequencies of comorbidities and medications were similar to large-scale population surveys suggesting that our study was representative of the Finnish population (Aromaa & Koskinen 2004, Helakorpi et al. 2005). For instance, hypertension and depression were reported by 15% and 3% in a population-based survey (Helakorpi et al. 2005) compared to 15% reporting physician-diagnosed hypertension and 5% mood disorder in our material. In the same study, use of insulin, other diabetes drugs, antidepressants, and cholesterol drugs was reported by 1%, 2%, 4% and 6% of subjects. In our sample, the corresponding figures were 1%, 3%, 5% and 7%. In another Finnish National Public Health Institute study (Aromaa & Koskinen 2004), one or more comorbidities were reported by 52%, which is comparable to our result, 48%. A slightly higher estimate in the earlier survey can be explained by a somewhat older population compared to ours.

Reproductive factors. Information on parity was based on nationwide, comprehensive database from the Finnish Population Register covering all residents in Finland. In our study, 69% of participants and 71% of non-participants were parous. In an interview-assisted study of approximately 9,500 women carried out by the National Public Health Institute (Koponen & Luoto 2004), 73% of Finnish women aged 18 to 84 years were parous. In the same study (Koponen & Luoto 2004), hysterectomy was reported by 13%, and use of MHT by 21% (among 35 to 84 year old women). In our study, 13% reported hysterectomy, and 20% use of MHT (among women aged 30 or more). In light of these findings, our study population appears representative of the Finnish population in terms of parity, menopausal status, use of MHT, and number of hysterectomies. All these findings indicate paucity of selective participation.

Lifestyle factors. The frequencies of lifestyle factors were similar to large-scale population surveys suggesting that our study was representative of the Finnish population (Laatikainen et al. 2003, Männistö et al. 2003, Aromaa & Koskinen 2004, Helakorpi et al. 2005). In the FINDIET 2002 study, reported use of coffee (4.4 cups/day among men and 3.1 in women) was practically identical to our sample (4.4 and 3.3 respectively) (Männistö et al. 2003). In a Finnish National Public Health Institute study (Aromaa & Koskinen 2004), 29% (18%) of men (women) reported daily smoking, which is comparable to our estimates; 29% of men (23% of women) were current smokers.

5.7 Limitations

This study has some limitations: 1) the cross-sectional study design limits conclusions about causality; 2) results from the Finnish population may not be directly generalisable to other ethnicities, 3) although the response rate was high, approximately one third of those contacted did not participate in the study; 4) impact of self-reporting on validity of the results remains unclear, and 5) identifying every potential risk and confounding was not achieved, however, this may be inevitable.

5.7.1 Study design and study population

This dissertation is based on the baseline data (cross-sectional) of the FINNO Study. The cross-sectional study design limits conclusions about causality. It is difficult, if not impossible, to separate cause from effect, as measurements of exposures and outcomes were conducted at the same time (except when their occurrence times could be established retrospectively). Furthermore, subject´s exposure status at the time of data collection may have had little to do with exposure status at the time the outcome first occurred. In future, the first survey of the FINNO Study will be the baseline of a prospective cohort study. However, as LUTS (including nocturia) are dynamic, symptoms fluctuate over time (Moller et al. 2000a, Häkkinen et al. 2006, Wennberg et al. 2009). This is likely to increase misclassification and bias any associations towards unity. Defining an incident case is a major methodological challenge for prospective studies of LUTS.

Descriptive results from the Finnish population may not be directly generalisable to other ethnicities. There may (Fitzgerald et al. 2007, Kupelian et al. 2009) or may not be (Liew et al. 2006) ethnic differences in the prevalence of nocturia. However, the potential differences may be largely explained by differences in socioeconomic status (Kupelian et al. 2009), while the direct impact of ethnicity remains unknown.

5.7.2 Self-reporting

We used postal questionnaires to explore the prevalence, impact and risk factors of urinary symptoms (especially nocturia and urinary urgency). Both nocturia and OAB are symptom-defined conditions requiring self-report (discussion regarding questionnaires and FVCs later). The validity of self-reported information is largely unclear. The agreement between questionnaire data and medical records has been shown to be good for major chronic diseases in Finland (Haapanen 1997). Patients´ self-reports have been shown to be reliable when estimating recent use of cardiovascular and diabetic drugs (Glintborg et al. 2007). Mailed questionnaires reflect urodynamics better than interview-assisted questionnaire responses (Khan et al. 2004). This may be due to feeling and not feeling embarrassed in interview-assisted and self-reporting situations respectively. Furthermore, mailed questionnaires yield more

reliable information than telephone surveys in several aspects, including higher participation (Armstrong et al. 1992).

5.7.3 Limitations related to potential risk or confounding factors

Anthropometric factors. BMI was used as an indicator of obesity. Although the correlation between BMI and body fat adjusted for age is high (r = 0.82–0.91) (Spiegelman et al. 1992), it is not possible to distinguish lean body mass from fat on the basis of BMI. For example, the proportion of body fat is higher among women than among men with a similar BMI. In addition, body fatness has been shown to increase with age; that is, similar BMIs may correspond to a greater body fat content in older subjects compared to younger subjects (Ross et al. 1994, Gallagher et al. 1996). Despite these limitations, BMI is a simple and useful measure of obesity in adults. A BMI of 30 is a widely recognised cutoff point for obesity, and the cutoff point for overweight (BMI ≥25) is recommended by the World Health Organization (World Health Organization 1995). However, waist circumference may be a better indicator of obesity. However, to the best of our knowledge, there is still a paucity of studies on this topic in general, and especially regarding LUTS (including nocturia).

Lifestyle factors. Our study was limited by fact that 14% of men and 24% of women did not report alcohol consumption. However, the prevalence of nocturia among subjects who provided alcohol consumption information did not differ from those who did not. Furthermore, reported alcohol consumption (daily mean consumption of absolute alcohol: 12 grams for men and 6 grams for women) corresponded very well with the statistics of the National Public Health Institute (Laatikainen et al. 2003). We did not have information on physical activity. In earlier reports, more physically active subjects had lower frequency of LUTS (Platz et al. 1998, Orsini et al. 2006, Litman et al. 2007), but not specifically nocturia (Schatzl et al. 2000). However, in a small uncontrolled study, significant improvement in nocturia (mean of nocturia decreased from 3.3 voids to 1.9 voids per night, $p < 0.001$) was achieved by a 8-week walking exercise programme (Sugaya et al. 2007). Furthermore, in a secondary analysis of an RCT, significant decrease of nocturia was achieved by a multicomponent behavioural

training programme (including pelvic floor muscle training) among incontinent, elderly women (Johnson et al. 2005a).

Reproductive factors. There are also potential limitations in the assessment of reproductive factors (Study V). We could not distinguish between delivery modes. This may be a minor limitation, given the little convincing evidence of its importance. No studies have examined the association between delivery mode and nocturia. Four earlier studies demonstrated no effect of delivery mode on prevalence of urgency, urgency incontinence or OAB (Parazzini et al. 2003, Handa et al. 2004, Zhang et al. 2006, van Brummen et al. 2007). By contrast, a study among customers of the Kaiser-Permanente health insurance plan found that those delivering vaginally were more likely to have OAB than those having Caesarean section (adjusted for parity, obesity and age) (Lukacz et al. 2006). The study was somewhat limited because of low participation (37%) and age differences between the groups (women delivering vaginally were older than those with Caesarean section). Hence, delivery mode seems not to be a risk factor of OAB in the earlier literature generally.

Another potential limitation is the lack of information on different surgical hysterectomy procedures and the indication for hysterectomy. This may not be an important limitation, as RCTs found no difference in prevalence of nocturia or urgency post-operatively between subtotal and total hysterectomies for benign indication with one (Thakar et al. 2002, Gimbel et al. 2005) or two-year (Learman et al. 2003) follow-up. Furthermore, reliability (Horwitz & Yu 1985) and validity (Brett & Madans 1994) of hysterectomy self-reporting has been established only for hysterectomy itself, not for the various techniques separately. Since post-operative nocturia and urgency RCTs comparing vaginal hysterectomy to other techniques are not available, current evidence suggests that surgical technique is unlikely to influence the effect (Roovers et al. 2001, Thakar & Sultan 2005). Additionally, no information was obtained in this study regarding type of SUI surgery. A Cochrane review found no difference in *de novo* detrusor overactivity after laparoscopic colposuspension compared to tension-free vaginal tape (Dean et al. 2006). RCTs reported no difference in *de novo* urgency incontinence after fascial sling compared to Burch colposuspension (Albo et al. 2007), or in *de novo* urgency after suburethral sling procedure by retropubic compared to transobturator route (Darai et al. 2007).

We had no laboratory (serum levels of follicle stimulating hormone) or other diagnostic studies to confirm menopausal status, which was based on reported menstruation during the past year. Those reporting hysterectomy or MHT were regarded as separate groups as their natural menopausal status remains unclear. We used age 40 years as a cut-off point for menopause, as amenorrhea is due to other reasons than menopause in the vast majority of women aged under 40 years (Nippita & Baber 2007). In our study, among women aged under 40 years, 46 (4%) reported no menstruation in the past year. Overall, we had abundant information on female reproductive factors compared to the earlier literature. However, further information on some aspects would have strengthened the study.

5.8 Use of questionnaire for assessment of nocturia

In this dissertation, the presence of nocturia is the main outcome. In the FINNO Study, we assessed occurrence and bother of LUTS by validated questionnaire instruments (primarily by DAN-PSS). In clinical trials, in addition to symptom questionnaires, FVCs (voiding diaries) have commonly been used as a primary tool for measuring LUTS. It is important to question whether a questionnaire is reliable for the assessment of nocturia episodes. Questionnaires have been reported to either overestimate (Ku et al. 2004, Yoshimura & Terai 2005) or underestimate (Blanker et al. 2000a), or neither (Jaffe et al. 2002, Stav et al. 2009) overestimate or underestimate prevalence estimates of nocturia.

Results from a recent retrospective US study suggested that women tend to overestimate their daytime urinary frequency, whereas they were accurate about their nocturnal frequency (Stav et al. 2009). The study was conducted among 601 women (aged 30 to 91) with completed FVC. The authors proposed that “awakening to the toilet is probably more bothersome and has more impact on patient memory” and “[d]uring the day patients can adjust urinary frequency. However, at night patients have less control over behaviour and urinary habits”. Both aspects were speculated to contribute to the overestimation of daytime, but not night-time frequency (when assessed by questionnaire compared to FVC). Overestimation was particularly marked

in patients who reported a daytime frequency greater than ten voids per day (Stav et al. 2009).

In the Krimpen study among a community-based sample of men aged 50 to 78, I-PSS nocturia item was compared to (3-day) FVC. Out of 3,924 contacted, 1,688 (50% of eligible men) responded to the questionnaire. Among those, 1,597 men completed the diary. However, nocturnal and diurnal voiding frequency could be estimated among 1,211 men (approximately 36% of eligible study sample; present author´s calculation) who also provided information on time of arising and bedtime. The results indicated a poor agreement between questionnaire and diary. Furthermore, questionnaires underestimated the prevalence of nocturia. A similar conclusion (although contradictorily stated) was also reported in a US study (Latini et al. 2004): poor agreement between questionnaire and FVC. In this particular study, the I-PSS nocturia question and FVC information were compared among 284 ambulatory men (aged 18 to 66, recruited by advertisements at hospitals). However, as stated by the authors, the main limitation of the study was comparing a 24-hour diary to the I-PSS assessing nocturia during the last month. Furthermore, there was no association between nocturia frequency and age thereby raising the question of the validity of the results (Latini et al. 2004).

There is no doubt as to whether questionnaires are vulnerable to recall bias: questionnaires rely on the subject's memory. He or she may totally forget an event or misrecall the timing. In earlier studies increasing accuracy of questionnaires (to estimate FVC result) has been found among those with few nocturia episodes (0, 1, or 2 voids/night) (Jaffe et al. 2002, Yoshimura & Terai 2005). These are ´the critical episodes´ in our nocturia case classification. Furthermore, *all* those who reported (by questionnaire) four, five, or six voids/night had at least two voids/night in the diary assessment in a recent US study (Jaffe et al. 2002). Hence, our classification of nocturia to two groups (subjects with <2 voids/night, and subjects with ≥2 voids/night) probably decreases the impact of recall uncertainty and bias. One can speculate that agreement between FVC and the questionnaire would have been better in earlier studies if fewer groups (of nocturia classification) had been used.

Questionnaires assess ´the typical frequency´ over a longer time period retrospectively (e.g. last month in the AUA-SI), whereas voiding diaries typically assess one, two, or three nights, or sometimes for one week prospectively. Hence, the studies compared two different time periods. The nights during FVC may not have been *typical*. Substantial temporal variation in the frequency of nocturnal voidings has been shown (Yoshimura & Terai 2005). Various reasons for such variation have been proposed, such as unusual fluid intake, unusual duration of time in bed, feeling colder or warmer during time in bed and more difficulty getting to sleep (Yoshimura & Terai 2005).

Earlier studies comparing questionnaires to FVCs used the I-PSS nocturia question (identical with the AUA-SI nocturia item). In the FINNO Study, responses to nocturia questions from the DAN-PSS (Schou et al. 1993) and the AUA-SI (Barry et al. 1992) were combined to assess occurrence of nocturia. In the case of conflict between the responses to the two questions, the DAN-PSS was regarded as the gold standard so that the DAN-PSS response nearer to the AUA-SI response was chosen. We have shown excellent consistency between the two nocturia questions. However, using the DAN-PSS as the ´gold standard´ question might provide a more reliable answer as the DAN-PSS nocturia question is shorter and probably easier to understand (both in English and Finnish) than AUA-SI (i.e. I-PSS) nocturia item.

Owing to the subjective and symptomatic nature of urinary incontinence, there is no gold standard for outcomes assessment (Dmochowski 2001). However, FVC is a key tool in diagnosing nocturia (Blanker et al. 2000a, Weiss 2006). By FVCs, one can assess nocturia episodes and *nocturnal polyuria*, the latter cannot be discovered by questionnaires. Hence, FVCs are indispensable in clinical practice (Weiss 2006). However, regarding the epidemiological research of nocturia, the case is unclear. Do diaries provide more accurate information in ´real-life research´? Besides the fluctuating character of nocturia, two other aspects are also important: 1) whether it is possible to obtain a representative sample when using diaries (of several days), and 2) whether FVCs impact on ´normal voiding habits´. When studying the prevalence and risk factors of nocturia, one should perform research at population level to avoid selection bias. The only large-scale study comparing diaries and questionnaires at population-level is the Krimpen study (conducted among men aged 50 to 78) (Blanker

et al. 2000a). Diaries were fully completed by 36% of the eligible study sample. In the FINNO Study, nocturia information was provided by more than 70% of men aged 50 to 79 years. The reason for this clear difference in response proportion is obvious. Completing a FVC (especially documenting volumes voided) is much more troublesome and time-consuming than filling in a questionnaire. Studies using FVCs (with lower response proportions) use probably more selected samples (non-response and non-compliance bias). It is harder to recruit subjects with less symptoms: this is also supported by higher I-PSS score among participants (than among non-participants) in the Krimpen study (Blanker et al. 2000a). Another unclear aspect is the potential psychological impact of the diary on the subject. Participating in a prospective FVC evaluation may alter voiding habits. Remarkable placebo response, which is commonly seen in drug trials may partly be due to the effect of FVC assessment (´bladder training effect´) (Stav et al. 2009).

Is questionnaire or FVC more reliable for the assessment of nocturia episodes? In a population-based study of all adult ages (also including young subjects with much less LUTS), this is a very difficult question to answer. Ideally, FVCs provide more (accurate) information, including information on NP. In reality, one should take into account: 1) increased selection bias, 2) fluctuating character of nocturia, and 3) possible impact of prospective evaluation on nocturnal voiding habits.

5.9 Future aspects

Present research findings show that nocturia is bothersome and associated with HRQL impairment. FINNO Study results suggest that nocturia has multifactorial background. Based on a review of the earlier literature and FINNO Study results, certain areas are proposed as top priority for future research:

1) Epidemiological research in general:

What is the ´best´ definition for incidental nocturia?

What are the most important (incidental) risk/causal factors for nocturia?

What is the impact of nocturia (e.g. major risk factor for fractures)?

Does nocturia predict mortality (after appropriate adjustments)?

2) Treatment of nocturia:

What is the comparative effectiveness of surgical, pharmacological, behavioural and combination treatments of nocturia on HRQL, morbidity and ultimately on mortality?

3) Nocturia and obesity specifically:

Can weight control and physical activity prevent the onset or increase of nocturia?

What is the effectiveness of weight loss for nocturia among overweight/obese subjects with nocturia?

These issues should be addressed in prospective cohort studies and RCTs.

6. Conclusions

Most studies have reported nocturia to be equally common among men and women. The overall results of our study confirm this finding, as approximately 40% of both men and women reported voiding at least once per night and approximately every eighth of both genders at least twice per night. However, in more detailed analyses clear differences between the genders emerged. Nocturia was more common among young women than men, but the prevalence among men reached that among women in middle age and exceeded that after age 60 years. We also found that the prevalence of OAB has been overestimated and that the true prevalence is approximately half of that proposed earlier. OAB affects approximately one out of twelve adults of Caucasian origin.

Generally, nocturia is a bothersome symptom for more than a fifth of general population (for a quarter of those moderate or major bother) and is associated with impaired quality of life. Our findings indicate that two episodes of nocturia constitute meaningful nocturia affecting well-being and perceived health, while a single episode does not. Three or more voids have a moderate effect on well-being. Frequency of nocturia is a strong determinant of problems, disruption, and resulting bother. This also contributes to the definition of treatment targets (i.e. significant nocturia reduction).

At population level, OAB, BPH and snoring for men, and overweight/obesity, OAB and snoring for women explained the largest proportion of nocturia, while obesity and antidepressant use in men, diabetes and CAD in women, and RLS in both sexes had less impact. Even though numerous risk factors for nocturia were identified, none of these was associated with nocturia in more than half of the affected subjects of both sexes, highlighting the multifactorial etiology. The clinical implication of this work is that health care providers should consider the lower urinary tract, but also beyond it, when treating bothersome nocturia.

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Appendices

Appendix 1. Analyses and exclusions in Study II in the FINNO Study, Finland, 2003-2004.[a]

Name of the analysis	Aim of the analysis	Exclusions performed
Urgency analysis	Prevalence of urgency in adult population	No exclusions
Overactive bladder analysis	Prevalence of OAB in adult population	Those with urinary tract infection or other obvious pathology referring to genitourinary cancer, excluding renal cancer; contracted bladder due to radiation or painful bladder syndrome; also prescribed loop diuretics; pregnant and puerperal women
All OAB symptoms analysis	Relationship of all symptoms of OAB	Same exclusions as in ´Overactive bladder analysis´

[a] We also performed ´OAB without BPH analysis´ where in addition to exclusions of ´Overactive bladder analysis´ also men with physician-diagnosed benign prostatic hyperplasia were excluded.

Appendix 2. Questionnaire

Kyselytutkimus [xxxx]

Huomatkaa, että kyselylomake on kaksipuolinen.

Tämän lomakkeen täyttämispäivämäärä. Tänään on ____/____ 2003.

Yleiset tiedot

1. Mikä on syntymävuotenne ja sukupuolenne?

Syntymävuosi *19_____*

Sukupuoli

1 mies
2 nainen

2. Mikä on nykyinen siviilisäätynne?

1 yksineläjä
2 avoliitossa/avioliitossa
3 eronnut
4 leski

3. Mikä seuraavista kuvaa saamaanne koulutusta?

1 perustaso (kansakoulu tai peruskoulu)
2 ammatillinen koulutus
3 opistotaso
4 yliopisto tai korkeakoulu

4. Oletteko ollut pääsääntöisesti (viimeksi kuluneiden kolmen kuukauden aikana)?

1 opiskelija
2 työllinen (ansiotyö, hoitovapaa, ...)
3 työtön (mukaanlukien pakkoloman)
4 eläkkeellä

5. Jos olette töissä, niin kuinka monta päivää olette viimeksi kuluneiden kolmen kuukauden aikana ollut töistä pois sairauden takia?

_____ *päivää*

6. Kuinka pitkä olette? _____ *senttimetriä*

7. Kuinka paljon painatte? _____ *kilogrammaa*

Aiemmat ja nykyiset sairaudet

8. Onko lääkäri todennut Teillä jonkin tai joitakin seuraavista sairauksista? (ympyröikää tarvittaessa useampia vaihtoehtoja)

Neurologiset sairaudet	1	Parkinsonin tauti
	2	Epilepsia
	3	MS-tauti
	4	Selkäydinvamma
	5	Muu neurologinen sairaus, mikä
		_____
Unihäiriöt	6	Uniapnea
	7	Levottomat jalat
	8	Narkolepsia
Psykiatriset sairaudet	9	Mielialahäiröt (esim. masennus)
	10	Ahdistuneisuushäiriöt/paniikkihäiriö
	11	Muu psykiatrinen sairaus, mikä
		_____
Muut yleiset sairaudet (urologiset sairaudet kysytään erikseen)	12	Sepelvaltimotauti
	13	Verenpainetauti
	14	Diabetes (sokeritauti)
	15	Keuhkoahtaumatauti (COPD) tai astma
	16	Reumasairaudet (esim. nivelreuma)
	17	Nivelkuluma (artroosi)
	18	Syöpätaudit, mikä
		_____
	19	Muu sairaus, mikä
		_____
		_____
		_____
		_____
		_____
		_____

9 **Urologiset sairaudet ja oireet** (tarvittaessa ympyröikää useampia kohtia)

Virtsapidätyskyvyn ongelmat

9.1 Onko Teillä virtsankarkaamista?

0 Ei
1 Kyllä

9.2 Jos Teillä on virtsanpidätyskyvyn ongelmia, niin mitä seuraavista:

1 Virtsan karkaamista ponnistaessa
2 Virtsan karkaamista äkillisen virtsaamispakon yhteydessä
3 Virtsan karkaamista sekä ponnistaessa että äkillisen virtsaamispakon yhteydessä
4 Virtsan jälkitiputtelua virtsaamisen jälkeen
5 Muuta, mitä _____

Eturauhasen sairaudet (Kohdat 9.3 – 9.6 koskettavat vain miehiä)

9.3 Onko lääkäri todennut Teillä *eturauhasen hyvänlaatuisen liikakasvun*?

0 Ei
1 Kyllä

9.4a Jos vastasitte ”kyllä” (kysymykseen 9.3), niin onko liikakasvua hoidettu lääkkein?

0 Ei
1 Kyllä

Lääkkeiden kauppanimet:

_____

9.4b Jos vastasitte ”kyllä” (kysymykseen 9.3), niin onko liikakasvua hoidettu höyläämällä tai leikkaamalla?

0 Ei
1 Kyllä

Ympyröikää, jos Teillä on jokin alla olevista sairauksista:

Eturauhasen sairaudet (ympyröikää tarvittaessa yksi tai useampia kohtia)

9.5 Krooninen eturauhastulehdus

9.6 Eturauhassyöpä

Virtsarakon sairaudet (myös naiset)

9.7 Krooninen virtsatietulehdus

9.8 Virtsarakon syöpä

9.9 Kutistusrakko (esimerkiksi sädehoidon pohjalta tai interstitielli kystiitti)

10. Seuraavat kysymykset käsittelevät erilaisia virtsaamiseen liittyviä oireita.

Tämä kysely koostuu kahdenlaisista kysymyksistä:
* A-kysymyksissä kysytään, kuinka ***voimakas*** oire on, ja
* B-kysymyksissä kysytään, kuinka paljon ***haittaa*** Teille on oireesta.

Vastatkaa jokaisen 12 kysymyksen kohdalla, kuinka voimakas ja kuinka häiritsevä kyseinen oire on ympyröimällä kohta, joka parhaiten kuvaa tilannettanne.

Mikäli olette A-kysymykseen ympyröineet "0"-kohdan, jättäkää vastamatta B-kysymkseen.

Kysymykset koskevat **viimeksi kulunutta 2 viikkoa**.

1 A	Täytyykö virtsaamisen alkamista odottaa?		1 B	Mikäli joudutte odottamaan virtsaamisen alkamista kuinka paljon siitä on Teille haittaa?	
	Ei koskaan	0		Ei lainkaan	0
	Harvoin	1		Vähän	1
	Usein	2		Kohtalaisesti	2
	Aina	3		Hyvin paljon	3
2 A	Tuleeko virtsa omasta mielestänne:		2 B	Mikäli virtsa tulee heikosti, kuinka paljon siitä on Teille haittaa?	
	Normaalisti	0		Ei lainkaan	0
	Heikosti	1		Vähän	1
	Hyvin heikosti	2		Kohtalaisesti	2
	Tipoittain	3		Hyvin paljon	3
3 A	Tuntuuko, että virtsatessanne rakko tyhjenee täysin?		3 B	Mikäli tuntuu, ettei rakko tyhjene täysin, kuinka paljon siitä on Teille haittaa?	
	Kyllä, aina	0		Ei lainkaan	0
	Usein	1		Vähän	1
	Harvoin	2		Kohtalaisesti	2
	Ei koskaan	3		Hyvin paljon	3
4 A	Joudutteko ponnistamaan virtsaamisen aloittamiseksi ja/tai virtsaamisen jatkamiseksi?		4 B	Mikäli joudutte ponnistelemaan, kuinka paljon siitä on Teille haittaa?	
	En koskaan	0		Ei lainkaan	0
	Harvoin	1		Vähän	1
	Usein	2		Kohtalaisesti	2
	Aina	3		Hyvin paljon	3

5 A	Mikä on pisin aika kahden virtsaamisen välillä noustuanne aamulla ylös ja ennen kuin menette illalla nukkumaan?		5 B	Mikäli joudutte virtsaamaan usein, kuinka paljon siitä on Teille haittaa?	
	Yli 3 tuntia	0		Ei lainkaan	0
	2 - 3 tuntia	1		Vähän	1
	1 - 2 tuntia	2		Kohtalaisesti	2
	Alle tunnin	3		Hyvin paljon	3
6 A	Kuinka monta kertaa joudutte virtsaamaan yön aikana?		6 B	Mikäli joudutte virtsaamaan yön aikana, kuinka paljon siitä on Teille haittaa?	
	0 kertaa	0		Ei lainkaan	0
	1 - 2 kertaa	1		Vähän	1
	3 - 4 kertaa	2		Kohtalaisesti	2
	5 kertaa tai useammin	3		Hyvin paljon	3
7 A	Tuleeko Teille äkillinen virtsaamistarve?		7 B	Mikäli Teille tulee äkillinen virtsaamistarve, kuinka paljon siitä on Teille haittaa?	
	Ei koskaan	0		Ei lainkaan	0
	Harvoin	1		Vähän	1
	Usein	2		Kohtalaisesti	2
	Aina	3		Hyvin paljon	3
8 A	Tuleeko virtsaamistarve niin voimakkaana, että virtsa karkaa ennen kuin ehditte WC:hen?		8 B	Mikäli ette pysty pidättelemään virtsaa, kunnes ehditte WC:hen, kuinka paljon siitä on Teille haittaa?	
	Ei koskaan	0		Ei lainkaan	0
	Harvoin	1		Vähän	1
	Usein	2		Kohtalaisesti	2
	Aina	3		Hyvin paljon	3
9 A	Tuntuuko virtsatessa kipua tai poltetta?		9 B	Mikäli virtsatessa tuntuu kipua tai poltetta, kuinka paljon siitä on Teille haittaa?	
	Ei koskaan	0		Ei lainkaan	0
	Harvoin	1		Vähän	1
	Usein	2		Kohtalaisesti	2
	Aina	3		Hyvin paljon	3

10 A	Tippuuko virtsaa vielä, vaikka luulitte virtsaamisen loppuneen (jälitippuminen)?		10 B	Mikäli jälkitippumista esiintyy, vaikka luulitte virtsaamisen loppuneen, kuinka paljon siitä on Teille haittaa?	
	Ei koskaan	0		Ei lainkaan	0
	Harvoin	1		Vähän	1
	Usein	2		Kohtalaisesti	2
	Aina	3		Hyvin paljon	3

(Seuraavat kysymykset eivät koske jälkitippumista)

11 A	Karkaako virtsaa fyysisen ponnistuksen aikana (esim. yskiessä, aivastaessa, nostaessanne jotain)?		11 B	Mikäli virtsa karkaa fyysisen ponnistuksen aikana, kuinka paljon siitä on Teille haittaa?	
	Ei koskaan	0		Ei lainkaan	0
	Harvoin	1		Vähän	1
	Usein	2		Kohtalaisesti	2
	Aina	3		Hyvin paljon	3

(Seuraavat kysymykset eivät koske jälkitippumista)

12 A	Karkaako virtsaa ilman fyysistä ponnistusta ja ilman virtsaustarvetta?		12 B	Mikäli virtsaa karkaa ilman virtsaustarvetta ja fyysistä ponnistusta, kuinka paljon siitä on Teille haittaa?	
	Ei koskaan	0		Ei lainkaan	0
	Harvoin	1		Vähän	1
	Usein	2		Kohtalaisesti	2
	Aina	3		Hyvin paljon	3

11. Kuinka monta kertaa olette käynyt virtsaamassa keskimäärin koko päivän aikana viimeksi kuluneen kuukauden aikana?

Keskimäärin _____ kertaa vuorokauden aikana.

12.1 Kuinka säännöllisesti olette joutunut yöllä virtsaamaan viimeksi kuluneen kuukauden aikana?

0 En lainkaan tai vähemmän kuin kerran kuussa
1 Alle kerran viikossa mutta useammin kuin kerran kuussa
2 1 – 2 kertaa viikossa
3 3 –5 kertaa viikossa
4 päivittäin tai lähes päivittäin

12.2 Kuinka usein viimeksi kuluneen kuukauden aikana olette tavallisimmin joutunut nousemaan virtsalle mentyänne illalla nukkumaan ja ennen kuin nousitte aamulla ylös?

0 en kertaakaan
1 kerran yössä
2 kaksi kertaa yössä
3 kolme kertaa yössä
4 neljä kertaa yössä
5 viisi kertaa tai useammin yössä

13.1 Onko Teille koskaan sattunut tapaturmaa noustuanne yöllä virtsaamaan?

0 Ei
1 Kyllä

Jos vastasitte kyllä, niin mitä? _____

Kuinka monta kertaa? _____ *kertaa*

13.2 Kuinka nopeasti yleensä nukahdatte herättyänne virtsaamaan?

Nukahtaminen kestää yleensä noin _____ minuuuttia.

14. Oletteko saanut antibioottikuurin virtsatietulehdukseen **viimeksi kuluneen kahden viikon aikana**?

0 Ei
1 Kyllä

15. Oletteko käyttänyt reseptillä määrättyjä **sydän-, verenpaine- tai nesteenpoistolääkkeitä** viimeksi kuluneiden kahden viikon aikana?

0 En lainkaan
1 Kyllä, tarvittaessa tai kuuriluontoisesti
2 Kyllä, säännöllisesti

Mitä lääkkeitä (jatkuu tarvittaessa seuraavalla sivulla):

Lääkkeen nimi	Ympyröikää kohdan 15 vastaus alle.	Vahvuus	Annos/vrk (tabl/vrk)	Pakkauskoko
	0 1 2			
	0 1 2			
	0 1 2			
	0 1 2			

Lääkkeen nimi	Ympyröikää kohdan 15 vastaus alle.	Vahvuus	Annos/vrk (tabl/vrk)	Pakkauskoko
	0 1 2			
	0 1 2			
	0 1 2			
	0 1 2			

16. Nukkumiseen ja unen laatuun liittyviä kysymyksiä

Pyydämme vastaamaan alla oleviin kysymyksiin **viimeisten kahden viikon** osalta.

16.1 Kuinka usein olette herännyt yöllä viimeisten kahden viikon kuluessa?

1 En koskaan tai harvemmin kuin kerran kuussa
2 Harvemmin kuin kerran viikossa
3 1-2 päivänä viikossa
4 3-5 päivänä viikossa
5 Päivittäin tai lähes päivittäin

16.2 Jos heräätte yleensä yöllä, kuinka monta kertaa yössä olette yleensä herännyt?

1 En yleensä herää öisin
2 Kerran yössä
3 Kahdesti yössä
4 3-4 kertaa yössä
5 Ainakin 5 kertaa yössä

16.3 Kuinka usein olette herännyt liian aikaisin aamulla pystymättä enää nukahtamaan uudelleen?

1 En kertaakaan tai harvemmin kuin kerran kuussa
2 Harvemmin kuin kerran viikossa
3 1-2 päivänä viikossa
4 3-5 päivänä viikossa
5 Päivittäin tai lähes päivittäin

16.4 Kuinka hyvin olette nukkunut viimeksi kuluneiden kahden viikon aikana?

1 Hyvin
2 Melko hyvin
3 En hyvin enkä huonosti
4 Melko huonosti
5 Huonosti

16.5 Kuinka pitkä on yöunenne yleensä?

Nukun yleensä _____ tuntia yössä.

16.6 Mihin aikaan menette yleensä nukkumaan iltaisin?

1 *Työpäivinä klo* _____

2 *Vapaapäivinä klo* _____

16.7 Mihin aikaan yleensä heräätte aamuisin?

1 *Työpäivinä klo* _____

2 *Vapaapäivinä klo* _____

16.8 Kuorsaatteko nukkuessanne? (Kysykää muilta, jos ette tiedä varmasti)

1 *Kerran kuussa tai harvemmin*
2 *Harvemmin kuin kerran viikossa*
3 *1-2 yönä viikossa*
4 *3-5 yönä viikossa*
5 *Joka yö tai lähes joka yö*

16.9 Millaista kuorsauksenne on laadultaan? (Kysykää tarvittaessa muilta)

1 *En kuorsaa*
2 *Kuorsaan hiljaa ja tasaisesti*
3 *Kuorsaan tasaisesti mutta melko äänekkäästi*
4 *Kuorsaan tasaisesti mutta niin äänekkäästi, että se kuuluu viereiseen huoneeseen*
5 *Kuorsaan hyvin äänekkäästi ja epätasaisesti (välillä on hengityskatkoja, jolloin ei kuulu mitään ääntä ja välillä kuuluu hyvin kovaa korahtelevaa kuorsausta)*

16.10 Oletteko huomannut (tai ovatko muut huomanneet) hengityskatkoja unessa?

1 *Ei koskaan tai harvemmin kuin kerran kuussa*
2 *Harvemmin kuin kerran viikossa*
3 *1-2 yönä viikossa*
4 *3-5 yönä viikossa*
5 *Joka yö tai lähes joka yö*

16.11 Kuinka monta tuntia unta tarvitsette yössä (kuinka monta tuntia nukkuisitte, jos voisitte nukkua niin pitkään kuin haluatte)?

Tarvitsen _____ tuntia ja _____ minuuttia yöunta.

Lääkkeiden ja terveyspalveluiden käyttö (viimeiset kolme kuukautta)

17.1 Oletteko käyttänyt **yövirtsaamisvaivoihin** tarkoitettuja **reseptillä** määrättyjä lääkkeitä viimeksi kuluneiden kolmen kuukauden aikana?

0 *En lainkaan*
1 *Kyllä, tarvittaessa tai kuuriluontoisesti*
2 *Kyllä, säännöllisesti*

17.2 Jos vastasitte ”kyllä”, niin kuinka usein niitä käytätte?

1 *Harvemmin kuin kerran kuussa*
2 *Harvemmin kuin kerran viikossa*
3 *1-2 päivänä viikossa*
4 *3-5 päivänä viikossa*
5 *Päivittäin tai lähes päivittäin*

Mitä lääkkeitä **yövirtsaamisvaivoihin**?

Lääkkeen nimi	Ympyröikää kohdan 17.2 vastaus alle.	Vahvuus	Annos/vrk (tabl/vrk)	Pakkauskoko
	1 2 3 4 5			
	1 2 3 4 5			
	1 2 3 4 5			

18. Oletteko käyttänyt **muihin virtsaamisvaivoihin** tarkoitettuja **reseptillä** määrättyjä lääkkeitä viimeksi kuluneiden kolmen kuukauden aikana?

0 *En lainkaan tai harvemmin kuin kerran kuussa*
1 *Harvemmin kuin kerran viikossa*
2 *1-2 päivänä viikossa*
3 *3-5 päivänä viikossa*
4 *Päivittäin tai lähes päivittäin*

Mitä **virtsaamisvaivoihin tarkoitettuja lääkkeitä**?

Lääkkeen nimi	Ympyröikää kohdan 18 vastaus alle.	Vahvuus	Annos/vrk (tabl/vrk)	Pakkauskoko
	1 2 3 4 5			
	1 2 3 4 5			
	1 2 3 4 5			
	1 2 3 4 5			

19. Oletteko käyttänyt **reseptillä** määrättyjä **unilääkkeitä** viimeksi kuluneiden kolmen kuukauden aikana?

0 *En lainkaan tai harvemmin kuin kerran kuussa*
1 *Harvemmin kuin kerran viikossa*
2 *1-2 päivänä viikossa*
3 *3-5 päivänä viikossa*
4 *Päivittäin tai lähes päivittäin*

Mitä **unilääkkeitä**?

Lääkkeen nimi	Ympyröikää kohdan 19 vastaus alle.	Vahvuus	Annos/vrk (tabl/vrk)	Pakkauskoko
	1 2 3 4 5			
	1 2 3 4 5			
	1 2 3 4 5			

20.1 Mitä muita **reseptillä** määrättyjä **lääkkeitä** käytätte tai olette käyttänyt viimeksi kuluneiden kolmen kuukauden aikana?

Lääkkeen nimi	Vahvuus	Annos/vrk (tabl/vrk)	Pakkauskoko

20.2 Mitä muita **lääkärin määrämiä** hoitoja olette saanut **yövirtsaamisvaivaan** viimeksi kuluneiden kolmen kuukauden aikana? (esimerkiksi fysikaalinen hoito)

Mikä hoito?	Kuinka monta kertaa?
1. _____	_____
2. _____	_____
3. _____	_____

21.1 Oletteko käyttänyt **yövirtsaamisvaivaan** tarkoitettuja **luontaistuotteita, yrttejä, lisäravinteita tai muita vastaavia tuotteita** viimeksi kuluneiden kolmen kuukauden aikana?

0 *En lainkaan*
1 *Kerran kuussa tai harvemmin*
2 *Harvemmin kuin kerran viikossa*
3 *1-2 päivänä viikossa*
4 *3-5 päivänä viikossa*
5 *Päivittäin tai lähes päivittäin*

Mitä tuotteita?

1. _____
2. _____
3. _____

21.2 Oletteko hoitanut **nimenomaan yövirtsaamisvaivaa** muilla vaihtoehtoisilla täydentävillä menetelmillä (jooga, erilaiset hieronnat, akupunktio, muut menetelmät) viimeksi kuluneiden kolmen kuukauden aikana?

1 *En lainkaan tai harvemmin kuin kerran kuussa*
2 *Harvemmin kuin kerran viikossa*
3 *1-2 päivänä viikossa*
4 *3-5 päivänä viikossa*
5 *Päivittäin tai lähes päivittäin*

Millä keinoin?

1. _____
2. _____
3. _____

22.1 Oletteko joutunut käyttämään **öisin karkaussuojia** (vaipat jms.) viimeisen kolmen kuukauden aikana?

0 *En*
1 Kyllä

22.2 Jos vastasitte kyllä, niin kuinka paljon olette kuluttanut **rahaa karkaussuojiin** arviolta viimeisen kolmen kuukauden aikana?

_____ *euroa (€)*

23. Kuinka paljon arvioitte, että olette käyttänyt **rahaa virtsaamisvaivojen** viimeisen kolmen kuukauden aikana?

Lääkärissäkäynnit	_____ €
Muut hoidot	_____ €
Lääkkeet	_____ €
Luontaistuotteet ja muut vastaavat tuotteet	_____ €
Muut tarvikkeet	_____ €
Muut kulut	_____ €
YHTEENSÄ	_____ €

24.1 Oletteko joutunut rajoittamaan juomista ennen nukkumaan menoa yövirtsaamisen takia?

0 *En*
1 Harvoin
2 Usein
3 Aina

Jos vastasitte ”En” 24.1-kohtaan, niin voitte jättää vastaamatta 24.2- ja 24.3-kohtiin.

24.2 Jos olette joutuneet rajoittamaan juomista, niin kuinka monta tuntia ennen nukkumaanmenoa rajoitatte juomista?

_____ *tuntia*

24.3 Kun rajoitatte juomistanne, niin miten sen teette?
(parhaiten sopiva vaihtoehto)

0 En juo mitään
1 Juon vain vettä
2 Rajoitan joidenkin juomien käyttämistä (esim. alkoholi, kahvi)
3 Juon samoja juomia kuin muutenkin, mutta pienemmän määrän

25.1 Oletteko käynyt lääkärissä viimeksi kuluneiden kolmen kuukauden aikana **yöllisen virtsaamistarpeen** takia?

0 En
1 Kyllä

25.1 Jos vastasitte ”kyllä”, niin minkä alan lääkärillä kävitte ja kuinka usein? (voi ympyröidä useita)?

1 Yleislääkärillä, _____ kertaa
2 Urologilla (virtsaelinkirurgi), _____kertaa
3 Gynekologilla (naistentautien erikoislääkäri), _____ kertaa
4 Muulla erikoislääkärillä, _____ kertaa

26.1 Oletteko käynyt lääkärissä viimeksi kuluneiden kolmen kuukauden aikana *väsymyksen* takia?

0 En
1 Kyllä

26.2 Jos vastasitte ”kyllä”, niin minkä alan lääkärillä kävitte ja kuinka usein? (voi ympyröidä useita)?

1 Yleislääkärillä, _____ kertaa
2 Minkä alan erikoislääkärillä?
_____, _____ kertaa
_____, _____ kertaa

Elämäntavat

27.1 Kuinka monta kupillista kahvia juotte tavallisesti päivässä?

_____ *kupillista päivässä*

27.2 Kuinka paljon juotte muita kofeiinipitoisia juomia päivässä (kolajuomat, energiajuomat)?

_____ *desilitraa päivässä*

28. Kuinka monta annosta yhteensä nautitte alkoholia viikossa? (annos vastaa keskimäärin pulloa keskiolutta (33 cl), lasillista viiniä (12 cl) tai ravintola-annosta viinaa (4 cl))

_____ *annosta viikossa*

29.1 Oletteko koskaan polttanut tupakkaa (savuke/piippu/sikari)?

0 *En*
1 *Kyllä*

29.2 Poltatteko edelleen?

0 *En*
1 *Kyllä*

29.3 Jos ette enää tupakoi, niin koska lopetitte? _____ *vuotta sitten*

29.4 Jos tupakoitte, niin kuinka monta savuketta/piipullista/sikaria keskimäärin?

1 *1 – 10 tupakkaa päivässä*
2 *11 – 20 tupakkaa päivässä*
3 *yli 20 tupakkaa päivässä*

30.1 Oletteko koskaan käyttänyt nuuskaa?

0 *En*
1 *Kyllä*

30.2 Nuuskaatteko edelleen?

0 *En*
1 *Kyllä*

30.3 Jos ette enää nuuskaa, niin koska lopetitte? _____ *vuotta sitten*

30.4 Jos nuuskaatte, niin kuinka monta annosta keskimäärin?

1 *1 – 10 annosta päivässä*
2 *11 – 20 annosta päivässä*
3 *yli 20 annosta päivässä*

Vain naisille seuraavat kysymykset (31.1 – 31.4):

31.1 Onko Teillä ollut viimeisen 12 kuukauden aikana kuukautisia?

0 *Ei*
1 *Kyllä*

31.2 Onko Teiltä poistettu kohtu?

0 *Ei*
1 *Kyllä*

31.3 Käytättekö hormonikorvaushoitoa vaihdevuosioireiden hoitoon?

0 *En*
1 *Kyllä*

31.4 Jos vastasitte ”kyllä”, niin käytättekö?

1 *Paikallishoitoa*
2 *Tablettihoitoa*
3 *Laastaria*

31.5 Onko teillä käytössä virtsankarkaamista estävä tuki eli ns. emätintuki?

0 *Ei*
1 *Kyllä*

31.6 Onko teille tehty leikkaus ponnistukseen liittyvän virtsankarkaamisen vuoksi?

0 *Ei*
1 *Kyllä, _____ vuotta sitten*

32. **KAIKILLE YLEISEEN TERVEYDENTILAAN LIITTYVIÄ KYSYMYKSIÄ**

Lukekaa seuraavissa kysymyksissä ensin huolellisesti läpi kunkin kysymyksen kaikki vastausvaihtoehdot ja ympyröikää sitten sen vaihtoehdon numero, joka parhaiten kuvaa **terveydentilaanne tai toimintakykyänne tänään.** Ympyröikää siis kustakin kysymyksestä yksi vaihtoehto, ellei kysymyksen kohdalla pyydetä toisin. Jos mikään vaihtoehto ei sovi aivan tarkasti, valitkaa lähinnä sopivin vaihtoehto.

Kysymyksissä saattaa tuntua esiintyvän toistoa, mutta on tärkeää, että vastaatte jokaiseen kysymykseen, sillä yhdessä ne muodostavat terveydentilaanne kuvaavan kokonaisuuden. Työskennelkää suhteellisen ripeästi takertumatta turhaan yksityiskohtiin.

30.1 Liikuntakyky

1 *Pystyn kävelemään normaalisti (vaikeuksitta) sisällä, ulkona ja portaissa.*
2 *Pystyn kävelemään vaikeuksitta sisällä, mutta ulkona ja/tai portaissa on pieniä vaikeuksia.*
3 *Pystyn kävelemään ilman apua sisällä (apuvälinein tai ilman), mutta ulkona ja/tai portaissa melkoisin vaikeuksin tai toisen avustamana.*
4 *Pystyn kävelemään sisälläkin vain toisen avustamana.*
5 *Olen ollut täysin liikuntakyvytön ja vuoteenomana.*

30.2 Näkö

1 Näen normaalisti eli näen lukea lehteä ja TV:n tekstejä vaikeuksitta (silmälaseilla tai ilman).
2 Näen lukea lehteä ja/tai TV:n tekstejä pienin vaikeuksin (silmälaseilla tai ilman).
3 Näen lukea lehteä tai TV:n tekstejä huomattavin vaikeuksin (silmälaseilla tai ilman).
4 En näe lukea lehteä tai TV:n tekstejä silmälaseilla tai niiden kanssa, mutta näen (näkisin) kulkea ilman opasta.
5 En näe (näkisi) kulkea ilman opasta eli olen lähes täysin sokea.

30.3 Kuulo

1 Kuulen normaalisti eli kuulen hyvin normaalia puheääntä (kuulokojeen kanssa tai ilman).
2 Kuulen normaalia puheääntä pienin vaikeuksin.
3 Kuulen normaalia puheääntä melkoisin vaikeuksin, keskustelussa on käytettävä normaalia kovempaa puheääntä.
4 Kuulen kovaakin puheääntä heikosti, olen melkein kuuro.
5 Olen täysin kuuro.

30.4 Hengitys

1 Pystyn hengittämään normaalisti eli minulla ei ole hengenahdistusta tai muita hengitysvaikeuksia.
2 Minulla on hengenahdistusta raskaassa työssä tai urheillessa, reippaassa kävelyssä tasamaalla tai lievässä ylämäessä.
3 Minulla on hengenahdistusta kävellessäni muitten samanikäisten vauhtia tasamaalla.
4 Minulla on hengenahdistusta pienenkin rasituksen jälkeen, esim. peseytyessä tai pukeutuessa.
5 Minulla on hengenahdistusta lähes koko ajan, myös levossa.

30.5 Nukkuminen

1 Nukun normaalisti eikä minulla ole mitään ongelmia unen suhteen.

2 Minulla on lieviä uniongelmia, esim. nukahtamisvaikeuksia tai heräilen satunnaisesti yöllä.

3 Minulla on melkoisia uniongelmia, esim. nukun levottomasti, uni ei tunnu riittävältä.

4 Minulla on suuria uniongelmia, esim. joudun käyttämään usein tai säännöllisesti unilääkettä, herään säännöllisesti yöllä ja / tai aamuisin liian varhain.

5 Kärsin vaikeasta unettomuudesta, esim. unilääkkeiden käytöstä huolimatta nukkuminen on lähes mahdotonta, valvon suurimman osan yöstä.

30.6 Syöminen

1 Pystyn syömään normaalisti eli itse ilman mitään vaikeuksia.

2 Pystyn syömään itse pienin vaikeuksin (esim. hitaasti, kömpelösti, vavisten tai erityisapuneuvoin).

3 Tarvitsen hieman toisen apua syömisessä.

4 En pysty syömään itse lainkaan, vaan minua pitää syöttää.

5 En pysty syömään itse lainkaan, vaan minua pitää syöttää joko letkulla tai suonen sisäisellä ravintoliuoksella.

30.7 Puhuminen

1 Pystyn puhumaan normaalisti eli selvästi, kuuluvasti ja sujuvasti.

2 Puhuminen tuottaa minulle pieniä vaikeuksia, esim. sanoja on etsittävä tai ääni ei ole riittävän kuuluva tai se vaihtaa korkeutta.

3 Pystyn puhumaan ymmärrettävästi, mutta katkonaisesti, ääni vavisten, sammaltaen tai änkyttäen.

4 Muilla on vaikeuksia ymmärtää puhettani.

5 Pystyn ilmaisemaan itseäni vain elein.

30.8 Eritystoiminta

1 Virtsarakkoni ja suolistoni toimivat normaalisti ja ongelmitta.

2 Virtsarakkoni ja/tai suolistoni toiminnassa on lieviä ongelmia, esim. minulla on virtsaamisvaikeuksia tai kova tai löysä vatsa.

3 Virtsarakkoni ja/tai suolistoni toiminnassa on melkoisia ongelmia, esim. minulla on satunnaisia virtsanpidätysvaikeuksia tai vaikea ummetus tai ripuli.

4 Virtsarakkoni ja/tai suolistoni toiminnassa on suuria ongelmia, esim. minulla on säännöllisesti ”vahinkoja” tai peräruiskeiden tai katetroinnin tarvetta.

5 En hallitse lainkaan virtsaamista ja/tai ulostamista.

30.9 Tavanomaiset toiminnot

1 Pystyn suoriutumaan normaalisti tavanomaisista toiminnoista (esim. ansiotyö, opiskelu, kotityö, vapaa-ajan toiminnot).

2 Pystyn suoriutumaan tavanomaisista toiminnoista hieman alentuneella teholla tai pienin vaikeuksin.

3 Pystyn suoriutumaan tavanomaisista toiminnoista huomattavasti alentuneella teholla tai huomattavin vaikeuksin tai vain osaksi.

4 Pystyn suoriutumaan tavanomaisista toiminnoista vain pieneltä osin.

5 En pysty suoriutumaan lainkaan tavanomaisista toiminnoistani.

30.10 Henkinen toiminta

1 Pystyn ajattelemaan selkeästi ja johdonmukaisesti, muistini toimii täysin moitteettomasti.

2 Minulla on lieviä vaikeuksia ajatella selkeästi ja johdonmukaisesti, muistini ei toimi täysin moitteettomasti.

3 Minulla on melkoisia vaikeuksia ajatella selkeästi ja johdonmukaisesti, minulla on jonkin verran muistinmenetystä.

4 Minulla on suuria vaikeuksia ajatella selkeästi ja johdonmukaisesti, minulla on huomattavaa muistinmenetystä.

5 Olen koko ajan sekaisin ja vailla ajan ja paikan tajua.

30.11 Vaivat ja oireet

1 Minulla ei ole mitään vaivoja tai oireita, esim. kipua, pahoinvointia, kutinaa jne.

2 Minulla on lieviä vaivoja ja oireita, esim. lievää kipua, särkyä, pahoinvointia, kutinaa jne.

3 Minulla on melkoisia vaivoja tai oireita, esim. melkoista kipua, särkyä, pahoinvointia, kutinaa jne.

4 Minulla on voimakkaita vaivoja tai oireita, esim. voimakasta kipua, särkyä, pahoinvointia, kutinaa jne.

5 Minulla on sietämättömiä vaivoja tai oireita, esim. sietämätöntä kipua, särkyä, pahoinvointia, kutinaa jne.

30.12 Masentuneisuus

1 En tunne itseäni lainkaan surulliseksi, alakuloiseksi tai masentuneeksi.

2 Tunnen itseni hieman surulliseksi, alakuloiseksi tai masentuneeksi.

3 Tunnen itseni melko surulliseksi, alakuloiseksi tai masentuneeksi.

4 Tunnen itseni erittäin surulliseksi, alakuloiseksi tai masentuneeksi.

5 Tunnen itseni äärimmäisen surulliseksi, alakuloiseksi tai masentuneeksi.

30.13 Ahdistuneisuus

1 En tunne itseäni lainkaan ahdistuneeksi tai pelokkaaksi.

2 Tunnen itseni hieman ahdistuneeksi, jännittyneeksi tai hermostuneeksi.

3 Tunnen itseni melko ahdistuneeksi, jännittyneeksi tai hermostuneeksi.

4 Tunnen itseni erittäin ahdistuneeksi, jännittyneeksi tai hermostuneeksi.

5 Tunnen itseni äärimmäisen ahdistuneeksi, jännittyneeksi tai hermostuneeksi.

30.14 Energisyys

1 Tunnen itseni terveeksi ja elinvoimaiseksi.

2 Tunnen itseni hieman uupuneeksi, väsyneeksi ja voimattomaksi.

3 Tunnen itseni melko uupuneeksi, väsyneeksi ja voimattomaksi.

4 Tunnen itseni hyvin uupuneeksi, väsyneeksi ja voimattomaksi, lähes loppuun kuluneeksi.

5 Tunnen itseni äärimmäisen uupuneeksi, väsyneeksi ja voimattomaksi, täysin loppuun kuluneeksi.

30.15 Sukupuolielämä

1 Terveydentilani ei vaikeuta mitenkään sukupuolielämääni.

2 Terveydentilani vaikeuttaa hieman sukupuolielämääni.

3 Terveydentilani vaikeuttaa huomattavasti sukupuolielämääni.

4 Terveydentilani tekee sukupuolielämäni lähes mahdottomaksi.

5 Terveydentilani tekee sukupuolielämäni mahdottomaksi.

Saako Teiltä tarvittaessa kysyä lisätietoja yövirtsaamisvaivaan liittyen?

Ei

Kyllä

Pyydämme tarkistamaan, että olette vastanneet kaikkiin kysymyksiin. Muistattehan, että kyselylomake on kaksipuolinen. Täytetty lomake palautetaan ohessa olevassa masuttomassa kuoressa.

Kiitos yhteistyöstä!

Appendix 3. Number of subjects with, and age-standardised prevalences (%) of self-reported physician-diagnosed conditions, and *p v*alues of the age-adjusted odds ratios for nocturia in the FINNO Study, Finland, 2003-2004.[a]

Physician-diagnosed conditions	Men			Women		
	No.	%[b]	*P* Value[c]	No.	%	*P* Value
Neurologic						
Parkinson disease	8	0	[d]	1	0	[d]
Epilepsy	19	1	0.88	14	1	0.81
Multiple sclerosis	4	0	[d]	10	1	0.31
Spinal cord injury	9	1	[d]	3	0	[d]
Migraine	9	0	[d]	49	2	0.43
Cerebrovascular accident	11	1	0.30	5	0	[d]
Psychiatric						
Mood disorder	89	6	**0.001**	15	8	**0.01**
Anxiety disorder	41	2	0.38	61	3	**0.01**
Sleep disorders						
Obstructive sleep apnea	49	3	**<0.001**	15	1	**0.06**
Restless legs syndrome	48	3	**<0.001**	54	4	**<0.001**
Narcolepsy	0	0	[d]	3	0	[d]
Urologic						
Benign prostatic hyperplasia	12	8	**<0.001**	-	-	-
Chronic prostatitis	17	1	0.72	-	-	-
Contracted bladder[e]	2	0	[d]	4	0	[d]
Prostate cancer	20	1	**0.01**	-	-	-
Urinary bladder cancer	0	0	[d]	1	0	[d]
Other						
Coronary artery disease[f]	97	6	**0.04**	50	4	**0.002**
Hypertension	20	14	**0.04**	22	16	0.17
Diabetes[g]	71	5	**0.01**	66	5	**<0.001**
Obstructive lung disease[h]	94	6	0.31	12	7	**0.04**
Rheumatoid arthritis	31	6	0.19	46	7	0.85
Osteoarthritis	97	6	0.16	13	10	**0.005**
Breast cancer[i]	0	0	[d]	24	2	0.48
Fibromyalgia	2	0	[d]	18	1	**0.09**
Psoriasis	11	1	0.72	11	1	0.92
Back pain	37	3	0.11	31	2	0.32
Osteoporosis[j]	1	0	[d]	19	1	0.96
Hypothyroidism[k]	9	1	[d]	88	5	0.73
Dyslipidemia[l]	11	8	0.93	79	7	0.40
Gout	12	1	0.66	5	0	[d]
Inflammatory bowel disease	8	0	[d]	14	1	0.51
Gastroesophageal reflux[m]	42	3	**0.03**	41	2	**<0.001**
Arrhythmia[n]	17	1	0.12	19	1	0.21
Hypersensitivity	22	1	0.99	45	2	0.76
Glaucoma	10	1	0.80	9	1	[d]
Hyperthyroidism	0	0	[d]	10	1	0.80

[a] Conditions in normal font (20/36) are those that were available in the questionnaire as a direct option, whereas conditions *in italics* (16/36) are those that were collected from the responses to the options: ”Other neurological conditions, which?”, ”Other psychiatric conditions, which?”, ”Other malignant conditions, which” or ”Other conditions, which?”. Only conditions reported by at least ten men or women were included as potential risk factors in analyses. Furthermore, with a single indication for a medication, those reporting using it were also taken to have the indication (condition).

[b] The age-standardised prevalence was calculated using the age structure of Finland (beginning of year 2004) (Population Register Centre 2004).

[c] The *P* values less than 0.10 (in the age-adjusted logistic regression) are in bold face. Conditions with *p* value less than 0.10 were included in the multivariate analysis. All associated factors ($p < 0.10$) found here were ´risk factors´, hence, no protective factors were found.

[d] Logistic regression was performed only if potential risk factor was reported by at least ten men or women.

[e] Due to e.g. painful bladder syndrome (interstitial cystitis) or radiation.

[f] Including those with heart failure (with or without including subjects regularly taking vasodilators used in cardiac diseases (Anatomical Therapeutic Chemical (ATC) code (WHO Collaborating Centre for Drug Statistics Methodology 2004): C01D); estimates did not differ).

[g] Including subjects regularly taking insulins and analogues (ATC code: A10A), oral blood glucose lowering drugs (A10B), and other drugs used in diabetes (A10X).

[h] Including those with asthma or chronic obstructive pulmonary disease and subjects regularly taking drugs for obstructive airway diseases (ATC code: R03).

[i] Including subjects regularly taking tamoxifen (ATC code: L02BA01).

[j] Including subjects regularly taking bisphosphonates (ATC code: M05BA/B).

[k] Including subjects regularly taking levothyroxine sodium (ATC code: H03AA01).

[l] Including subjects regularly taking lipid modifying agents (ATC code: C10)

[m] Including subjects regularly taking drugs for acid related disorders (ATC code: A02)

[n] Including subjects regularly taking antiarrhythmics, class I and III (ATC code: C01B).

Appendix 4. Number of subjects on prescribed medication and age-standardised prevalences (%) (classified by the Anatomical Therapeutic Chemical Classification (WHO Collaborating Centre for Drug Statistics Methodology 2004)) and *p* values of the age-adjusted odds ratios for nocturia in the FINNO Study, Finland, 2003-2004.[a]

Medication groups (ATC code)	Men			Women		
	No.	%[b]	*P* Value[c]	No.	%	*P* Value
Drugs for acid related disorders (A02)	35	2	[d]	38	2	[d]
Insulins and analogues (A10A)	17	1	[d]	16	1	[d]
Oral blood glucose lowering drugs (A10B/X)[e]	38	3	[d]	34	3	[d]
Cardiac glycosides (C01A)	10	1	0.65	9	1	[a]
Vasodilators used in cardiac diseases (C01D)	36	2	[d]	30	2	[d]
Diuretics (other than high-ceiling) (C03A/B/D/E)[f]	62	5	0.16	84	6	0.43
High-ceiling diuretics (C03C)[f]	16	1	0.31	25	2	0.63
Beta blocking agents (C07)	146	10	0.86	154	11	0.32
Calcium channel blockers (C08)	71	5	**0.07**	79	6	**0.01**
Agents acting on the renin-angiotensin system (C09)	153	11	0.33	136	10	0.95
Lipid modifying agents (C10)	112	8	[d]	87	7	[d]
Contraceptives (G02BB01, G03AA/AB/H)[g]	-	-	-	106	5	0.90
Menopausal hormone therapy (G03CA03, G03F)[h]	-	-	-	212	16	[h]
Urinary antispasmodics (G04BD)	6	0	[i]	10	1	[i]
Alpha-adrenoreceptor antagonists (G04CA)	39	3	[i]	1	0	[i]
Testosterone-5-alpha reductase inhibitors (G04CB)	22	1	[i]	-	-	-
Corticosteroids for systemic use, plain (H02A)	15	1	0.66	19	1	0.40
NSAIDs (M01A, M01B)[j]	97	6	0.14	129	7	0.28
Muscle relaxants (M03)	19	1	0.99	21	1	0.84
Antigout preparations (M04)	10	1	0.77	2	0	[a]
Opioids (N02A)	28	2	**0.10**	26	2	**0.03**
Antiepileptics (N03)	23	1	0.56	25	1	0.91
Antipsychotics (N05AA-AL, N05AX, N06CA)[k, m]	19	1	0.97	25	2	**0.02**
Anxiolytics (N05B, N06CA, A03CA)[k, l]	41	2	0.41	48	3	**0.03**
Hypnotics and sedatives (N05C)	95	6	0.53	140	9	0.14
Antidepressants (N06A, N06CA)[k]	42	3	**0.001**	107	7	0.21
Drugs for obstructive airway diseases (R03)	49	3	[d]	82	5	[d]

[a] Logistic regression was performed if potential risk factor was reported by at least ten men or women.

[b] The age-standardised prevalence was calculated using the age structure of Finland (Population Register Centre 2004).

[c] The p values < 0.10 (in the age-adjusted logistic regression) are in bold face. Conditions with p values < 0.10 were included in the multivariate analysis. All associated factors (p < 0.10) found here were ´risk factors´, hence, no protective factors were found.

[d] With a single indication for a medication, those reporting using it were also taken to have the indication (condition). Therefore, logistic regression was not performed separately for those medication groups.

[e] Including oral blood glucose lowering drugs (A10B) and other drugs used in diabetes (A10X) excluding insulins and analogues (A10A).

[f] High-ceiling diuretics and loop-diuretics are used synonymously. We also performed an extra analysis for combination of ”Diuretics” and ”High-ceiling diuretics” but no statistically significant associations were found (p = 0.18 for men, and p = 0.78 for women).

[g] Contraceptives included progestogens and estrogens, fixed combinations (G03AA); progestogens and estrogens, sequential preparations (G03AB); antiandrogens (G03H); and vaginal ring with progestogen and estrogen (G02BB01). Furthermore, we performed an extra analysis for contraceptives also including subjects regularly taking progestin-only contraceptives (G03AC) but the results remained similar.

[h] Subjects regularly taking MHT (vaginal or systemic) were regarded as MHT users in the classification of the menopausal status. The prevalence of nocturia was similar between subjects regularly taking vaginal and systemic MHT. Hence, we combined these.

[i] For urinary antispasmodics (also referred to as antimuscarinics), alpha-adrenoreceptor antagonists (synony also referred to as alpha blockers), and testosterone-5-alpha reductase inhibitors analyses were not performed due to strong overlapping of medication and symptoms.

[j] Including non-steroid anti-inflammatory and antirheumatic products (M01A) and anti- inflammatory and antirheumatic agents in combination (M01B).

[k] Partly including antidepressants in combination with psycholeptics (N06CA).

[l] Partly including synthetic anticholinergic agents in combination with psycholeptics (A03CA).

[m] We performed an extra analysis for Antipsychotics including subjects regularly taking lithium (N05AN) but the results remained similar.

Appendix 5. Number of subjects with and age-standardised prevalences (%) of symptoms and lifestyle factors and *p* values of the age-adjusted odds ratios for nocturia in the FINNO Study, Finland, 2003-2004.[a]

	Men			Women		
	n	**%**[a]	***p* value**[b]	**n**	**%**	***p* value**
Symptoms						
Snoring[c]	552	35	**0.001**	290	19	**<0.001**
Stress urinary incontinence	7	0	[d]	174	11	**<0.001**
Urinary urgency	121	8	**<0.001**	163	10	**<0.001**
Lifestyle factors						
Body mass index						
Normal-weight (<25)	684	40	referent	1042	54	referent
Overweight (25-30)	749	46	0.43	522	32	**<0.001**
Obesity (≥30)	216	14	**0.001**	223	13	**<0.001**
Smoking						
Never	583	34	referent	905	53	referent
Former	594	37	0.46	461	24	0.72
Current	490	29	0.98	471	23	0.17
	Mean (SD)	**Median**	***p* value**	**Mean (SD)**	**Median**	***p* value**
Alcohol (units per week)	7.1 (8.3)	5	0.21	3.3 (4.3)	2	0.19
Coffee (cups per day)	4.4 (3.1)	4	0.71	3.3 (2.4)	3	0.69

[a] The age-standardised prevalence was calculated using the age structure of Finland (beginning of year 2004) (Population Register Centre 2004).

[b] The *p* values < 0.10 (in the age-adjusted logistic regression) are in bold face. Those with *p* value < 0.10 were included in the multivariate analysis. All associated factors ($p < 0.10$) found here were ´risk factors´, hence, no protective factors were found.

[c] Snoring was termed abnormal if reported at least on 3-5 nights per week and normal if reported on 1-2 nights per week or less to the question *"How often do you snore while sleeping (ask other people if you are not sure)?"* (responded by 97% of men and 91% of women of final study population). For those who did not answer to previous question, *"How do you snore (ask other people about the quality of sleep)?"* was used for classification (if answered); scale: I don´t snore; My snoring sounds regular and it is of low voice; It sound regular but rather loud; It sounds regular but it is very loud (other people hear my snoring in the next room); I snore very loudly and intermittently (there are silent breathing pauses when snoring is not heard and at times very loud snorts with gasping). Snoring was termed abnormal if any of the two latter options was reported, and normal if any of the two first options was reported. Combination of questions did not affect estimates: age-adjusted odds ratios of snoring for nocturia were 1.79 (1.79) for men and 2.43 (2.44) for women with (without) combining.

[d] Logistic regression was performed if potential risk factor was reported by at least ten subjects.

Appendix 6. Physician-diagnosed diseases/conditions and regular use of prescribed medications (with ATC-DDD code (WHO Collaborating Centre for Drug Statistics Methodology 2004)) included[a] in the models of Nocturia and Urgency Confounder Scores of the Study V in the FINNO Study, Finland, 2003-2004.

Nocturia Confounder Score		**Urgency Confounder Score**	
Diseases/conditions	**Medication** (ATC-DDD)	**Diseases/conditions**	**Medication** (ATC-DDD)
Anxiety disorders	Antipsychotics (N05A)[e]	Anxiety disorders	Antidepressants (N06A)[g]
Coronary disease[b]	Anxiolytics (N05B)[f]	Arrhythmia	Antiepileptics (N03A)
Diabetes mellitus	Calcium channel blockers (C08)	Back pain	Antipsychotics (N05A)[e]
Fibromyalgia	Opioids (N02A)	Breast neoplasms	Hypnotics and sedatives (N05C)
Gastroesophageal reflux		Diabetes mellitus	Loop-diuretics (C03C)[h]
Mood disorders		Epilepsy	
Obstructive lung diseases[c]		Gastroesophageal reflux	
Osteoarthritis		Mood disorders	
Restless legs syndrome		Obstructive lung diseases[c]	
Sleep apnea syndromes		Multiple sclerosis	
Stress urinary incontinence[d]		Restless legs syndrome	
		Sleep apnea syndromes	
		Stress urinary incontinence[d]	

[a] All factors (of comorbidity and medications reported by at least 10 women) associated ($p < 0.10$) with nocturia or urgency (after adjustment for age) were included in the models of Nocturia Confounder Score or Urgency Confounder Score respectively. With a single indication for a drug, those reporting using it were also deemed to have the indication (disease/condition). Furthermore, if both drug and indication were associated with a symptom, we only included the indication in the formula of Nocturia Confounder Score or Urgency Confounder Score.

[b] Including those with heart failure.

[c] Including those with asthma and/or chronic obstructive pulmonary disease.

[d] Based on response to stress urinary incontinence question of the DAN-PSS with answer options never-rarely-often-always (99% of women responded). Women who reported having stress urinary incontinence often or always (during last 2 weeks) were classified as abnormal.

[e] Antipsychotics (N05AA-AL, N05AX) excluding lithium (N05AN), and partly including antidepressants in combination with psycholeptics (N06CA).

[f] Anxiolytics (N05B), and partly including antidepressants in combination with psycholeptics (N06CA) and synthetic anticholinergic agents in combination with psycholeptics (A03CA).

[g] Antidepressants (N06A), and partly including antidepressants in combination with psycholeptics (N06CA).

[h] Loop-diuretics used as synonym for high-ceiling diuretics (as in ATC-DDD classification (WHO Collaborating Centre for Drug Statistics Methodology 2004)).

Appendix 7. Age-standardised proportions (%) for degree of bother by frequency of nocturia and response round in both sexes in the FINNO Study, Finland, 2003-2004.

Age-standardisation was performed using the age structure of Finland (Population Register Centre 2004).

Frequency of nocturia (voids per night)	**Degree of bother from nocturia**								
	None			**Small**			**Moderate or major**		
	Response round[a]								
	1st	**2nd**	**3rd**	**1st**	**2nd**	**3rd**	**1st**	**2nd**	**3rd**
One	48	55	63	45	39	28	6	6	8
Two	24	31	45	56	54	36	20	15	19
Three	13	16	25	34	34	15	53	50	59
Four or more	5	29	0	0	9	30	95	62	70

Appendix 8. Age-adjusted means for 15D dimensions and 15D Score by frequency of nocturia and response round in men (women) in the FINNO Study, Finland, 2003-2004.

15D dimensions and 15D Score	No nocturia			1 void per night			2 voids per night			≥3 voids per night		
	Response round			Response round			Response round			Response round		
	1st	2nd	3rd	1st	2nd	3rd	1st	2nd	3rd	1st	2nd	3rd
Moving	0.981 (0.986)	0.985 (0.986)	0.986 (0.979)	0.977 (0.978)	0.966 (0.962)	0.956 (0.979)	0.973 (0.947)	0.962 (0.957)	0.980 (0.888)	0.871 (0.919)	0.955 (0.848)	0.862 (0.951)
Seeing	0.983 (0.983)	0.977 (0.967)	0.965 (0.982)	0.969 (0.980)	0.973 (0.970)	0.972 (0.951)	0.960 (0.955)	0.960 (0.927)	0.939 (0.937)	0.952 (0.950)	0.983 (0.857)	0.849 (0.766)
Hearing	0.971 (0.989)	0.969 (0.977)	0.974 (0.992)	0.973 (0.978)	0.964 (0.974)	0.973 (0.979)	0.907 (0.949)	0.946 (0.949)	0.927 (0.995)	0.905 (0.937)	0.959 (0.965)	0.924 (0.665)
Breathing	0.958 (0.961)	0.967 (0.949)	0.958 (0.961)	0.941 (0.935)	0.929 (0.923)	0.927 (0.962)	0.889 (0.907)	0.900 (0.872)	0.859 (0.930)	0.797 (0.886)	0.803 (0.726)	0.687 (0.783)
Sleeping	0.895 (0.877)	0.908 (0.884)	0.919 (0.899)	0.834 (0.830)	0.839 (0.822)	0.837 (0.830)	0.787 (0.762)	0.819 (0.798)	0.795 (0.844)	0.764 (0.692)	0.805 (0.755)	0.709 (0.754)
Eating	0.998 (0.997)	1.000 (1.000)	0.997 (1.000)	0.991 (0.999)	0.996 (0.993)	0.997 (0.994)	0.997 (0.992)	0.988 (1.000)	0.979 (1.000)	0.988 (0.984)	0.997 (1.000)	1.000 (1.000)
Speech	0.989 (0.993)	0.986 (0.993)	0.991 (1.000)	0.988 (0.988)	0.978 (0.994)	0.992 (0.995)	0.979 (0.985)	0.972 (0.991)	0.943 (0.980)	0.959 (0.971)	0.895 (1.000)	0.956 (1.000)
Eliminating	0.954 (0.935)	0.954 (0.922)	0.967 (0.942)	0.897 (0.885)	0.932 (0.892)	0.912 (0.899)	0.848 (0.836)	0.906 (0.818)	0.772 (0.864)	0.687 (0.813)	0.817 (0.678)	0.708 (0.692)
Usual activities	0.966 (0.969)	0.974 (0.954)	0.955 (0.968)	0.923 (0.957)	0.956 (0.931)	0.930 (0.947)	0.900 (0.888)	0.911 (0.932)	0.950 (0.873)	0.823 (0.874)	0.842 (0.793)	0.856 (0.934)
Mental function	0.952 (0.968)	0.959 (0.964)	0.970 (0.965)	0.909 (0.948)	0.913 (0.941)	0.933 (0.964)	0.903 (0.922)	0.940 (0.915)	0.792 (0.876)	0.814 (0.895)	0.841 (0.855)	0.731 (0.678)
Discomfort	0.890 (0.875)	0.899 (0.886)	0.900 (0.885)	0.839 (0.845)	0.844 (0.836)	0.846 (0.875)	0.813 (0.775)	0.795 (0.790)	0.682 (0.844)	0.714 (0.689)	0.736 (0.799)	0.819 (0.788)
Depression	0.933 (0.916)	0.947 (0.917)	0.950 (0.922)	0.902 (0.880)	0.909 (0.897)	0.926 (0.897)	0.849 (0.822)	0.897 (0.878)	0.857 (0.918)	0.834 (0.754)	0.889 (0.865)	0.813 (0.612)
Distress	0.934 (0.925)	0.942 (0.911)	0.941 (0.921)	0.897 (0.889)	0.903 (0.901)	0.901 (0.911)	0.833 (0.796)	0.902 (0.869)	0.856 (0.949)	0.772 (0.780)	0.905 (0.878)	0.832 (0.640)
Vitality	0.906 (0.888)	0.918 (0.895)	0.916 (0.904)	0.868 (0.844)	0.891 (0.848)	0.880 (0.858)	0.829 (0.748)	0.853 (0.821)	0.812 (0.825)	0.704 (0.714)	0.755 (0.771)	0.752 (0.659)
Sexual activity	0.936 (0.954)	0.929 (0.952)	0.941 (0.946)	0.881 (0.926)	0.915 (0.910)	0.927 (0.923)	0.822 (0.843)	0.868 (0.888)	0.761 (0.844)	0.626 (0.822)	0.824 (0.833)	0.644 (0.733)
15D Score	0.952 (0.951)	0.958 (0.947)	0.958 (0.954)	0.922 (0.928)	0.929 (0.923)	0.929 (0.936)	0.893 (0.883)	0.912 (0.898)	0.864 (0.903)	0.817 (0.854)	0.861 (0.838)	0.809 (0.796)

Appendix 9. Age-standardardised prevalence (%) (with 95% confidence intervals) of sociodemographic factors by mailing round in men and women in the FINNO Study, Finland, 2003-2004.[a]

Characteristics	Men: mailing round						Women: mailing round					
	First round		Second round		Third round		First round		Second round		Third round	
Marital status												
Married/living together	74	(68-80)	72	(63-80)	69	(59-80)	67	(61-72)	67	(60-75)	66	(55-76)
Widowed	0.9	(0.3-1.5)	0.8	(0.0-1.5)	3.6	(1.1-6.2)	7.4	(4.8-10)	7.3	(4.9-9.8)	10	(5.6-15)
Divorced/separated	5.0	(3.3-6.8)	5.0	(2.7-7.3)	4.7	(2.1-7.4)	8.5	(6.5-11)	8.2	(5.5-11)	8.8	(4.5-13)
Never married	20	(17-23)	22	(18-26)	22	(17-27)	17	(15-20)	16	(13-20)	14	(10-18)
No response	0.3	(0.0-0.8)	0.8	(0.1-1.6)	0.5	(0.0-1.2)	0.2	(0.0-0.4)	0.8	(0.1-1.5)	1.3	(0.0-3.1)
Education												
Basic level	24	(21-28)	32	(27-38)	36	(28-44)	27	(23-31)	30	(25-35)	30	(23-38)
Vocational school	31	(27-35)	35	(30-41)	36	(29-43)	29	(25-33)	32	(27-38)	33	(25-40)
College	22	(19-25)	17	(13-20)	15	(11-20)	25	(22-28)	20	(16-24)	20	(14-25)
University	22	(19-25)	15	(12-18)	12	(8.6-16)	18	(16-21)	15	(12-19)	16	(11-21)
No response	0.4	(0.0-0.9)	0.4	(0.0-0.9)	0.6	(0.0-1.4)	0.6	(0.1-1.0)	1.8	(0.6-3.0)	0.8	(0.0-1.7)
Employment												
Student	11	(8.6-13)	8.7	(6.2-11)	6.0	(3.6-8.4)	10	(8.7-12)	11	(8.0-13)	11	(7.2-14)
Employed	58	(53-64)	61	(53-68)	60	(51-69)	56	(52-61)	55	(48-61)	51	(42-60)
Unemployed	7.2	(5.2-9.3)	6.8	(3.9-9.6)	7.6	(4.5-11)	6.8	(5.1-8.4)	7.4	(4.9-10)	8.8	(4.8-13)
Retired	23	(19-26)	22	(18-26)	25	(18-32)	26	(21-30)	26	(21-31)	29	(21-36)
No response	1.1	(0.3-2.0)	1.9	(0.6-3.3)	1.2	(0.0-2.3)	1.2	(0.5-1.9)	1.1	(0.1-2.0)	0.9	(0.0-2.0)
Urbanity												
Small community	61	(56-67)	65	(57-73)	60	(50-70)	60	(55-66)	61	(54-68)	59	(49-70)
Large community	38	(34-43)	34	(28-39)	39	(32-47)	39	(35-44)	39	(33-44)	39	(31-48)
Unknown	0.4	(0.0-9.9)	1.1	(0.2-2.1)	0.6	(0.0-1.8)	0.2	(0.0-0.5)	0.3	(0.0-0.8)	1.2	(0.1-2.3)

[a] Age-standardisation was performed using the age structure of Finland (Population Register Centre 2004).

Appendix 10. Reproductive factors by mailing round among 1,728 women in the FINNO Study, Finland, 2003-2004.

	First mailing round			Second mailing round			Third mailing round		
	Crude	Age-standardised[a]		Crude	Age-standardised		Crude	Age-standardised	
Characteristic	**N (%)**	**Prevalence**	**95% CI**	**N (%)**	**Prevalence**	**95% CI**	**N (%)**	**Prevalence**	**95% CI**
Parity									
0	381 (39)	32	28-35	140 (32)	29	24-34	76 (34)	27	21-34
1	138 (14)	15	12-18	72 (16)	17	13-21	27 (12)	13	8-18
2	269 (28)	32	28-37	134 (30)	31	25-36	62 (28)	32	23-41
≥3	184 (19)	21	17-24	96 (22)	24	19-29	56 (25)	28	20-36
Postpartum period[a]	32 (3)	2	2-3	14 (3)	2	1-4	7 (3)	2	0-4
Menopausal status									
Premenopausal	680 (70)	53	48-57	285 (64)	53	47-59	153 (69)	52	44-61
Postmenopausal	127 (13)	22	18-27	88 (20)	27	21-33	38 (17)	28	19-36
Women with MHT[b]	72 (7)	10	8-13	30 (7)	9	6-13	11 (5)	8	3-12
Hysterectomised	93 (10)	15	12-18	39 (9)	11	7-14	19 (9)	12	7-18
Surgery for SUI[b]	17 (2)	2	1-3	8 (2)	2	1-4	3 (1)	3	0-5

[a] Postpartum period was defined as more than 6 weeks but not more than one year after delivery.

[b] MHT, menopausal hormone therapy; SUI, stress urinary incontinence.

Appendix 11. Prevalence (%) of and risk factors (*in alphabetical order*) for nocturia by mailing round and sex in the FINNO Study, Finland, 2003-2004.

	First mailing round				Second mailing round				Third mailing round			
	Crude		Age-standardised		Crude		Age-standardised		Crude		Age-standardised	
	N	(%)	Prevalence	95% CI	N	(%)	Prevalence	95% CI	N	(%)	Prevalence	95% CI
Men												
Nocturia	95	(13)	13	10-16	48	(10)	13	9-17	16	(6)	8	4-12
Antidepressant use	25	(3)	3	2-5	6	(1)	2	0-3	4	(1)	1	0-2
Benign prostatic hyperplasia	63	(8)	9	6-11	29	(6)	8	5-11	7	(3)	4	1-7
Obesity	88	(12)	12	9-15	62	(13)	14	10-18	40	(15)	17	11-22
Prostate cancer	9	(1)	1	0-2	5	(1)	1	0-2	1	(0)	1	0-2
Restless legs syndrome	25	(3)	4	2-5	11	(2)	2	1-4	4	(1)	2	0-4
Snoring	262	(35)	36	32-41	15	(33)	35	29-42	79	(29)	30	23-38
Overactive bladder	70	(9)	9	7-12	19	(4)	5	3-7	14	(5)	7	3-11
Women												
Nocturia	95	(10)	13	10-16	37	(8)	11	7-14	15	(7)	9	4-14
Coronary artery disease	17	(2)	5	3-7	15	(3)	5	2-7	5	(2)	4	1-8
Diabetes	29	(3)	4	2-6	14	(3)	4	2-6	10	(5)	7	2-11
Obesity	104	(11)	12	9-15	63	(14)	16	12-20	33	(15)	16	10-22
Overweight	269	(28)	31	27-36	12	(29)	32	26-38	61	(27)	29	21-38
Restless legs syndrome	22	(2)	3	2-4	15	(3)	4	2-7	6	(3)	4	1-8
Snoring	158	(16)	20	16-23	68	(16)	18	14-23	32	(14)	16	10-22
Urinary urgency	90	(9)	11	8-14	30	(7)	8	5-11	18	(8)	9	5-14

Appendix 12. Prevalence (%) of major comorbidities by HRQL and frequency of nocturia among both sexes in the FINNO Study, Finland, 2003-2004.

Men	Health-related quality of life[a]			Frequency of nocturia		
	Reference group (>0.923) (n = 1149)	1-2 MCID[b] less (0.893-0.923) (n = 159)	≥2 MCID less (≤0.893) (n = 340)	No nocturia (n = 1077)	One void/night (n = 385)	≥2 voids/night (n = 186)
	Prevalence[c] (95% CI), %	Prevalence (95% CI), %	Prevalence (95% CI), %	Prevalence (95% CI), %	Prevalence (95% CI), %	Prevalence (95% CI), %
Obstructive sleep apnea	2 (1-2)	3 (1-5)	2 (1-4)	2 (1-3)	7 (2-11)	7 (2-11)
Mood disorder	3 (1-4)	6 (2-11)	5 (4-7)	5 (3-7)	12 (5-19)	12 (5-19)
Coronary artery disease	4 (3-6)	5 (2-9)	5 (3-7)	6 (4-8)	10 (6-14)	10 (6-14)
Obstructive lung disease	4 (2-5)	9 (4-15)	6 (4-7)	5 (3-7)	7 (3-12)	7 (3-12)
Osteoarthrosis	4 (2-5)	9 (4-15)	5 (3-7)	7 (4-9)	6 (3-8)	6 (3-8)

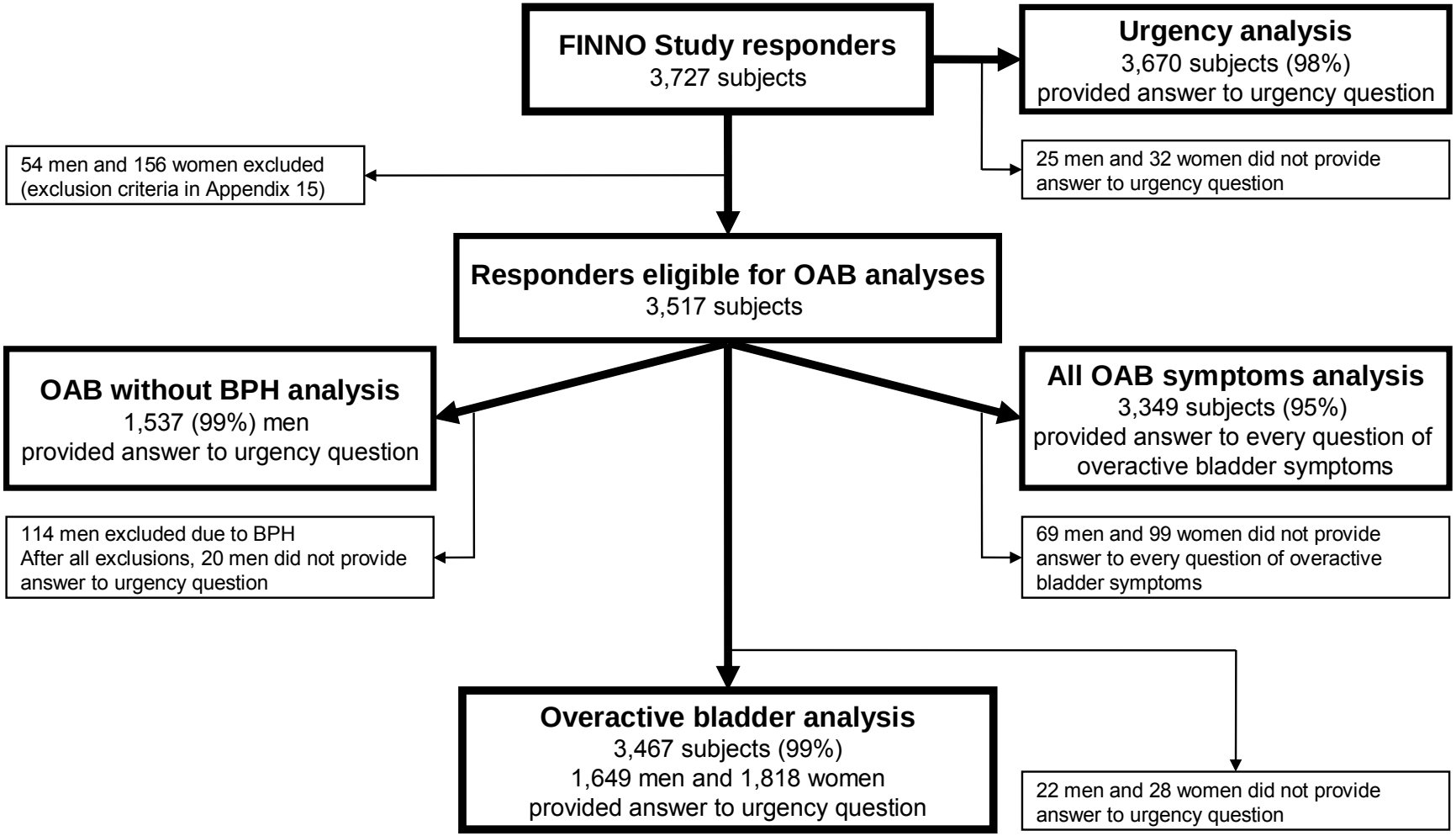
Women	Health-related quality of life			Frequency of nocturia		
	Reference group (>0.920) (n = 1295)	1-2 MCID less (0.890-0.920) (n = 175)	≥2 MCID less (≤0.890) (n = 356)	No nocturia (n = 1094)	One void/night (n = 550)	≥2 voids/night (n = 182)
	Prevalence (95% CI), %	Prevalence (95% CI), %	Prevalence (95% CI), %	Prevalence (95% CI), %	Prevalence (95% CI), %	Prevalence (95% CI), %
Obstructive sleep apnea	0 (0-1)	1 (0-2)	1 (0-1)	1 (0-2)	3 (0-5)	3 (0-5)
Mood disorder	4 (2-5)	10 (5-15)	7 (5-9)	10 (7-13)	14 (8-20)	14 (8-20)
Coronary artery disease	3 (2-5)	3 (0-6)	4 (2-6)	3 (2-5)	7 (4-11)	7 (4-11)
Obstructive lung disease	5 (4-6)	10 (5-15)	5 (4-7)	8 (6-11)	10 (5-14)	10 (5-14)
Osteoarthrosis	7 (5-9)	11 (5-16)	7 (4-9)	10 (7-13)	16 (10-21)	16 (10-21)

[a] Subjects were classified into three groups with cut-off points defined as 15D Scores corresponding to minimum clinically important difference and twice minimum clinically important difference below average of subjects without nocturia (separately for both sexes; 15D Scores in parentheses).

[b] MCID, minimum clinically important difference.

[c] Age-standardised prevalence was calculated using the age structure of Finland (beginning of 2004) (Population Register Centre 2004).

Appendix 13. Flow chart of the different analyses in Study II in the FINNO Study, Finland, 2003-2004.



Appendix 14. Number of subjects in different analyses by mailing round in Study II in the FINNO Study, Finland, 2003-2004.

Age groups (years)	Original sample	Eligible sample	Partici-pants	Urgency analysis[b]	Overactive bladder analysis†	Subjects by response round in Overactive bladder analysis				OAB[a] without BPH[a] analysis[b]	All OAB symptoms analysis†
						1st	2nd	3rd	Missing[c]		
Men											
18–29	800	796	388	386	385	167	121	82	15	385	379
30–39	800	798	428	425	424	188	139	77	20	424	415
40–49	600	600	335	330	324	155	96	59	14	316	314
50–59	300	300	197	194	190	99	44	34	13	175	188
60–69	300	298	226	221	208	103	57	21	27	160	199
70–79	200	196	151	144	118	59	29	14	16	77	107
All men	3,000	2,988	1,725	1,700	1,649	771	486	287	105	1,537	1,602

Women										
18–29	800	797	510	504	455	273	110	63	9	445
30–39	800	798	495	493	452	255	117	66	14	441
40–49	600	597	408	404	395	233	97	44	21	385
50–59	300	299	213	210	199	108	55	22	14	187
60–69	300	299	237	231	209	107	53	25	24	195
70–79	200	199	139	128	108	33	39	14	22	94
All women	3,000	2,989	2,002	1,970	1,818	1,009	471	234	104	1,747
Both	6,000	5,977	3,727	3,670	3,467	1,780	957	521	209	3,349

[a] OAB, overactive bladder; BPH, benign prostatic hyperplasia.

[b] Urgency analysis was performed with all participants who provided answers to urgency question; Overactive bladder analysis was the main study group (for both sexes) with exclusions; OAB without BPH analysis was performed for men after further exclusion of those with BPH; All OAB symptoms analysis was performed for both sexes with all subjects who provided answer to every urgency, UUI, frequency, and nocturia questions after same exclusions as for ´Overactive bladder analysis´.

[c] Mailing round could not be defined due to lack of date of questionnaire completion.

Appendix 15. Number of excluded subjects among 1725 men and 2002 in the ´Overactive bladder analysis´ in the Study II in the FINNO Study, Finland, 2003-2004.

Characteristics	Men	Women	Both sexes
Urinary tract infection	16	59	75
Genitourinary cancer[b]	22	11	33
Contracted bladder[c]	2	5	7
Puerperium[d]		8	8
Pregnancy		49	49
Taking loop-diuretics	19	30	49
Together	**54**	**156**	**210**

[a] Acute (in past 2 weeks) or chronic urinary tract infection.

[b] Excluding renal cancer.

[c] Due to e.g. painful bladder syndrome or radiation.

[d] Puerperium defined as 6 weeks after childbirth.

Appendix 16. Published population-based studies assessing the prevalence of overactive bladder among both sexes in chronological order (PubMed indexed articles before beginning year 2009).

Origin of the study sample	**European** (F,G,I,Sp,Sw,UK)	**USA**	**Canada**	**Japan**	**Porto Alegre** (Brazil)	**Matsu** (Taiwan)	**International** (C,G,I,Sw,UK)	**Finland**	**Korea**	**Canada**
Reference	(Milsom et al. 2001)	(Stewart et al. 2003)	(Corcos & Schick 2004)	(Homma et al. 2005)	(Teloken et al. 2006)	(Yu et al. 2006a)	(Irwin et al. 2006)	present study	(Choo et al. 2008)	(Herschorn et al. 2008)
Design	Telephone interview (85%)[a]	Telephone interview	Telephone interview	Mailed questionnaire	Mailed (?) questionnaire	Questionnaire administered by nurse	Telephone interview	Mailed questionnaire	Telephone interview	Telephone interview
Respondents	16,776	5,204	3,249	4,570	913	1,921	19,165	3,727	2,005	1,000
Response proportion (%)	Not reported	44.5/57.1[b]	43.4	45.3	Not reported	67.0	33.0	62.4	13.8	Not reported
Age range (years)	40-75+	18-75+	35-75+	40-100	15-55	30-79	18-70+	18-79	40-89	18+
Representative age-distribution of adults[c]	No	Yes	No	No	No	No	Yes	Yes	No	Yes
Current definition of OAB[d]	No	No	No	No	Yes	No	Yes	Yes	No	No
Time period[e]	Not defined	Past 4 weeks	Past month	Past month	Not defined	Past 4 weeks	Not defined	Past 2 weeks	Past 4 weeks	Not defined
Exclusion criteria - UTI[e]/other	Yes/No	Yes/Yes	No/No	No/No	Yes/Yes	No/Yes	No/No	Yes/Yes	No/No	No/No
Prevalence of OAB (%)	17	16	18	12	19	17	12	8	22	14

Abbreviations: C, Canada, F, France; G, Germany; I, Italy; Sp, Spain; Sw, Sweden; UK, the United Kingdom, US, the United States.

[a] In the European study, telephone interviews were used (excluding Spain where direct interviews were conducted due to lower proportion of households having telephone).

[b] Out of 11,740 participants (of 17,231 households contacted), 5,539 were considered ineligible. To calculate the response proportion, the number of respondents was divided by eligible participants (*the former response proportion)*. If same proportion of non-participants as there were ineligible among participants (47%), were also considered ineligible, response proportion was greater (*the latter response proportion)*.

[c] Study sample was close to representative of the general population regarding age, and/or age-standardization was used.

[d] OAB, overactive bladder; UTI, urinary tract infection.

[e] Time period during which the occurrence of symptoms was asked.

Original communications

Is Nocturia Equally Common Among Men and Women? A Population Based Study in Finland

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Purpose: We assessed the prevalence of nocturia and its association with sociodemographic factors.
Materials and Methods: Information was collected with a questionnaire mailed to a random sample of 6,000 subjects 18 to 79 years old, identified from the Finnish Population Register Centre. Nocturia was defined as 1 or more, or 2 or more voids per night. Information was collected using the DAN-PSS questionnaire with an additional question from the AUA-SI questionnaire. Age standardized prevalence was calculated using the European standard population. Logistic regression was used for multivariate analysis.
Results: Of the 6,000 subjects 62.4% responded and 97.9% of the participants provided information on all nocturia questions. The age standardized prevalence of nocturia (1 or more voids per night) was 37% (95% CI 34%-40%) among men and 43% (95% CI 40%-46%) among women. With criterion of 2 or more voids per night prevalence was 12% (95% CI 10%-14%) for men and 13% (95% CI 11%-14%) for women. Women 18 to 49 years old had more nocturia than men. At 50 to 59 years old half of men and women reported nocturia. In older age groups nocturia was more frequent among men than women. The prevalence of nocturia increased at a constant rate with age. It increased twice as rapidly in men as among women (increase in OR 7.3% [95% CI 6.5%-8.2%] and 3.5% [95% CI 2.9%-4.1%] per year among men and women, respectively).
Conclusions: The age standardized prevalence of nocturia (1 or more voids per night) was approximately 40% for both genders. In men the prevalence of nocturia increases more rapidly with age than in women. Nocturia is more common among women at a younger age but the differences disappear by middle age. In the elderly nocturia is more frequent among men.

Key Words: urination disorders, prevalence, age factors, sex, socioeconomic factors

Nighttime voiding is one of the most common and bothersome of all urological symptoms.[1] The ICS Subcommittee defined nocturia as "waking at night to void. This applies to any number of voids during the night . . ."[2] This definition does not provide an indication about the bother of nocturia,[3] yet, it is simple as it encompasses any nighttime voiding.

A substantial body of knowledge exists regarding nocturia in men 50 years old or older. Lately several studies have been conducted with younger men and women. In several studies nocturia has been reported with similar frequency among men and women. The estimated prevalence of nocturia has varied, largely due to different definitions. In all studies nocturia increased with patient age.[4–10] Most studies have not used age standardization which impedes comparison of their results. Schatzl et al reported 11% of men and 12% of women having nocturia in general population, defined as at least 2 voids per night.[11] They had a study population of approximately 2,500 people from the Vienna area undergoing voluntary health examination with an age range of 20 to 70 years old.[11] Coyne et al reported similar results with nocturia affecting men and women equally. Of 5,071 people 720 (14.2%) voided at least twice per night. The survey was conducted using a clinically validated computer assisted telephone interview.[3,12] In a Japanese study Yoshimura et al did not report differences in prevalence of nocturia between genders based on a health screening questionnaire. They reported nocturia (at least 2 voids per night) for 28.5% in a study of 4,568 men and 1,949 women.[13] In Sweden Rembratt et al asked about nocturia in 2,866 subjects older than 65 years.[14] Men had more nocturia than women (31% vs 26%, at least 2 voids per night).[14] In this study we assessed the prevalence of nocturia with a comprehensive, population based study comprising both genders and all adult age groups.

SUBJECTS AND METHODS

Study design. A questionnaire was mailed to a random sample of 3,000 women and 3,000 men 18 to 79 years old identified from the Finnish Population Register Centre. Stratification by age was used in the subject selection, with over-sampling of the younger age groups to obtain similar accuracy even in the age groups with lower nocturia frequency (table 1). No exclusions were made based on medical conditions or medications. Information on voiding symptoms was collected using the validated DAN-PSS questionnaire,[15] with an additional question from the AUA-SI.[16] The questionnaire included also items related to sociodemographic factors such as marital status, education, employment and

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TABLE 1. *Number of subjects and response rates by age and sex*

Age Group	Original Sample	Ineligible	Real Sample	Participants	Response Rate (%)
Men:					
18–29	800	4	796	388	48.7
30–39	800	2	798	428	53.6
40–49	600	0	600	334	55.7
50–59	300	0	300	198	66.0
60–69	300	2	298	227	76.2
70–79	200	4	196	151	77.0
Men overall	3,000	12	2,988	1,726	57.8
Women:					
18–29	800	3	797	510	64.0
30–39	800	2	798	496	62.2
40–49	600	3	597	408	68.3
50–59	300	1	299	212	70.9
60–69	300	1	299	238	79.6
70–79	200	1	199	139	69.8
Women overall	3,000	11	2,989	2,003	67.0
Both genders	6,000	23	5,977	3,729	62.4

urbanity. Questionnaires were first sent in late November 2003. Reminders were sent a month later. To those who did not respond the final round was mailed in February 2004.

Nocturia was defined as nighttime voiding. Responses to nocturia questions from DAN-PSS ("How many times do you have to void per night?") and AUA-SI ("Had to get up to urinate from the time you went to bed at night until you got up in the morning?") were combined. DAN-PSS questions were asked concerning last 2 weeks and the AUA-SI question concerning last month. In this study the definition of nocturia was 1 or more voids per night. A secondary analysis was conducted with nocturia defined as 2 or more voids per night.

Statistical analysis. Adjustment to correct for selection bias from nonresponse was used. First prevalence of nocturia by mailing round was calculated (by age and sex). As the prevalence decreased from the first to the second and third round responses, the mean decrease per screening round was calculated. The prevalence of nocturia among nonparticipants was assumed to be lower than among participants by a similar difference (ΔP) as had been observed between the first rounds, using the formula $P_{Nonrespondents} = P_{Participants} + \Delta P$. Age standardized prevalence was calculated using the European standard population. Logistic regression was used for multivariate analysis with presence or absence of nocturia as outcome measure. All confidence intervals are likelihood based.

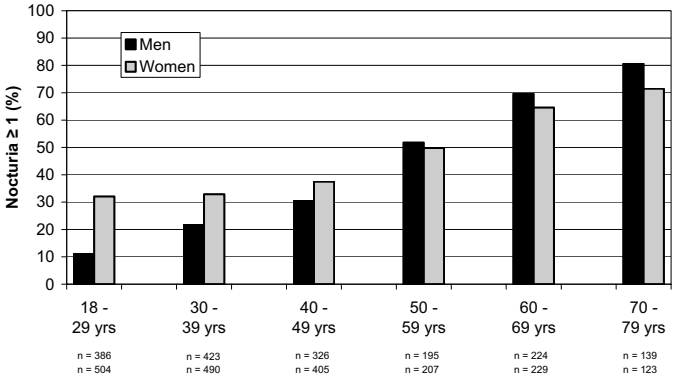

FIG. 1. Prevalence of nocturia defined as at least 1 void per night by age and sex.

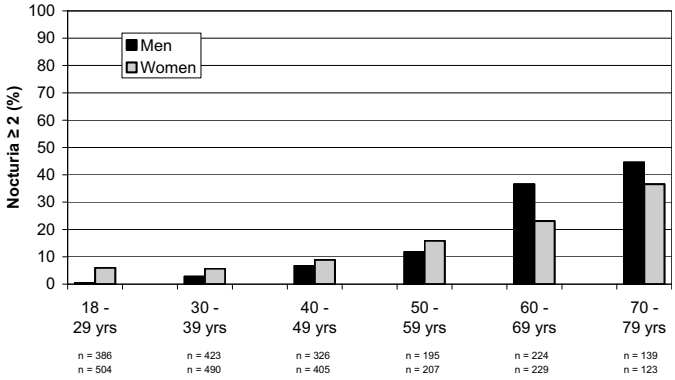

FIG. 2. Prevalence of nocturia defined as at least 2 voids per night by age and sex.

RESULTS

Of the 6,000 subjects 3,729 (62.4%) participated in the survey and 23 (0.4%) were ineligible being unable to complete the questionnaire due to grave disability or disease, death or living abroad (table 1). Of the respondents 3,651 (97.9%) completed all the nocturia questions. The response proportion by mailing round was 50.7% (1,891 subjects), 27.8% (1,036 subjects) and 15.1% (562 subjects). In addition 240 respondents (6.4%) did not give the date and, therefore, the mailing round could not be defined. Mean respondent age was 44.0 years (SD 16.5) and median 42.0 years for men, and mean 42.5 years (SD 16.0) and median 40.0 years for women. Of the respondents 61.2% did not report any nocturia, 27.1% reported voiding once per night and 11.7% twice or more per night.

Among men the prevalence of nocturia (defined as at least 1 void per night) increased from 1 per 9 in the youngest age group (18 to 29 years) to 1 per 5 at age 30 to 39 years, 3 per 10 at 40 to 49 years and slightly more than half in the age group 50 to 59 years. In the older age groups approximately 7 of 10 men in their 60s and 4 of 5 in their 70s reported nocturia. In absolute terms prevalence increased by approximately 10 percentage points per decade between 20 and 49 years old and twice as rapidly between age 50 and 69 years (fig. 1).

Among women approximately a third reported nocturia in the youngest age group (18 to 29 years), with only a slight increase up to age 49 years. At age 50 to 59 years the prevalence reached 50% while 2-thirds of women in the age group 60 to 69 years and nearly 3 quarters voided during the night at age 70 to 79 years. Hence, the most rapid increase in prevalence of nocturia in absolute terms occurred between age 50 and 69 years (fig. 1).

Nocturia (defined as at least 1 void per night) was more common among young women than young men. At age 18 to 29 years prevalence of nocturia was 3-fold higher among women and at age 30 to 39 years it was approximately 50% higher than among men. Prevalence among men started to approach that in women in the age group 40 to 49 years and reached the same prevalence at age 50 to 59 years, when half of men and women reported nocturia. In older age

TABLE 2. *Odds ratios of nocturia defined as at least 1 void per night by age groups and per year of age for men and women*

	Men				Women			
Age Group	No.	Odds Ratio	(95% CI)	p Value	No.	Odds Ratio	(95% CI)	p Value
18–29	386	1.0	(reference)		504	1.0	(reference)	
30–39	423	2.2	1.5–3.3		490	1.0	0.8–1.3	
40–49	326	3.5	2.3–5.2		405	1.3	0.9–1.7	
50–59	195	8.6	5.6–13.1		207	2.1	1.5–2.9	
60–69	224	18.3	11.9–28.0		229	3.9	2.8–5.4	
70–79	139	33.1	19.5–56.0		123	5.3	3.4–8.2	
Continuous age (per yr)	1,693	1.073	1.065–1.082	<0.001	1,958	1.035	1.029–1.041	<0.001

groups nocturia was more common among men, although the prevalence was high in both sexes (fig. 1).

When defined as at least 2 voids per night, nocturia increased linearly with age among both genders. Young women (18 to 29 years old) were more than 10 times more nocturic than young men (prevalence ratio 11.5). Men reached women in 50s to 60s. At age 50 to 59 years approximately 12% of men and 16% of women voided at least twice per night. In older age groups men had more nocturia than women. In the age group 60 to 69, approximately 2 of 5 men and every fourth woman voided at least 2 times per night. At age 70 to 79 years approximately 45% of men and 37% of women voided at least twice per night (fig. 2).

The age standardized (European standard) prevalence of nocturia (at least 1 void per night) was 36.5% (95% CI 33.5%-39.5%) for men and 43.3 (40.3%-46.4%) for women. With the criterion of 2 voids or more per night rates were 11.8% (10.2%-13.5%) for men and 12.6% (10.9%-14.3%) for women.

The prevalence of nocturia increased at a constant rate. Mean increases in ORs were 7.3% (6.5%-8.2%) per year for men and 3.5% (2.9%-4.1%) per year for women. So the increase in OR was more than 2 times higher in men than in women (table 2). There was no statistically significant departure from linearity in either sex. The trend was also similar defined as at least 2 voids per night (table 3).

After nonrespondent analysis the corrected prevalence of nocturia in men (at least 1 void per night) from the youngest age group to the oldest was 6.8%–16.6%–23.5%–44.6%–67.3%–76.0%. Corresponding figures among women were 27.4%–30.2%– 30.7%–40.8%–57.2%–71.7%. Corrected age standardized nocturia prevalence was 31.3% (95% CI 29.0%-33.5%) for men and 37.8% (95% CI 35.4%-40.1%) for women.

There were no statistically significant differences in the age standardized prevalence of nocturia (defined as at least 1 void per night) between married or cohabiting, divorced, widowed or single subjects. In large communities (population greater than 50,000) there were no differences in the prevalence of nocturia compared to small communities (population less than 50,000) after age standardization. Education did not affect prevalence of nocturia after standardizing for age. The prevalence of nocturia was similar among unemployed people compared to employed, retired people and students (table 4).

DISCUSSION

Overall, in our cross-sectional study of approximately 3,700 individuals more than a third of men and more than 2 fifths of women voided at least once per night after age standardization (European standard). With the definition of nocturia as at least 2 voids per night, approximately 1 of 8 men and women had nocturia. Nocturia was more common in women in younger age groups. By age 50 to 59 years, prevalence in men reached that in women in nighttime voiding. In the older age groups nocturia was more common in men. Prevalence of nocturia increased with age in men twice as rapidly as in women.

We use the ICS definition of nocturia. It is idealistic and conceptually easy to use. However, the ICS criterion is ambiguous and difficult to apply. It does not define nocturia by the severity or symptom bother. In most of earlier studies nocturia was defined as nighttime voiding at least twice per night and, therefore, we used this definition in the secondary analysis.

Our aim was to obtain a generalizable, unbiased estimate of the prevalence of nocturia. Therefore, we used no exclusion criteria such as pregnancy. Our study population was representative of the Finnish population according to the data from Statistics Finland.[17] The proportion of urban population was 39.6% among study participants, compared with 38.8% in the entire population. As for education the proportion with a university degree was 22.0% in our study and 24.6% in the whole country. The proportion unemployed was 7.0% in our material while the official figure at the time of the study was 8.0%. Also, the marital status distribution corresponded well to population data.[18]

TABLE 3. *Odds ratios of nocturia defined as at least 2 voids per night by age groups and per year of age for men and women*

	Men				Women			
Age Group	No.	Odds Ratio	(95% CI)	p Value	No.	Odds Ratio	(95% CI)	p Value
18–29	386	1.0	(reference)		504	1.0	(reference)	
30–39	423	5.6	1.2–25.2		490	1.0	0.6–1.6	
40–49	326	13.9	3.2–59.6		405	1.5	0.9–2.6	
50–59	195	25.7	6.0–110.1		207	3.0	1.8–5.1	
60–69	224	110.9	26.9–456.8		229	4.8	2.9–7.7	
70–79	139	154.6	37.0–645.5		123	9.1	5.4–15.3	
Continuous age (per yr)	1,693	1.096	1.082–1.109	<0.001	1,958	1.051	1.041–1.060	<0.001

TABLE 4. *Number of subjects and prevalence of nocturia by sex and sociodemographic characteristics*

	Men				Women			
	No Nocturia (less than once/night)		Nocturia (once or more/night)		No Nocturia (less than once/night)		Nocturia (once or more/night)	
	No.	%	No.	%	No.	%	No.	%
Marital status:								
Married/living together	754	69.2	453	75.1	770	67.3	553	67.9
Widowed	6	0.6	18	3.0	35	3.1	67	8.2
Divorced/separated	42	3.9	34	5.6	83	7.3	65	8.0
Never married	283	26.0	93	15.4	249	21.8	125	15.4
Missing	5	0.5	5	0.8	7	0.6	4	0.5
Education:								
Basic level	235	21.6	228	37.8	222	19.4	248	30.5
Vocational school	381	35.0	190	31.5	360	31.5	238	29.2
College	229	21.0	95	15.8	282	24.7	193	23.7
University	240	22.0	88	14.6	265	23.2	131	16.1
Missing	5	0.5	2	0.3	15	1.3	4	0.5
Employment:								
Student	145	13.3	26	4.3	188	16.4	79	9.7
Employed	747	68.5	261	43.3	737	64.4	418	51.4
Unemployed	74	6.8	36	6.0	82	7.2	60	7.4
Retired	106	9.7	274	45.4	120	10.5	250	30.7
Missing	18	1.7	6	1.0	17	1.5	7	0.9
Urbanity:								
Small community	637	58.4	400	66.3	668	58.4	487	59.8
Large community	445	40.8	201	33.3	467	40.8	326	40.0
Missing	8	0.7	2	0.3	9	0.8	1	0.1

To further improve the validity, we estimated the corrected prevalence of nocturia with adjustment for selection bias due to nonresponse. The corrected prevalence of nocturia was 31.3% among men and 37.8% among women. This indicates that a simple, naïve analysis overestimates the prevalence in men and women, but the difference between the genders remains similar after adjustment. Hence, this finding confirms our results.

The outcome of our study is comparable with a Swedish study,[14] which reported men having more nocturia than women in the elderly. It was also a population based survey and the response rate was high. However, it included only subjects at least 65 years old and so did not give any information about the younger population. Most earlier studies reported nocturia equally for both genders but they have not been population based and wide-ranging comprising both genders and all adult age groups.[4–10] In Austria Schatzl et al performed a study with almost 2,500 individuals including both genders.[11] The age adjusted prevalence of nocturia in their survey (defined as at least 2 voids per night) was similar to our finding. However, they reported nocturia to be almost equally common among men and women in all age groups. However, their study was not based on a representative study population. Their results were consistent with ours although differences between men and women were not statistically significant due to small sample sizes. Similarly Coyne et al in the United States using a telephone survey did not find any significant differences between the genders although the prevalence of nocturia increased with age like in our study.[3,12] The explanation for the different kind of results may again be the different methods used, as questionnaires can provide more reliable information than telephone surveys in several respects, including higher participation.[19]

Our study is the first population based cross-sectional study from youth to elderly with both genders. It is representative of Finnish adults. Our results were further strengthened by the results of the nonrespondent analysis and correction for selection bias. Age standardization improves comparability with other studies and generalizability to other population.

CONCLUSIONS

Most of earlier studies have reported nocturia equally commonly among men and women. The overall results of our study confirm this finding, as approximately 40% of men and women reported voiding at least once per night and approximately every eighth of both genders at least twice per night. However, in more detailed age specific analyses clear differences between the genders emerged. Nocturia was more common among young women than men, but the prevalence among men reaches that among women in the middle age and exceeds that after age 60 years.

Abbreviations and Acronyms

AUA-SI = American Urological Association symptom index
CI = confidence interval
DAN-PSS = Danish Prostatic Symptom Score
ICS = International Continence Society
OR = odds ratio

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Is the Prevalence of Overactive Bladder Overestimated? A Population-Based Study in Finland

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Background. **In earlier studies, one in six adults had overactive bladder which may impair quality of life. However, earlier studies have either not been population-based or have suffered from methodological limitations. Our aim was to assess the prevalence of overactive bladder symptoms, based on a representative study population and using consistent definitions and exclusions.** ***Methodology/Principal Findings.*** **The aim of the study was to assess the age-standardized prevalence of overactive bladder defined as urinary urgency, with or without urgency incontinence, usually with urinary frequency and nocturia in the absence of urinary tract infection or other obvious pathology. In 2003–2004, a questionnaire was mailed to 6,000 randomly selected Finns aged 18–79 years who were identified from the Finnish Population Register Centre. Information on voiding symptoms was collected using the validated Danish Prostatic Symptom Score, with additional frequency and nocturia questions. Corrected prevalence was calculated with adjustment for selection bias due to non-response. The questionnaire also elicited co-morbidity and socio-demographic information. Of the 6,000 subjects, 62.4% participated. The prevalence of overactive bladder was 6.5% (95% CI, 5.5% to 7.6%) for men and 9.3% (CI, 7.9% to 10.6%) for women. Exclusion of men with benign prostatic hyperplasia reduced prevalence among men by approximately one percentage point (to 5.6% [CI, 4.5% to 6.6%]). Among subjects with overactive bladder, urgency incontinence, frequency, and nocturia were reported by 11%, 23%, and 56% of men and 27%, 38%, and 40% of women, respectively. However, only 31% of men and 35% of women with frequency, and 31% of subjects of both sexes with nocturia reported overactive bladder.** ***Conclusions/Significance.*** **Our results indicate a prevalence of overactive bladder as low as 8% suggesting that, in previous studies, occurrence has been overestimated due to vague criteria and selected study populations regarding age distribution and low participation.**

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INTRODUCTION

Research on urinary storage problems has focused on incontinence in women, but during recent years other urinary storage problems (urgency, frequency, and nocturia) and their treatment among both sexes has commanded attention worldwide [1]. According to the International Continence Society, overactive bladder is a symptom-defined condition characterized by urinary urgency, with or without urgency incontinence, usually with urinary frequency and nocturia. The term overactive bladder is appropriate if there is no proven infection or other obvious pathology [2].

Overactive bladder is a poorly understood disorder [1]. In earlier reports, overactive bladder impaired quality of life [3,4], was underdiagnosed and undertreated [3,5–10], and cost more than $9 billion in the United States in 2000 [4,11]. However, the value of current overactive bladder treatment with antimuscarinics (with an increasing market [11% annual growth] worldwide of more than $2.2 billion in 2005 [12]) was questioned by the Cochrane Review [13].

Most earlier studies on overactive bladder have reported a prevalence of 10%–20% [3–7,9,14–16], the most widely cited studies estimating prevalence of overactive bladder as one in six [3,4]. Some studies have reported prevalence as high as 30% to 53% [8,10], while one showed only 8% [17], and one as low as 2% [18]. Unfortunately, all these studies have had methodological limitations [3,4,6,7,9,14–17] or have not been population-based [5,8,10,18].

We assessed the prevalence of overactive bladder in a population-based study of subjects of both sexes aged 18–79 years.

METHODS

Study design

Between November 2003 and February 2004, a questionnaire was mailed to a random sample of 3,000 men and 3,000 women aged

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Competing Interests: Aila Rissanen, Heini Huhtala, and Anssi Auvinen declare no conflict of interest, whereas Kari Tikkinen declares honorarium for Pfizer, Teuvo Tammela consultancies and honoraria for Pfizer, UCB and Astellas Pharma, and Antti Valpas consultanties for Pfizer and honoraria for Astellas Pharma.

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18–79 years drawn from the Finnish Population Register Center. Stratification by age was used in subject selection, with oversampling of the younger age groups to achieve a similar number of subjects with urgency/overactive bladder even in age groups with lower prevalence of urgency/overactive bladder (Table S1). We selected the target level of accuracy so that, given a true prevalence of 15%, we could exclude a prevalence of 10% or lower. Information on voiding symptoms was collected using the validated Danish Prostatic Symptom Score (Table 1) [19]. The questionnaire included items related to physician-diagnosed comorbidity (such as gynecological, internal, mental, musculoskeletal, neurological, and/or urological conditions), prescribed medication (over the last 3 months) and socio-demographic factors (such as marital, educational and employment status). Information on pregnancy was based on both questionnaire and data from the Finnish Population Register Center which also provided information on puerperium and urbanity. Questionnaires were first mailed in late November 2003, with reminders a month later. To persons who did not respond, final questionnaire was sent in February 2004. The last questionnaires were returned in June 2004. In accordance with Finnish regulations on questionnaire surveys, an exemption from ethical review was granted by the ethical committee of Tampere University Hospital (Tampere, Finland).

Exclusions and definitions

In the first analysis (Urgency analysis), we assessed the prevalence of urgency in adult population without applying any exclusion criteria (Figure 1). In the main analysis (Overactive bladder analysis), we assessed the prevalence of overactive bladder in adult population excluding those with physician-diagnosed: 1) chronic or acute urinary tract infection (in the past 2 weeks); 2) genitourinary cancer (excluding renal); or 3) contracted bladder (due to radiation or painful bladder syndrome), also 4) prescribed loop diuretics; and 5) pregnant or puerperal women, with puerperium defined as 6 weeks after childbirth (Table 2). In the third analysis (OAB without BPH analysis), in addition to above mentioned exclusions (of Overactive bladder analysis), we excluded men reporting physician-diagnosed benign prostatic hyperplasia. We performed a fourth analysis (All OAB symptoms analysis), to assess the relationship of all symptoms of overactive bladder with the same exclusions as used in the Overactive bladder analysis (Figure 1).

The urgency question from the validated Danish Prostatic Symptom Score was used to assess the prevalence of urgency and overactive bladder [19]. Overactive bladder with or without urgency incontinence classification was subdivided into overactive bladder cases based on the urinary urgency incontinence question of the Danish Prostatic Symptom Score. The mean daily number of voids was used for urinary frequency classification, whereas responses to nocturia questions from the Danish Prostatic Symptom Score and American Urological Association Symptom Index were combined [19,20]. The Danish Prostatic Symptom Score questionnaire was applied for the past 2 weeks, while frequency question and nocturia question of American Urological Association Symptom Index pertained to the past month (Table 1).

Statistical analysis

Subjects were stratified into 10-year age groups (18–29, 30–39, 40–49, 50–59, 60–69, and 70–79 years). The age-standardized prevalence was calculated using the general population of Finland (end of year 2003) by the Finnish Population Register Centre [21] (and the European standard population [22]). Binomial regression with identity link was used with presence of overactive bladder as outcome for extrapolation of age-specific prevalence of overactive bladder among people aged 80 years or more. All confidence intervals were likelihood-based. Confidence Interval Analysis 2.0.0 software (Trevor Bryant, University of Southampton, United Kingdom) was used for calculating age-standardized prevalences and confidence intervals (CI). Other analyses were performed using the Stata 9 (StataCorp LP, College Station, United States).

Adjustment for selection bias due to non-response was made for each symptom and combination of symptom (urgency, overactive bladder with or without urgency incontinence, frequency, and nocturia) after possible exclusions. First, prevalence of symptoms was calculated by mailing round (defined by date of questionnaire completion). As the prevalence of symptoms was lower in the subsequent than in the first round responses, the prevalence among non-participants (of the eligible study population) was assumed to be similar to the late responders, using formula:

$$P_{\text{Non-participants}} = (P_{\text{2nd round participants}} + P_{\text{3rd round participants}})/2$$

where P is prevalence of symptom (urgency, overactive bladder with or without urgency incontinence, frequency or nocturia).

Hence, based on the number of non-participants and prevalence of symptoms, we calculated the number of subjects with each symptom (and combinations in the All OAB symptoms analysis). The corrected prevalence of symptom was calculated using the formula:

$$P_{\text{corrected}} = (N_{\text{Participants}} \times P_{\text{Participants}} + N_{\text{Non-participants}} \times P_{\text{Non-participants}})/(N_{\text{Participants}} + N_{\text{Non-participants}})$$

Table 1. Overactive bladder symptom-related questions and definitions of the study in Finland, 2003–2004

Symptoms	Defining questions (with answer options)	Normal	Abnormal
Urgency and overactive bladder*	"Do you experience an imperative (strong) urge to urinate?" with answer options: never-rarely-often-always.	Never or rarely	Often or always
Urgency incontinence	"Is the urge so strong that urine starts to flow before you reach the toilet?" with answer options: never-rarely-often-always.	Never or rarely	Often or always
Frequency	"How many times did you usually urinate per day during the last month?"	≤8 voids per day	>8 voids per day
Nocturia	"How many times do you have to void per night?" and "How many times did you most typically get up to urinate from the time you went to bed at night until you got up in the morning?" were combined.	≤1 void per night	>1 void per night

*Urgency classification without any exclusions; overactive bladder classification was performed after exclusion of subjects with urinary tract infection or other obvious pathology (Table 2).

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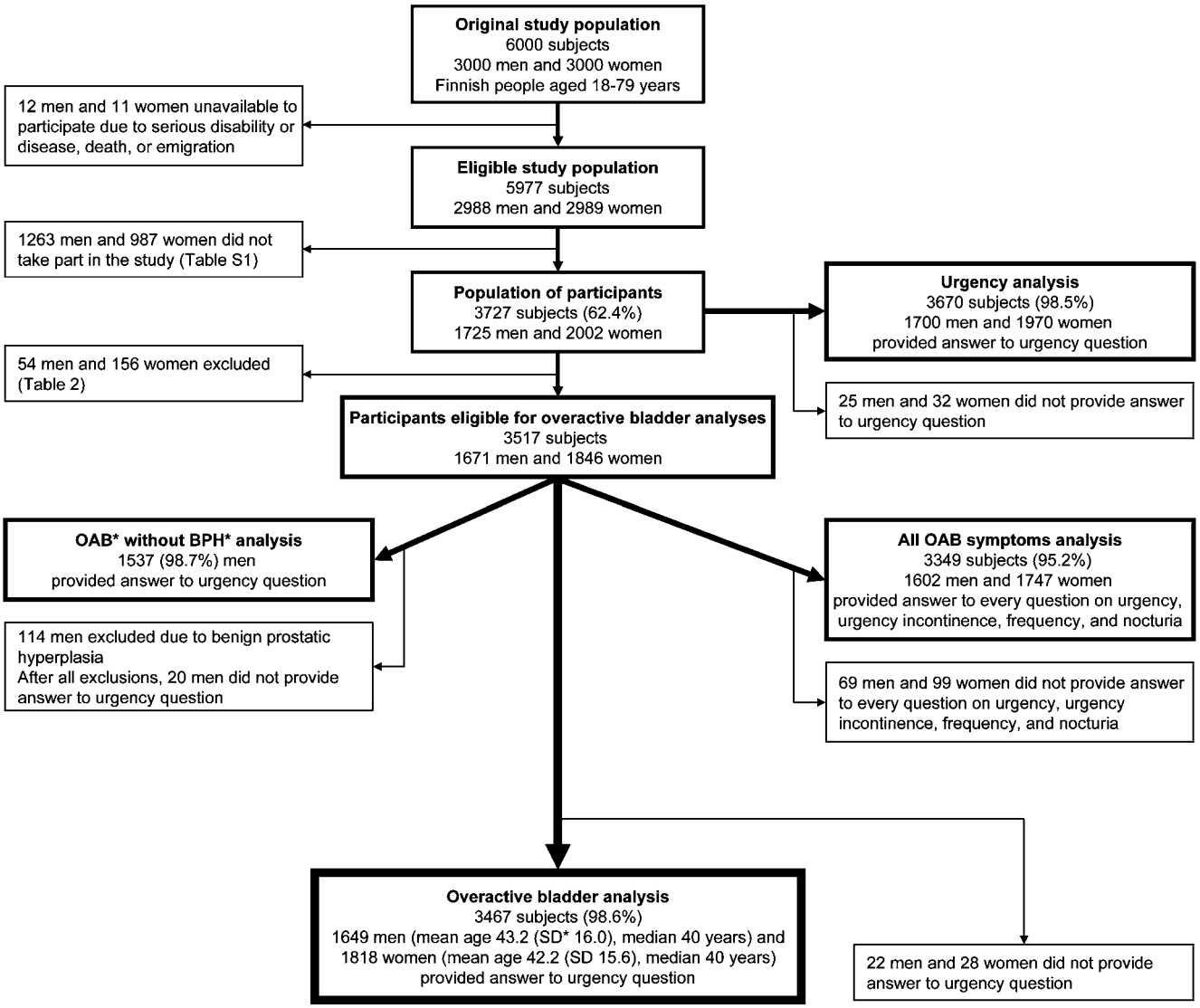

Figure 1. Flow chart of the study in Finland, 2003–2004. * OAB, overactive bladder; BPH, benign prostatic hyperplasia; SD, standard deviation.
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Table 2. Exclusions of the study population of overactive bladder analysis: number of excluded subjects among 1725 men and 2002 women in Finland, 2003–2004

Characteristics	Men	Women	Both sexes
Urinary tract infection*	16	59	75
Genitourinary cancer†	22	11	33
Contracted bladder‡	2	5	7
Puerperium§		8	8
Pregnancy		49	49
Taking loop-diuretics	19	30	49
Together	**54**	**156**	**210**

*Acute (in past 2 weeks) or chronic urinary tract infection.
†Excluding renal cancer.
‡Due to e.g. painful bladder syndrome or radiation.
§Puerperium defined as 6 weeks after childbirth.
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where P is prevalence of symptom (or combination of symptom) and N is number of subjects.

Concerning analyses for corrected prevalence of symptoms, we also performed an analysis excluding the same proportion of subjects among non-participants as we had done among participants, but the results did not materially change.

RESULTS

Of the 6,000 subjects approached for the study, 3,727 (62.4%) participated; 23 were unavailable because of serious disability or disease, death, or emigration (Figure 1). Of all participants, 98.5% ($n = 3670$) responded to the Danish Prostatic Symptom Score urgency question (Urgency analysis). For the assessment of overactive bladder prevalence (Overactive bladder analysis), we excluded 210 participants (Table 2). Most of the included participants (94.0%) also gave the date of questionnaire completion (Table S1). To assess the effect of benign prostatic hyperplasia on overactive bladder (OAB without BPH analysis), we further excluded 114 men. For comparison of all symptoms of overactive bladder, every

question on urgency, urgency incontinence, frequency, and nocturia was answered by 95.2% of subjects (Figure 1).

After age-standardization (to the Finnish general population), prevalence of urgency was 7.0% (95% CI, 5.9% to 8.1%) for men and 10.3% (CI, 8.9% to 11.6%) for women. The age-standardised prevalence of overactive bladder was 6.5% (CI, 5.5% to 7.6%) for men and 9.3% (CI, 7.9% to 10.6%) for women (Figure 2). Exclusion of men with benign prostatic hyperplasia decreased the prevalence of overactive bladder among men to 5.6% (CI, 4.5% to 6.6%). The effect of benign prostatic hyperplasia on the prevalence of overactive bladder was strongest in elderly with the prevalence decreasing from 17.5% to 13.5% at age 60–69 years and from 17.6% to 14.0% at age 70–79 years after further exclusion of men with benign prostatic hyperplasia.

In general, overactive bladder was slightly more common among women than men after age-standardization (Figure 2). It was more common among women in younger ages while among men it was more common in those aged 60 years and above. Among men, the sharpest increase occurred at age 60–69 years while among women the increase was more steady. The mean increases in prevalence of overactive bladder were 2.4 percentage point (CI, 1.9%-point to 3.0%-point) per 10-year age group for men and 1.9 percentage point (CI, 1.2%-point to 2.6%-point) per 10 years for women. There was no statistically significant departure from linearity in either sex (Figure 2).

In the All OAB symptoms analysis (Figure 3), urgency incontinence was reported by 11% of men and 27% of women among those with overactive bladder. Urinary frequency was reported by 23% of men and 38% of women with overactive bladder whereas the corresponding figures for nocturia were 56% and 40%. On the other hand, even though subjects with overactive bladder reported more frequency and nocturia than subjects without overactive bladder, only 31% of men and 35% of women with frequency, and 31% of subjects among both sexes with nocturia reported overactive bladder (Figure 3).

Without corrections for non-response, urgency was reported by 7.9% (CI, 6.5% to 9.3%) of men and 10.7% (CI, 9.0% to 12.3%) of women after age-standardization. The corresponding figures for overactive bladder were 7.3% (CI, 5.9% to 8.7%) for men and 9.7% (CI, 8.0% to 11.3%) for women. Further exclusion of men with benign prostatic hyperplasia decreased the non-corrected prevalence of overactive bladder to 6.3% (CI, 4.8% to 7.7%) among men aged 18–79 years.

DISCUSSION

In our study, the prevalence of overactive bladder was 6.5% for men and 9.3% for women, i.e. no more than 8% of adult population aged 18–79 years had overactive bladder. Subjects with overactive bladder reported more frequency and nocturia than those without overactive bladder, but the majority of subjects with frequency, or nocturia did not report overactive bladder.

The reported prevalence of overactive bladder has varied widely in earlier studies due to differences in symptom assessment, study population, data collection, and definition of overactive bladder including exclusion criteria. Most other studies have reported greater prevalence of overactive bladder than found in our study [3–10,14–16]. Some [3–5,15–17] but not all studies [6] have also reported more urgency incontinence among subjects with overactive bladder than we found.

The definition of a symptom-defined disorder, such as overactive bladder, has a major impact on outcome [23]. We used the overactive bladder definition of International Continence Society, with urgency (defined as sudden compelling desire to void) as a sufficient criterion for overactive bladder [2]. This definition is idealistic and ambiguous. The qualitative definition disregarding severity or symptom bother makes it difficult to apply. The classification of a symptom (including the time period during which the occurrence of symptoms is asked) strongly influences the result, due in part to fluctuating character and very high remission rates of lower urinary tract symptoms, including urgency [24]. We asked about urgency in the last 2 weeks with four response option: if urgency was reported "never" or "rarely", the subject was classified as normal, while "often" and "always" were regarded as abnormal. Our classification of urgency differed slightly from the Austrian study, where a five-point scale was used for the last 4 weeks and subjects who "occasionally" had urgency were also defined as abnormal [5]. Similarly, in the Chinese community-based study, women who reported urgency "occasionally" were

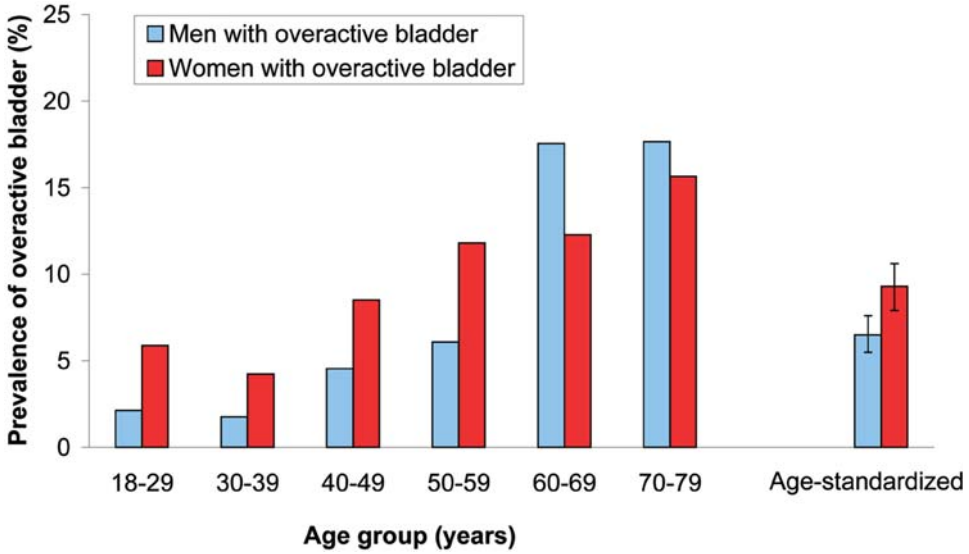

Figure 2. The prevalence of overactive bladder in Finland, 2003–2004. The blue bars indicate men with overactive bladder and the red bars women with overactive bladder. Age-standardization was performed using the general population [21].
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regarded abnormal but only in the presence of other symptoms (with criteria every 3 hour for frequency, twice per night for nocturia, and once a week or less frequent for urge incontinence) [17]. In the US study, those who reported four or more urgency episodes during the last 4 weeks and who also reported more than eight voids per day, or at least one coping strategy were classified as abnormal [4]. Some studies asked symptoms over a very long or unspecified time [3,9,16,18] whereas some did not exactly describe symptom classification, questions asked, or time concerning the symptom question [7,8,10,14,15]. Overall, in all symptom-defined disorders (including overactive bladder), defining very mild/rare symptoms as pathological blurs the distinction between mild and severe, causing a considerable risk of encouraging healthy people to perceive themselves as sick [25].

In the standardization report [2], the current definition of overactive bladder includes "…usually with frequency and nocturia.", and those symptoms are defined as complaints without any severity assessment. We defined frequency as more than 8 voids per day and nocturia as more than one void per night (as in some earlier reports [3–5,18]) while those definitions are presumably clinically more relevant based on prevalences of frequency and nocturia in earlier studies [9,16,26,27]. On the other hand, the definition of frequency or nocturia has no effect on the prevalence of overactive bladder when based on the current definition.

According to the standardization report [2], for the diagnosis of overactive bladder subjects with "urinary infection or other obvious pathology" should be excluded. Identification of overactive bladder without excluding known reasons causing urgency can result in overestimate of prevalence. We excluded subjects with urinary tract infection, genitourinary cancer, contracted bladder, or loop diuretics, as well as pregnant and puerperal women. In addition, we performed an analysis excluding men with benign prostatic hyperplasia as its effect on overactive bladder is unclear [1]. Some earlier studies did not report any exclusion criteria [6,8–10,14,16–18], or excluded only subjects with urinary tract infection [3]. In the Austrian and Brazilian studies [5,7], exclusions were slightly broader (for example, diabetes) than in our study and in the US study [4] even more extensive (including diabetes, congestive heart failure, and excessive fluid intake). In the Austrian study, exclusions were performed for subjects with urgency, not for the whole study sample.

Several articles have been published on the prevalence of overactive bladder (English-language MEDLINE and PubMed search to December 2006). However, many of these studies have not been population-based [5,8,10,18], whereas the population-based studies [3,4,6,7,9,14–17] have failed to: 1) apply the current definition of overactive bladder [3,4,6,14,15,17], 2) report any exclusions [6,9,16,17], 3) include all adult ages [3,6,7,9,15], 4) include both sexes [17], 5) report response rate or non-participants [3,7,9], or 6) achieve good response rate [4,6,9,16] (Table 3). Furthermore, none of the earlier studies used non-response analysis to adjust for selection bias. On the other hand, as long as the symptom definition of overactive bladder is more like a description without any severity or bother assessment, there is no absolutely correct way to study the epidemiology of overactive bladder.

We used postal questionnaires to assess both the prevalence of urinary symptoms and co-morbidity. Overactive bladder is a symptom-defined condition requiring self-report. Mailed questionnaires reflect urodynamics better than interview-assisted questionnaire responses [28]. Furthermore, mailed questionnaires provide more reliable information than telephone surveys in several aspects, including higher participation [29]. Telephone surveys have commonly been used, including the most cited figures [3,4,9,16].

Even though most studies reported higher prevalence estimates than ours, the differences can be readily explained by dissimilarities in study procedures. For instance, Milsom and colleagues stated in their multinational study that 16.6% had overactive

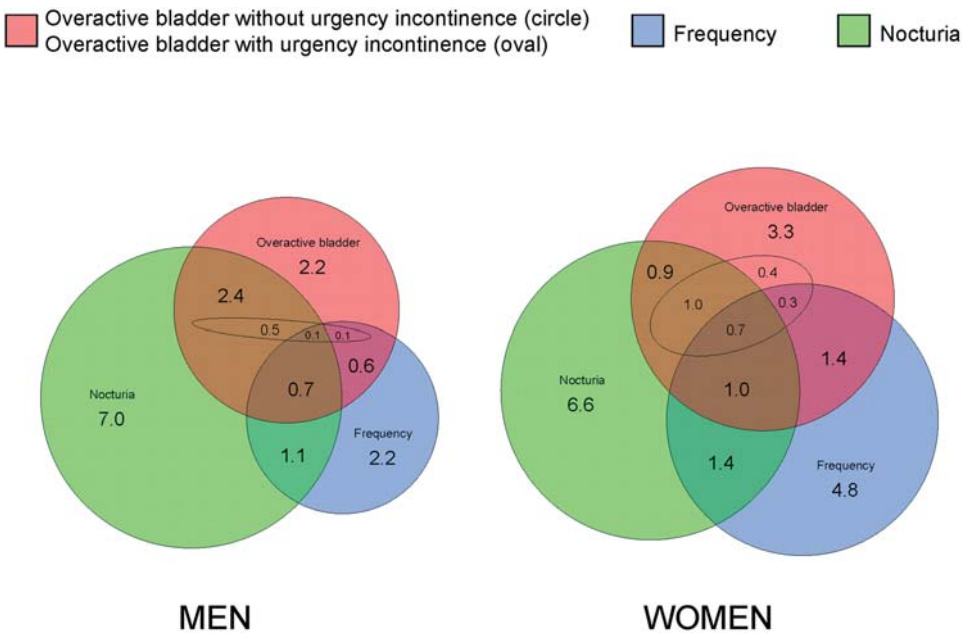

Figure 3. Age-standardized prevalence of overactive bladder symptoms among Finnish people aged 18–79 years, 2003–2004. The red circle represents subjects with overactive bladder without urgency incontinence excluding the area of the red oval representing subjects with overactive bladder with urgency incontinence. The blue circle represents subjects with urinary frequency (defined as more than eight voids per day) and the green circle nocturia (defined as more than one void per night). Age-standardization was performed using the general population [21].
doi:10.1371/journal.pone.0000195.g003

Table 3. Overview of published population-based studies assessing the prevalence of overactive bladder (OAB*) among both sexes (MEDLINE and PubMed search to December 2006) with present study (*in chronological order*)

	Origin of the study sample							
	European [3]	**USA [4]**	**Canada [9]**	**Japan [6]**	**Porto Alegre [7]**	**Matsu [15]**	**International [16]**	**Finland**
Design	Telephone interview (85%)†	Telephone interview	Telephone interview	Mailed questionnaire	Mailed (?) questionnaire	Questionnaire administered by nurse	Telephone interview	Mailed questionnaire
Respondents	16,776	5,204	3,249	4,570	913	1,921	19,165	3,727
Response rate (%)	Not reported	44.5/57.1‡	43.4	45.3	Not reported	67.0	33.0	62.4
Age range (years)	40–75+	18–75+	35–75+	40–100	15–55	30–79	18–70+	18–79
Representative age-distribution of adults§	No	Yes	No	No	No	No	Yes	Yes
Current definition of OAB	No	No	No	No	Yes	No	Yes	Yes
Time period	Not defined	Last 4 weeks	Past month	Past month	Not defined	Past 4 weeks	Not defined	Last 2 weeks
Exclusion criteria - UTI*/other	Yes/No	Yes/Yes	No/No	No/No	Yes/Yes	No/Yes	No/No	Yes/Yes
Non-response analysis for prevalence estimate	No	No	No	No	No	No	No	Yes
Prevalence of OAB (%)	17	16	18	12	19	17	12	8

*OAB, overactive bladder; UTI, urinary tract infection

†In the European study, in five out of six countries, telephone interview was used (excluding Spain where direct interviews were conducted due to lower proportion of households having telephone)

‡Out of 11,740 participants (of 17,231 households contacted), 5,539 were considered ineligible. To calculate response rate, the number of respondents was divided by eligible participants (*the former response rate*). If same proportion of non-participants, as there were ineligible among participants (47%), were also considered ineligible, response rate was greater (*the latter response rate*).

§Study sample was close to representative of the general population regarding age, and/or age-standardization was used.

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bladder [3]. They did not use the current definition of overactive bladder and excluded only subjects with urinary tract infection. In their study (all subjects at least 40 years old) only 54% of subjects with overactive bladder reported urgency corresponding approximately to 9.0% prevalence of urgency. Hence, based on their study population 9.0% prevalence of overactive bladder would also be overestimated due to age distribution and absence of other exclusion criteria and non-response analysis. This estimate concurs with our results.

Of the Finnish adult population, 5% are aged 80 years or more [21]. As our sample did not include this age group, we extrapolated the prevalence rates for people aged 80 years or more. Based on extrapolated prevalence rates of overactive bladder among this age group (20.0% for men and 17.5% for women), we calculated age-standardized prevelance of overactive bladder for men (6.9%) and women (9.8%). Adjustment for people aged 80 years or more did not materially change prevalence rates as they were within the confidence limits of our estimates indicating that one in twelve (8.4%) had overactive bladder in the general population. However, our study population was Caucasian, which may diminish generalizability to other ethnicities. Most reported studies also used a study population that was mainly or totally Caucasian without proper comparison of prevalence of overactive bladder between different ethnicities [3–5,7,9,16,18]. Consequently, there is a need to examine the effect of ethnic differences on the prevalence of overactive bladder.

Our aim was to obtain a generalizable, unbiased estimate of the prevalence of overactive bladder in both genders. Our study population from youth to old age was representative of Finnish adults in terms of socio-demographic and anthropometric factors [27,30] and included people aged 18–79 years. Age-standardization was used to improve comparability with other studies and generalizability to other populations. Current population distribution of Finland was used so as not to underestimate prevalences. We calculated corresponding figures also using European standard population [22], but as the age structure was younger in that, the prevalence rates were slightly lower (not reported). To further improve the generalizability, we estimated corrected prevalence of overactive bladder with adjustment for people aged at least 80 years. After adjustment for people aged 80 years or more, the results remained substantially the same. A good response rate was achieved, but to further improve the validity, we estimated the corrected prevalence of overactive bladder with adjustment for selection bias due to non-response. We corrected prevalence for selection bias on the assumption that overactive bladder was equally common among non-responders and in late responders. The corrected estimate was smaller, indicating that naïve analysis overestimates prevalence.

Our results suggest that the prevalence of overactive bladder has been overestimated so that the true prevalence is approximately half of that proposed earlier. Overactive bladder affects approximately one out of twelve adults of Caucasian origin.

SUPPORTING INFORMATION

Table S1 Number of subjects in different analyses and in overactive bladder analysis.
Found at: doi:10.1371/journal.pone.0000195.s001 (0.07 MB DOC)

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Author Contributions

Other: Designed the study: KT TT AA. Peformed further statistical analyses: KT HH AA. Contributed to the interpretation of the findings and formulation of the report: KT TT AR AV HH AA. Wrote the first draft of the manuscript: KT. Contributed to revision of the manuscript: KT TT AR AV HH AA.

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Voiding Dysfunction

Nocturia Frequency, Bother, and Quality of Life: How Often Is Too Often? A Population-Based Study in Finland

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Abstract

Background: Nocturia (ie, waking at night to void) is common and disrupts sleep. Traditionally, one nightly episode has been regarded as clinically meaningless, yet the justification for this belief remains weak.
Objective: To evaluate the association among frequency of nocturia and bother and health-related quality of life (HRQoL).
Design, setting, and participants: In 2003–2004, a survey was mailed to a random sample of 6000 subjects aged 18–79 yr who were identified from the Finnish Population Register Centre (response proportion was 62.4%; 53.7% were females).
Measurements: HRQoL and bother from nocturia were examined in relation to self-reported nocturia frequency (using the American Urological Association Symptom Index and the Danish Prostatic Symptom Score). Bother from nocturia was assessed on a four-point scale (none, small, moderate, major). HRQoL was measured with the generic 15D instrument on a 0–1 scale with a minimum clinically important difference of 0.03.
Results and limitations: Degree of bother increased with nocturia frequency ($p < 0.01$). The most commonly cited degree of bother for those with one, two, and three nightly voids was no bother, small bother, and moderate bother, respectively. The mean age-adjusted 15D score for men (and women) without nocturia was 0.953 (0.950) and 0.925 (0.927) with one void per night, 0.898 (0.890) with two voids per night, and 0.833 (0.840) with three or more voids per night. Statistically significant decreases were found in 15D score and in all 15D dimensions except eating. Although the response rate was high, approximately one third of those contacted did not participate in the study.
Conclusions: At least two voids per night is associated with impaired HRQoL. The majority of people report having bother when the number of nocturia episodes is two and moderate or major bother when the number is three or more. One void per night does not identify subjects with interference from nocturia and, thus, is not a suitable criterion for clinically relevant nocturia.

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1. Introduction

Nocturia is a highly prevalent symptom [1] that can result from primary sleep disorders, from overproduction of urine at night (nocturnal polyuria), and/or from conditions causing low voided volumes (eg, benign prostatic hyperplasia, detrusor overactivity). In 2002, the International Continence Society defined nocturia as waking up at night from sleep to void. This consensus definition made explicit that *nocturia* was the term to be used whether or not the subject perceived bother and even if there were only a single nightly void [2].

Deciding the level of nocturia that is *too often* is a meaningful practical and theoretical consideration. Bothersome symptoms of patients should not be trivialised or ignored; alternatively, expected symptoms should not be excessively medicalised. If one episode of nocturia is to be regarded as usual, does the condition become *abnormal* with two episodes, or should that number be three or more? Although it is obvious that more frequent nocturia likely causes more bother, the relationship is not perfectly correlated [3]. Past studies on the impact of nocturia on health have been inconsistent or nonspecific regarding how the degree of nocturia affects bother (and quality of life [QoL]). In one study, nocturia of "2 or more times per night" (or nocturia that occurred "fairly often") was associated with lower self-rated physical and mental health [4]. Elsewhere, female patients were shown to seek medical advice about nocturia if they averaged three or more episodes [5]. There is also evidence suggesting that the impact of nocturia may differ by gender. Early use of the International Consultation on Incontinence Modular Questionnaire–Nocturia Quality of Life questionnaire in a mixed gender population suggested that the impact of nocturia was greater for women [6]. By contrast, the effect size of the association for nocturia and major depression may be twice as great in men than in women [7].

It is important to understand the associated bother and QoL impact of nocturia. This population-based study aims to examine (1) the bother from nocturia by age and sex, (2) the relationship between nocturia frequency and bother, and (3) the impact of nocturia on health-related QoL (HRQoL).

2. Methods

2.1. Design

In 2003–2004, questionnaires were mailed to 3000 men and 3000 women (aged 18–79) who were drawn randomly from the Finnish Population Register. Stratification by age was used in subject selection, with oversampling of the younger age groups to ensure sufficient precision, even in age groups with lower nocturia frequency [1,8]. The questionnaires elicited information on occurrence and bother of nocturia and on HRQoL [9–11]. The questionnaire also included items on sociodemographic, anthropometric and reproductive factors. Information on pregnancy was based on the questionnaire and on data from the Finnish Population Register, which also provided information on parity (including delivery dates) and urbanity. More detailed study procedures have been published [1,8,12]. Under the Finnish regulations on surveys, exemption from ethical review was granted by the ethics committee of the Pirkanmaa Hospital District (Tampere, Finland).

2.2. Exclusions and measures

We excluded pregnant and puerperal (6 wk after delivery) women and those subjects reporting urinary tract infection. Responses to nocturia questions from the Danish Prostatic Symptom Score (DAN-PSS) [10] and the American Urological Association Symptom Index (AUA-SI) [9] were combined to assess nocturia. The DAN-PSS has four response options for nocturia, whereas the AUA-SI has six (Table 1). Subjects who did not respond to the AUA-SI were not included in the analyses because of the lack of precise information on the number of nocturnal voids. In the case of conflict between the responses to the two questions, the DAN-PSS was regarded as the gold standard, and the DAN-PSS response nearer to the AUA-SI response was chosen. We have earlier shown that consistency between the two nocturia questions is excellent [12]. In this study, the frequency of nocturia was classified as one, two, three, or at least four voids per night for bother analyses. The DAN-PSS was also used for bother assessment (Table 1). For HRQoL analyses, subjects were classified by reported nocturia into those without nocturia (reference group), those with one void per night, those with two voids per night, and those with three or more voids per night.

HRQoL was measured with the generic 15D instrument [11]. All 15 dimensions have a single question with five response options. The 15D

Table 1 – Questions for frequency and bother of nocturia with response options*

	Defining questions	Response options
Frequency of nocturia	How many times do you have to void per night? [10]	None 1–2 times 3–4 times 5 or more times
	How many times did you most typically get up to urinate from the time you went to bed at night until you got up in the morning? [9]	Never 1 time 2 times 3 times 4 times 5 or more times
Bother of nocturia	If you have to urinate during the night, is this a bother for you? [10]	No Small Moderate Major

* The Danish Prostatic Symptom Score covered the previous 2 wk [10], and the American Urological Association Symptom Index covered the previous month [9].

instrument can be used as a profile measure or for a single index score (15D score) by means of population-based preference weights. They generate the dimension-level values on a 0–1 scale for profiles and the index score on a 0–1 scale (0 = dead, 1 = full health); the minimum clinically important difference in the 15D score is 0.03 (corresponds to minimum generally distinguishable difference). Missing values on one to three dimensions were imputed using linear regression analysis with the other 15D dimensions, age, and sex as explanatory variables or predictors [11]. Responsiveness, reliability, and validity of the 15D instrument have been thoroughly established, and it has been used extensively in clinical and health care research [13].

2.3. Statistical analysis

Subjects were stratified into age groups: 18–29, 30–39, 40–49, 50–59, 60–69, and 70–79 yr. Age-standardised prevalence was calculated using the population structure of Finland at the beginning of 2004. Confidence Interval Analysis v.2.0.0 software (Trevor Bryant, University of Southampton, Southampton, UK) was used for calculating age-standardised prevalences and confidence intervals (CI). Other analyses were performed with SPSS v.15.0.1 (SPSS Inc., Chicago, IL, USA). The effect of nocturia frequency (one, two, three, or four or more voids per night) on bother was assessed using the Fisher exact test for grouped data. To assess the effect of age on perceived bother, a linear-by-linear association test was used separately for both sexes. Effect modification was assessed according to the statistical significance of the interaction term (age × sex) added in a model containing the main effects (age, sex). For effect modification analyses, we performed logistic regression with (1) any bother from nocturia and (2) at least moderate bother from nocturia as outcomes (separately for various nocturia frequencies: one, two, three, or four or more voids per night).

The age-adjusted mean 15D score and dimension-level values for the 15D dimensions were calculated by frequency of nocturia (zero, one, two, or three or more voids per night). The effect of nocturia on HRQoL (15D score and dimension-level values) was assessed using analysis of covariance with adjustment for age (by sex; sex was significantly associated [$p < 0.05$] with seven dimensions); tests for trend were conducted by including nocturia in four categories (zero, one, two, or three or more voids per night) as a linear term in the model. Regarding 15D score, effect modification was assessed according to the statistical significance of the interaction terms (nocturia × age and nocturia × sex) in models containing the main effects (age, sex, and nocturia).

Association of major comorbidity (coronary artery disease, mood disorder, obstructive lung disease, obstructive sleep apnea, osteoarthrosis) with HRQoL and nocturia was assessed. Subjects were classified into three groups with cut-off points defined as 15D scores corresponding to the minimum clinically important difference (0.03) and twice the minimum clinically important difference (0.06) below the average of subjects without nocturia. By nocturia, subjects were classified as those free of nocturia, those with one void per night, and those with two or more voids per night. Separately for each major comorbidity, test for trend was obtained with logistic regression by including HRQoL/nocturia in three categories as a linear term in the age-adjusted model.

To estimate possible selection bias due to nonresponse, age-standardised bother from nocturia and age-adjusted mean 15D score and dimension-level values were compared among three mailing rounds [8]. Differences among rounds were small and nonsystematic.

3. Results

Of 6000 subjects who were approached for the study, 3727 (62.4%) participated; 23 subjects were unavailable and 130 were excluded (Fig. 1). Of the 3597 subjects included, 97% answered questions on both frequency of nocturia and degree of bother and completed 15D. (Of the final analysis population, 94% answered all 15 questions of 15D, 5% answered 14 questions, and 1% answered 13 questions.)

Nocturia and no bother were reported by 15.8% (95% CI: 13.7–17.9) of the men and by 20.5% (95% CI, 18.1-23.0) of

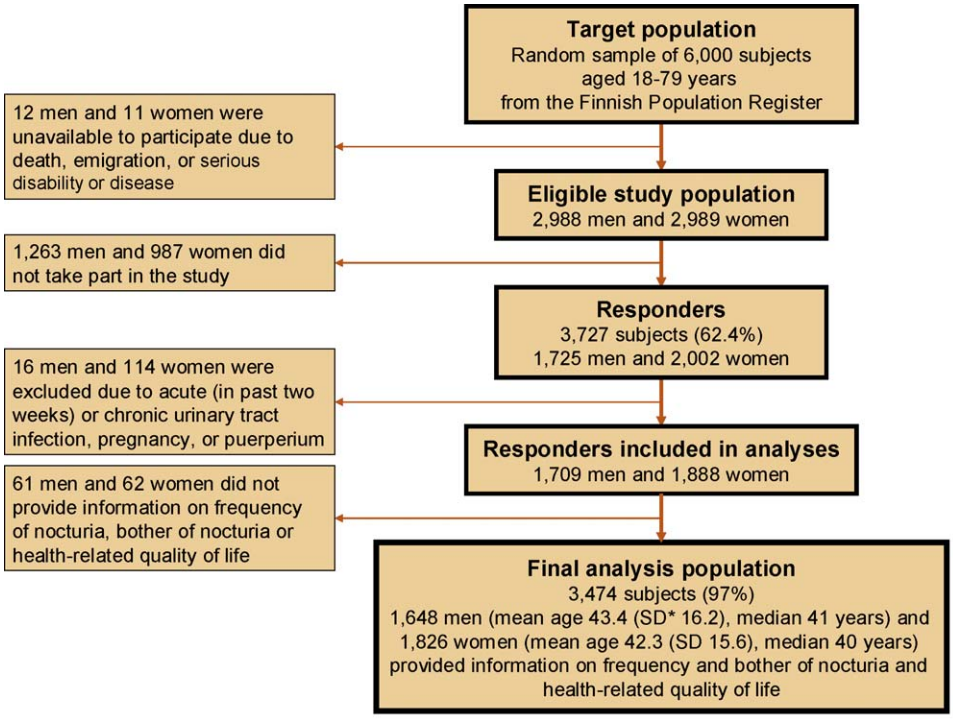

Fig. 1 – Study flow chart. SD = standard deviation.

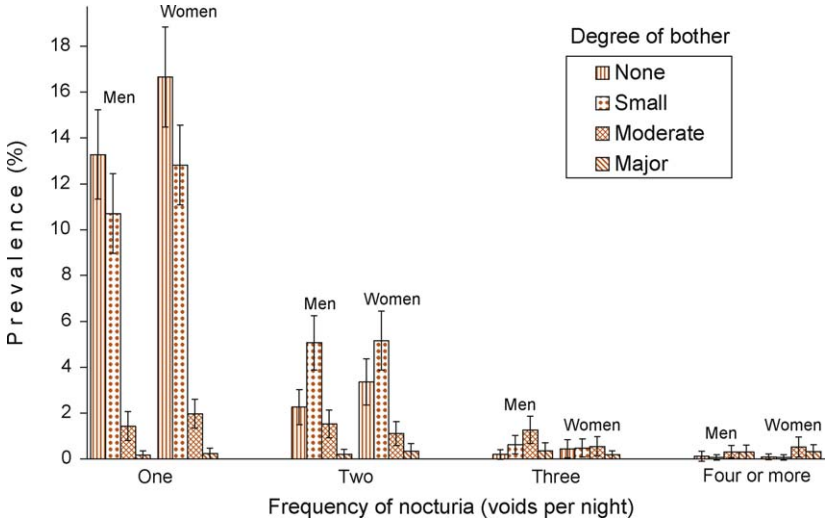

Fig. 2 – Prevalence of bother by frequency of nocturia (one, two, three, or four or more voids per night) among men and women. Age standardisation was performed using the age structure of Finland (beginning of 2004). Error bars represent 95% confidence intervals.

the women; 16.4% (95% CI: 14.3–18.6) of the men and 18.5% (95% CI: 16.3–20.7) of the women reported small bother from nocturia; 4.5% (95% CI: 3.4–5.6) of the men and 4.1% (95% CI: 3.1–5.2) of the women reported moderate bother from nocturia; and 1.0% (95% CI: 0.5–1.6) of the men and 1.2% (95% CI: 0.7–1.8) of the women reported major bother from nocturia. Overall, there was no gender difference in prevalence of bothersome nocturia or degree of bother among those with bothersome nocturia (Fig. 2).

The degree of bother increased with frequency of nocturia in both sexes ($p < 0.01$ for each age group). Moreover, comparing two adjacent categories at a time, the increase was statistically significant with each increment in number of nightly voids. Slightly more than half of respondents with one void per night reported no bother, and a similar proportion of subjects with two voids per night reported small bother. Of those with three and four or more voids per night, slightly > 40% reported moderate bother, with 14% and 36% reporting major bother, respectively (Table 2). Based on the logistic regressions, age did not affect perceived bother among men, but among women, bother from nocturia decreased with increasing age

Table 2 – Age-standardised proportions for degree of bother by frequency of nocturia in both sexes*

Frequency of nocturia (voids per night)	Degree of bother from nocturia			
	None	Small	Moderate	Major
One, %	52.2	41.1	5.9	0.7
Two, %	29.3	53.8	13.9	3.1
Three, %	17.4	26.7	41.9	14.0
Four or more, %	11.3	7.0	46.0	35.7

* Age standardisation was performed using the age structure of Finland at the beginning of 2004.

($p < 0.001$, $p < 0.01$, $p = 0.02$, and $p = 0.08$ for women with one, two, three, or four or more voids per night, respectively) (Fig. 3). Interaction was found between age and sex for any bother among subjects with one void per night ($p < 0.01$) and for at least moderate bother among subjects with two voids per night ($p = 0.02$), indicating effect modification (different effect of age on bother by gender).

The age-adjusted mean 15D score was 0.953 (95% CI: 0.948–0.957) for men without nocturia, 0.925 (95% CI: 0.918–0.932) for men with one void per night, 0.898 (95% CI: 0.886–0.910) for men with two voids per night, and 0.833 (95% CI: 0.813–0.853) for men with three or more voids per night. Among women, the corresponding figures were 0.950 (95% CI: 0.946–0.954) without nocturia, 0.927 (95% CI: 0.921–0.933) with one void per night, 0.890 (95% CI: 0.879–0.901) with two voids per night, and 0.841 (95% CI: 0.818–0.863) with three or more voids per night. The findings remained similar when men and women were stratified into three age groups (18–39, 40–59, and 60–79 yr) (Fig. 4). Generally, the 15D score did not differ between sexes ($p = 0.79$) and relation between nocturia and HRQoL was similar in both sexes ($p = 0.38$ for interaction term). Impact of nocturia, however, was weaker among young women than among young men ($p = 0.01$ for interaction term) (Fig. 4). In both sexes, nocturia was associated with statistically significant decrease on all dimensions of HRQoL except eating (Fig. 5).

Major comorbidities assessed were more common among those with impaired HRQoL (Table 3) ($p < 0.001$ for trend of each comorbidity). Parallel results were also observed for most of the major comorbidities assessed by increasing nocturia ($p < 0.05$ for all except obstructive lung disease and osteoarthrosis in men). Furthermore, calculating the age-adjusted 15D dimension-level values and score for both sexes without imputation for missing values

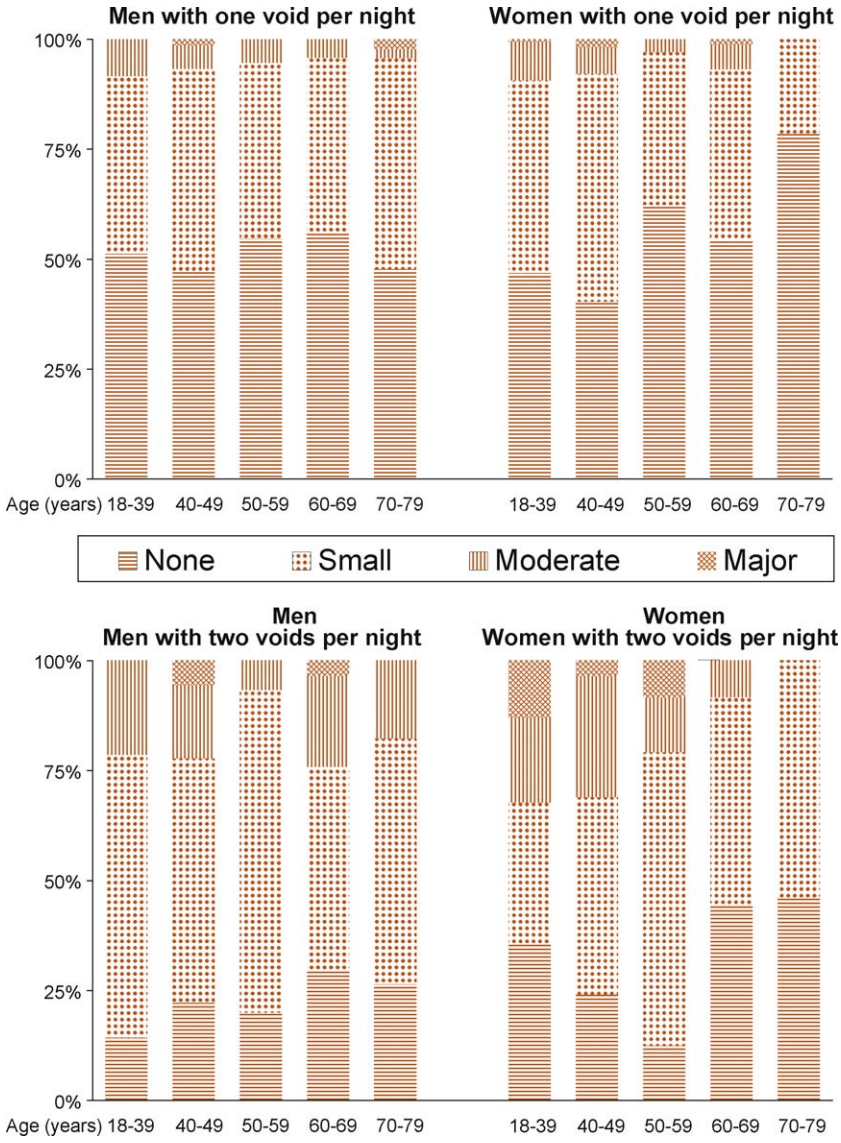

Fig. 3 – Degree of bother (scale: none, small, moderate, major) from nocturia by age group among men and women (A) with one void per night and (B) with two voids per night.

yielded similar results (eg, 15D scores were 0.953, 0.928, 0.899, and 0.835 for men and 0.952, 0.929, 0.895, and 0.863 for women with zero, one, two, or three or more voids per night, respectively).

4. Discussion

We report the bother and HRQoL effects of nocturia as a function of frequency of nocturia episodes using a population-based sample of both sexes aged 18–79. Most respondents reported bother from nocturia with two or more nightly nocturia episodes and moderate bother only with three or more nocturia episodes. Two nocturia episodes impaired HRQoL compared with those with no nocturia. At least three episodes of nocturia resulted in further impairment of similar magnitude. Using a standardised measure of a clinically important difference in a 15D score, those reporting one nocturia episode were not meaningfully different from those reporting none.

In this study, only 1% of respondents (regardless of nocturia status) reported that waking up at night to urinate was a major bother, while 4% reported moderate bother from nocturia. Among those with any nocturia, approximately one in eight reported moderate or major bother, while either no or small bother was reported by slightly >40% of subjects with nocturia. Generally, degree of bother increased with nocturia frequency; hence, of those with four or more voids per night, 36% regarded it as a major bother and 46% regarded it as a moderate bother.

Our results provide new insights into the impact of nocturia. Earlier results suggest that nocturia may impair well-being more than generally recognised. Nocturia can be bothersome [6,14–20], entailing sleep loss, daytime fatigue, and perceived health issues [21,22]. Among men with lower

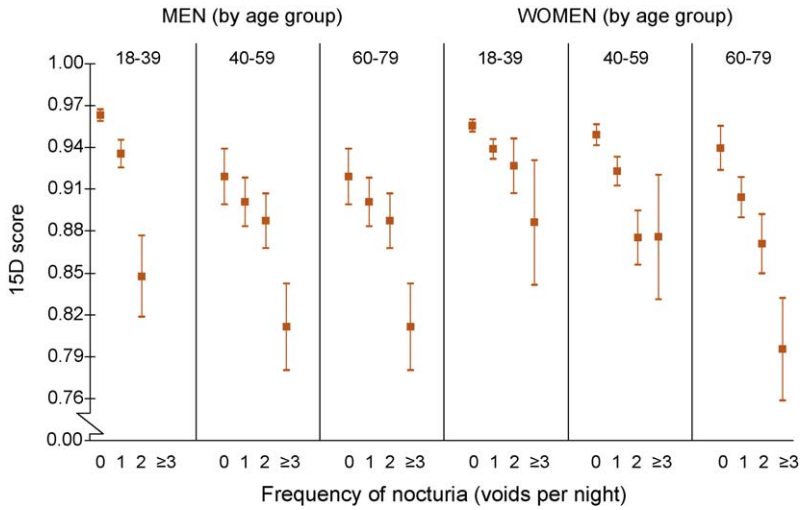

Fig. 4 – Age-adjusted means for 15D score by frequency of nocturia (zero, one, two, or three or more voids per night) among men and women aged 18–39, 40–59, and 60–79 yr. Error bars represent 95% confidence intervals. A difference of 0.03 is considered the minimum clinically important difference in the 15D score [11].

urinary tract symptoms (LUTS) suggestive of benign prostatic obstruction, nocturia has been rated as more bothersome than other LUTS [14,23]. In a clinical study, bother of nocturia predicted impaired QoL more strongly than other LUTS [24].

Perceived bother from LUTS varies considerably among individuals [25]. In this study, as in others [6,16–20,26], bother from nocturia depended on its frequency. In Asian population-based studies, nocturia was not bothersome for most subjects [18,20]. In a Viennese health screening study,

Table 3 – Prevalence of major comorbidities by quality of life and nocturia among men and women

	Health-related quality of life*			Frequency of nocturia		
	Reference group (>0.923) (*n* = 1149)	1–2 MCID less (0.893–0.923) (*n* = 159)	≥2 MCID less (≤0.893) (*n* = 340)	No nocturia (*n* = 1077)	One void per night (*n* = 385)	≥2 voids per night (*n* = 186)
	Prevalence‡ (95% CI†), %	Prevalence (95% CI), %	Prevalence (95% CI), %	Prevalence‡ (95% CI), %	Prevalence (95% CI), %	Prevalence (95% CI), %
Men						
Obstructive sleep apnea	2 (1–2)	3 (1–5)	6 (3–8)	2 (1–4)	2 (1–3)	7 (2–11)
Mood disorder	3 (2–4)	6 (2–10)	16 (12–21)	5 (4–7)	5 (3–7)	12 (6–18)
Coronary artery disease	4 (3–6)	5 (2–9)	10 (7–12)	5 (3–7)	6 (4–8)	10 (6–14)
Obstructive lung disease	4 (2–5)	9 (4–14)	9 (6–12)	6 (4–7)	5 (3–7)	7 (3–12)
Osteoarthrosis	4 (2–5)	9 (5–14)	10 (7–12)	5 (3–7)	7 (5–9)	6 (3–8)
	Health-related quality of life			Frequency of nocturia		
	Reference group (>0.920) (*n* = 1295)	1-2 MCID less (0.890–0.920) (*n* = 175)	≥2 MCID less (≤0.890) (*n* = 356)	No nocturia (*n* = 1094)	One void per night (*n* = 550)	≥2 voids per night (*n* = 182)
	Prevalence (95% CI), %	Prevalence (95% CI), %	Prevalence (95% CI), %	Prevalence (95% CI), %	Prevalence (95% CI), %	Prevalence (95% CI), %
Women						
Obstructive sleep apnea	0 (0–1)	1 (0–2)	3 (1–5)	1 (0–1)	1 (0–2)	3 (1–5)
Mood disorder	4 (2–5)	10 (5–15)	25 (20–30)	7 (5–8)	10 (7–12)	14 (8–20)
Coronary artery disease	3 (2–5)	3 (1–6)	7 (5–10)	4 (2–5)	3 (2–5)	7 (4–10)
Obstructive lung disease	5 (4–6)	10 (5–14)	11 (8–14)	5 (4–7)	8 (6–10)	10 (5–14)
Osteoarthrosis	7 (5–9)	11 (6–16)	16 (12–19)	7 (5–9)	10 (7–12)	16 (11–20)

MCID = minimum clinically important difference; CI = confidence interval.
* Subjects were classified into three groups with cut-off points defined as 15D scores corresponding to MCID and twice MCID below average of subjects without nocturia (separately for both sexes; 15D scores [11] in parentheses).
‡ Age-standardised prevalence was calculated using the age structure of Finland at the beginning of 2004.

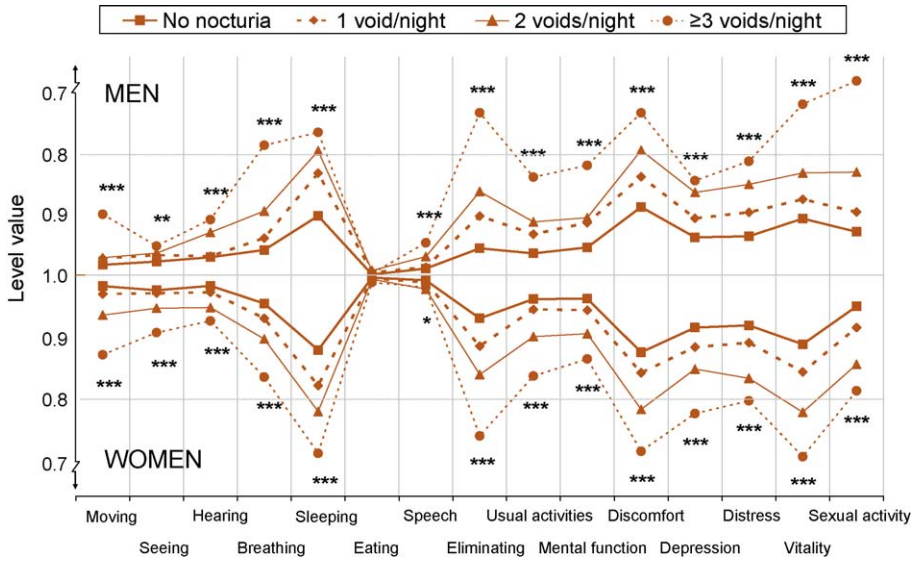

Fig. 5 – Age-adjusted means for dimension-level values (profiles) of the 15D instrument [11] by frequency of nocturia (zero, one, two, or three or more voids per night). Dimension-level values of health-related quality of life on a 0–1 scale (0 = dead, 1 = full health) for profiles by sex. The effect of nocturia on dimension-level values was assessed using analysis of covariance with adjustment for age; tests for trend (* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$) were conducted by including nocturia in four categories (zero, one, two, or three or more voids per night) as a linear term in the model.

most participants with nocturia reported "no" or only "a bit of problem" from it [26]. In a US urogynaecology clinic-based study, the mean bother score of ≥5 out of 10 was reported only for three or more nocturia episodes [19]. Our results concur with these data: Approximately half of subjects with one void per night reported no bother from nocturia, and of those with two voids per night, the most common response was small bother. Subjects with three voids per night most commonly reported moderate bother followed by small bother, while those with four or more voids per night most commonly reported moderate bother followed by major bother. Nevertheless, number of nocturia episodes does not completely predict perceived bother [3]. In this study, too, bother from nocturia varied widely.

Overall, both sexes were equally bothered by nocturia; older women were less bothered than younger women, but no such difference was observed among men. Although the prevalence of nocturia increases with age, the prevalence of nocturia in men rises more steeply [1]. A plausible explanation is that older women acquiesce, reporting less bother from nocturia because they are less likely to develop it as a *new* condition with increasing age, but these cross-sectional data cannot prove this. In contrast to other studies, a Viennese study reported no gender differences in bother from nocturia [26]. A population-based study in Taiwan among adults >40 yr showed that men had more bother and concern related to nocturia than women did [6]. A Danish survey of adults aged 60–80, however, showed that women with three or more nocturia episodes were more bothered than men; in less severe nocturia, no gender difference was found [27]. The Danish study also showed that nocturia caused more concern in younger age groups.

In both sexes, two nightly voids adversely affected HRQoL, but 15D scores among subjects with one void per night did not differ in a clinically important way from those without nocturia. In both sexes, subjects with three or more voids per night reported inferior HRQoL to subjects without nocturia or with one or two voids per night. Hence, our findings indicate that two or more episodes of nocturia distinguish those subjects reporting substantial bother from nocturia and impaired HRQoL. These findings were consistent across age groups (and excluding those with missing values). A US study found that scores from the Overactive Bladder Questionnaire (OAB-q), an HRQoL instrument designed specifically for overactive bladder, differed in a statistically significant way between subjects with one, two, and three episodes of nocturia (as in our study); however, the clinical importance of the differences remained unclear [16]. Another US study (among female urology clinic patients) and a community-based study from Taiwan (subjects aged ≥40) proposed that clinically significant nocturia is two or more voids per night based on bother [6,17].

While more frequent nocturia results in greater bother and lower HRQoL, not all bother from nocturia is explained by number of nocturia episodes [3]. Nocturia may also indicate other factors causing impaired HRQoL rather than directly affecting self-rated health. This is supported by the association of nocturia with almost all dimensions of HRQoL, not only those related to urination or sleep. Moreover, major comorbidity was strongly associated with impaired HRQoL and also with nocturia, indicating confounding. Treatment to reduce episodes of nocturia may not relieve all impairment among subjects with nocturia; increasing nocturia may be a proxy indicator of comorbidity.

This study has many strengths. It benefited from a good response rate (62%) and a high degree of completion of the nocturia, bother, and 15D questions. The study population is representative of Finns from early adulthood to old age in terms of sociodemographic, anthropometric, and female reproductive factors [1,12,28]. Furthermore, age-standardised bother from nocturia, age-adjusted mean 15D score, and dimension-level values were similar by response round, indicating absence of selection bias in relation to these factors. Because there may be slightly more symptomatic subjects among responders than among nonresponders (and as approximately one third did not participate), the true prevalence estimates may be somewhat smaller [1,8].

The study has some limitations. Depression or sleep disturbances may be involved in bother from nocturia, but we had no such condition-specific information. In a recent study among community-dwelling women aged 20–70, nocturia was the only urogenital symptom consistently associated with depression [29]. The association between nocturia and depression (odds ratio [OR] for nocturia: 1.4; 95% CI: 1.1–1.8) was stronger for bothersome nocturia alone (OR: 2.0; 95% CI: 1.3–3.2). In a separate study, life disruption from nocturia was associated with mental and physical functioning. After adjustment for sleep problems, nocturia no longer predicted poorer physical and mental functioning [30].

5. Conclusions

Nocturia is a bothersome symptom for a remarkable proportion of the general population and is associated with impaired QoL. Health care providers should be more cognizant of nocturia, and further (prospective) studies are certainly needed. Our findings indicate that two episodes of nocturia constitute meaningful nocturia affecting well-being and perceived health. Frequency of nocturia defines problems, disruption, and resulting bother. This also contributes to the definition of treatment targets (ie, significant nocturia reduction). Two nightly voids result in slightly impaired QoL; a single episode does not. Three or more voids moderately affect well-being. In conclusion, one void per night does not identify subjects with interference from nocturia and, thus, is not a suitable criterion for clinically relevant nocturia.

Author contributions: Kari A.O. Tikkinen had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Tikkinen, Johnson, Tammela, Auvinen.
Acquisition of data: Tikkinen.
Analysis and interpretation of the data: Tikkinen, Johnson, Tammela, Sintonen, Haukka, Huhtala, Auvinen.
Drafting of the manuscript: Tikkinen, Johnson.
Critical revision of the article for important intellectual content: Tikkinen, Johnson, Tammela, Sintonen, Haukka, Auvinen.
Statistical analysis: Tikkinen, Sintonen, Haukka, Huhtala, Auvinen.
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Editorial Comment on: Nocturia Frequency, Bother, and Quality of Life: How Often Is Too Often? A Population-Based Study in Finland

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The study by Tikkinen et al highlights the importance of nocturia as a key symptom in urology, with a number of potential causes [1]. As the authors describe, nocturia appears to be the most bothersome of all lower urinary tract symptoms, with the most impact on quality of life (QoL) [1,2]. Although in men and women aged 60–80 yr nocturia is the most frequent self-reported reason for waking at night [3], it can be difficult to identify a principal cause; as such, it is a symptom with relevance for all physicians [4]. Voiding symptom questionnaires alone (such as the International Prostate Symptom Score), however, may not accurately identify the level of nocturia, and frequency volume charts may be useful [2]. Clearly, we still have a lot left to learn about nocturia.

Tikkinen et al's study [1] adds to the knowledge base of this common and important symptom, and this data may enable us to define the problem more clearly in the population, to design research more accurately, and to tailor and monitor treatments more appropriately. In their questionnaire-based study of both men and women, the authors have demonstrated that two episodes of nocturia constitute meaningful nocturia that affects well-being and perceived health and that one void per night is not a suitable criterion for clinically relevant nocturia. Although previous authors have alluded to these findings [4,5], this study has confirmed them for both men and women and for both bother and health-related QoL. This study, however, does not include any responders >79 yr of age; the very elderly may experience more bother from nocturia, which may also increase their risk of falls [2,5].

Moreover, we may now need to revisit our symptom score questionnaires to place appropriate emphasis on

two or more episodes of nocturia—a bothersome symptom with a clear impact on QoL.

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Editorial Comment on: Nocturia Frequency, Bother, and Quality of Life: How Often Is Too Often? A Population-Based Study in Finland

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Nocturia, defined by the International Continence Society as waking up at night one or more times to void [1], is a urological symptom. Plausibly, it is the frequency of nocturia that has a direct impact on bother and health-related quality of life (HRQoL) [2] of those people who have the symptom. The study by Tikkinen et al [3] contributes to the literature of nocturia by indicating that the frequency of two or more voids per night results in impaired HRQoL and well-being, whereas the frequency of one void does not. This study provides empirical evidence for a meaningful practical consideration of the clinical treatment targets.

The Tikkinen et al study [3] is unique in its research population, which consists of a large pool of Finnish people (up to 6000) who were drawn randomly from the Finnish Population Register. Stratification by age was implemented in sample selection, and the younger age groups were oversampled to ensure a precise estimate in age groups with potentially low nocturia frequency. The analysis was separately conducted by sex and by age groups to draw a clear picture. Previous studies have suggested similar findings, but they had limited samples with only females [4] or elderly men [5]. This study by Tikkinen et al [3] demonstrated that one nocturia episode per night is not meaningfully different from no nocturia, and this finding can be confirmed by additional studies in populations from other countries.

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Editorial Comment on: Nocturia Frequency, Bother, and Quality of Life: How Often Is Too Often? A Population-Based Study in Finland

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The current study, a cross-sectional analysis by Tikkinen et al [1], examines the association between frequency of nocturia and health-related quality of life (HRQoL). The authors determined, based on a survey with 3727 responders (62.4% participation), that bothersome symptoms do not become apparent until episodes of nocturia number two or more. There was no effect of age

on bothersome symptoms in men, whereas younger women perceived greater bother than their older counterparts. Additionally, increasing frequency of nocturia was associated with worsening perceptions of many domains of HRQoL.

The study is very important as a description of the prevalence and impact of nocturia symptoms; however, like any cross-sectional study, there are limitations to its interpretation. While we may be convinced, both intuitively and statistically, of an association between increasing frequency of nocturia and bothersome symptoms, we cannot know the direction of causation. The results of the study are certainly provocative and should be utilized in clinical practice. Specialists as well as primary care physicians should screen their patients for nocturia and its frequency, considering how strongly nocturia may affect quality of life. In the future, longitudinal studies and randomized trials should be designed to evaluate frequency of nocturia as a separate end point because, while nocturia may be associated with negative symptoms, it is not clear how much of an impact reduction in nocturia would have on those symptoms.

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Original Contribution

Nocturia and Obesity: A Population-based Study in Finland

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The authors' aim in this study was to analyze the association of nocturia with overweight and obesity. In 2003–2004, a questionnaire was mailed to 6,000 randomly selected Finns aged 18–79 years who were identified from the Finnish Population Register Centre. Information on nocturia was collected through questionnaires using the Danish Prostatic Symptom Score and the American Urological Association Symptom Index. Self-reported body weight and height were used to calculate body mass index (BMI; weight (kg)/height (m)^2). Subjects were classified on the basis of BMI as nonoverweight (BMI <25), overweight (BMI 25–29.9 kgm^2), or obese (BMI ≥ 30). Of the 6,000 subjects, 62.4% participated. Among men, the age-standardized prevalence of nocturia, defined as at least one void per night, was 33.4% (95% confidence interval (CI): 28.5, 38.3) in the nonoverweight, 35.8% (95% CI: 31.4, 40.1) in the overweight, and 48.2% (95% CI: 38.8, 57.6) in the obese. Among women, the corresponding figures were 37.2% (95% CI: 33.0, 41.5) in the nonoverweight, 48.3% (95% CI: 42.5, 54.2) in the overweight, and 53.6% (95% CI: 43.9, 63.2) in the obese. The associations remained similar when nocturia was defined as two or more voids per night. The age-standardized attributable fraction (population) of increased BMI for nocturia was 17.7% for men and 18.5% for women, corresponding to an 8.5% increase in the crude prevalence of nocturia in men and a 13.9% increase in women. The authors conclude that obesity is associated with increased nocturia, more strongly among women than among men.

age factors; body mass index; obesity; prevalence; sex; urination disorders

Abbreviations: BMI, body mass index; CI, confidence interval.

Nocturia is one of the most common and bothersome of all urologic symptoms. It is among the most important reasons for persistent insufficient sleep, which contributes to mental and somatic disease (1). The International Continence Society defines nocturia as waking at night one or more times to void (2).

Obesity is a worldwide epidemic with numerous medical consequences (3). In the United States, obesity was not considered an issue of interest in the mid-1980s, but it had become more common; and by 2000, approximately 20 percent of the US adult population was obese (4). In Finland, body mass index (BMI; weight (kg)/height (m)^2) and the prevalence of obesity are also increasing to nearly the same magnitude (5).

Among men, prostate size or prostate growth rate has been found to be positively associated with BMI (6). The associations are still unclear for lower urinary tract symptoms. Weight gain and central adiposity may be associated with lower urinary tract symptoms (7). Rohrmann et al. (7) and Haidinger et al. (8) found a positive association between lower urinary tract symptoms and waist circumference but not between lower urinary tract symptoms and current BMI. Several controversies persist concerning an association between nocturia and benign prostatic hyperplasia. Blanker

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et al. (9) concluded that nocturia is highly associated with benign prostatic hyperplasia. On the other hand, in Japan, Homma et al. (10) reported that nocturia is the least specific symptom associated with benign prostatic hyperplasia and the symptom that is least responsive to treatment for benign prostatic hyperplasia.

Among women, a clear association between BMI and urinary incontinence has been found in several studies (11), but Elia et al. (12) did not find any association between nocturia and BMI. On the other hand, Asplund and Åberg (13) found that high BMI increased nocturia among women aged 40–64 years. Moreover, in their questionnaire study of 430 patients of both sexes with type 2 diabetes, Bulpitt et al. (14) found that reported frequency of nocturia increased with BMI independently of other symptoms.

We aimed to explore the association between nocturia and obesity in a comprehensive, population-based study comprising persons of both sexes aged 18–79 years.

MATERIALS AND METHODS

Study design

Between November 2003 and February 2004, a questionnaire was mailed to a random sample of 3,000 men and 3,000 women aged 18–79 years who were identified from the Finnish Population Register Centre. Stratification by age was used in subject selection, with oversampling of the younger age groups to ensure similar levels of accuracy even in age groups with lower nocturia frequency. Information on voiding symptoms was collected using the validated Danish Prostatic Symptom Score questionnaire (15), with an additional question from the American Urological Association Symptom Index (16). The questionnaire also included items related to anthropometric factors (weight and height) and comorbidity (gynecologic, internal, musculoskeletal, neurologic, psychiatric, and/or urologic diseases). Questionnaires were first mailed in late November 2003, with reminders being sent a month later. To persons who did not respond, a final round of questionnaires was mailed in February 2004.

Nocturia was defined as any nighttime voiding (2). Responses to nocturia questions from the Danish Prostatic Symptom Score (''How many times do you have to void per night?'') and the American Urological Association Symptom Index (''Had to get up to urinate from the time you went to bed at night until you got up in the morning?'') were combined. Danish Prostatic Symptom Score was elicited for the past 2 weeks, and the American Urological Association Symptom Index question pertained to the past month. In this study, the definition of nocturia was at least one void per night. A secondary analysis was conducted with nocturia defined as at least two voids per night.

Current self-reported body weight and height were used to calculate BMI. As suggested by the World Health Organization (17), subjects with BMIs of 25–29.9 were classified as overweight, and those with BMIs of 30 or more were classified as obese.

Only five male respondents (0.3 percent) were underweight (BMI <18.5), while 57 female respondents (3.0 percent) were underweight. There was no difference in the prevalence of nocturia among underweight women compared with normal-weight women by either criterion (≥ 1 void/night or ≥ 2 voids/night). Hence, we used nonoverweight (normal-weight and underweight; BMI <25) persons as the reference group for both men and women.

In accordance with Finnish regulations on questionnaire surveys, an exemption from ethical review was granted by the ethical committee of Tampere University Hospital (Tampere, Finland).

Statistical analysis

Subjects were stratified into six 10-year age groups (18–29, 30–39, 40–49, 50–59, 60–69, and 70–79 years). Age-standardized prevalence was calculated using the European standard population (18). Logistic regression was used for multivariate analysis, with the presence or absence of nocturia used as the outcome measure. All confidence intervals were likelihood-based. All analyses were performed using the SPSS program, version 12.0.1 (SPSS, Inc., Chicago, Illinois).

Tests for trend were conducted with logistic regression by including trichotomous BMI as a continuous variable in the models. Departure from linearity was assessed by adding a continuous BMI term to a model already containing a categorical BMI variable and assessing the improvement in the fit of the model (likelihood ratio test). Effect modification was assessed on the basis of the statistical significance of the interaction term (BMI $\times$ age) in a model containing the main effects (BMI, age).

The attributable fraction in the exposed, the attributable fraction in the population, and the attributable number were calculated according to *A Dictionary of Epidemiology* (19). The attributable fraction in the exposed (AF_e) is the proportion by which the prevalence of nocturia among exposed persons (the overweight and the obese) would be reduced if the exposure (overweight and obesity) were eliminated. It can be estimated using the formula

$$AF_e = (P_e - P_u)/P_e,$$

where P_e is the prevalence of nocturia among the exposed (the overweight and the obese) and P_u is the prevalence of nocturia among the unexposed (the nonoverweight; BMI <25).

The attributable fraction in the population (AF_p) is the proportion by which the prevalence of nocturia in the entire population would be reduced if overweight and obesity were eliminated. It can be estimated using the formula

$$AF_p = (P_p - P_u)/P_p,$$

where P_p is the prevalence of nocturia in the total population and P_u is the prevalence of nocturia among the nonoverweight.

The attributable number (AN) is the number of prevalent cases of nocturia attributable to overweight and obesity. It can be estimated using the formula

$$AN = N_e \times (P_e - P_u),$$

where N_e is the number of persons in the exposed population (the overweight and the obese), P_e is the prevalence of

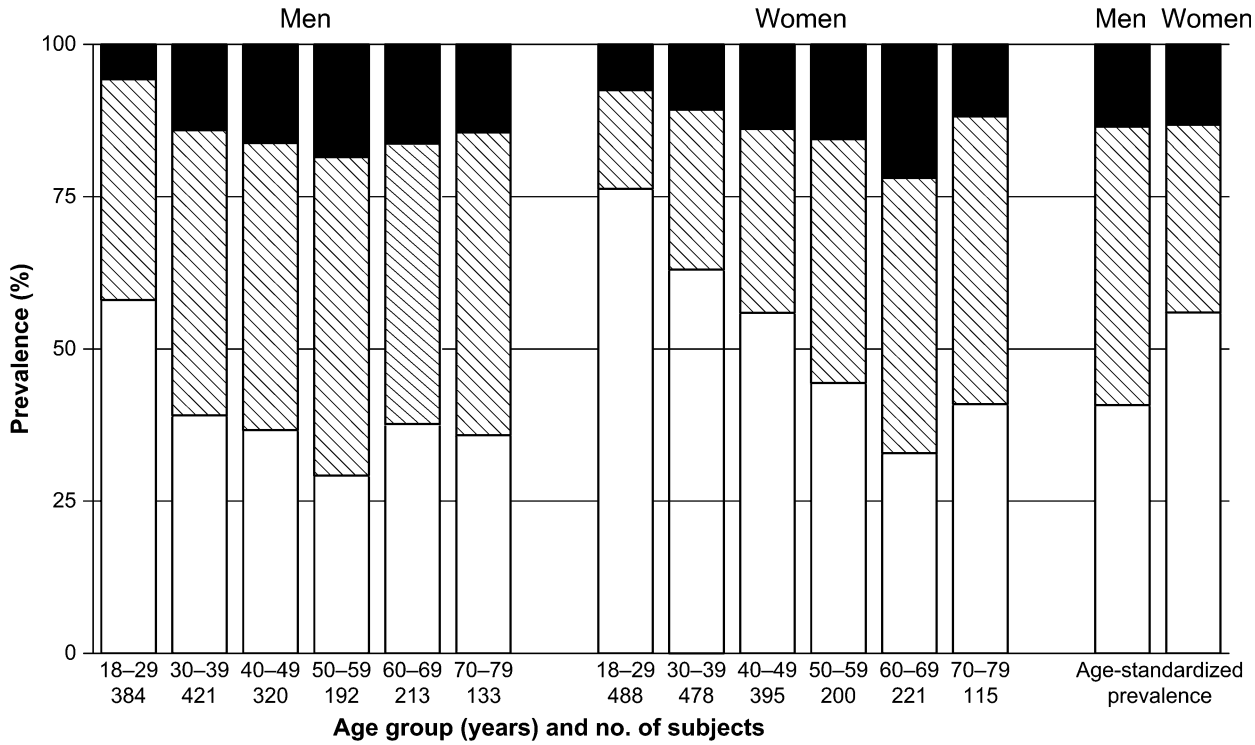

FIGURE 1. Prevalence of overweight and obesity among men and women in a random sample of 3,560 people in Finland, 2003–2004. The white bars indicate subjects with a body mass index (BMI; weight (kg)/height $(m)^2$) under 25 (reference group); the bars with diagonal lines indicate subjects with a BMI of 25–29.9 (overweight); and the black bars indicate subjects with a BMI of 30 or more (obese). Age-standardization was performed using the European standard population (18).

nocturia among the overweight and obese, and P_u is the prevalence of nocturia among the nonoverweight.

Regarding all of the above formulas, it is assumed that causes other than the one under investigation have had equal effects on the exposed and unexposed groups. The attributable fractions in the exposed and in the population were calculated as percentages, and the attributable number was calculated as number of cases per 1,000 subjects.

The mean BMIs for all mailing rounds were calculated by sex and age group for estimation of possible selection bias due to nonresponse. The differences between rounds were small and nonsystematic (mean BMIs by round among men: 26.10, 26.39, and 26.31; mean BMIs by round among women: 24.67, 25.37, and 25.36).

RESULTS

Of the 3,000 men approached for the study, 1,726 (57.8 percent) took part; 12 (0.4 percent) were ineligible because of serious disability or disease, death, or emigration. Of the 3,000 women approached, 2,003 (67.0 percent) participated; 11 (0.4 percent) were ineligible. Hence, overall 62.4 percent of the eligible subjects responded. Of the participants, 1,663 men (96.3 percent) and 1,897 women (94.7 percent) answered all of the nocturia questions and responded to both anthropometric questions (height and weight). Among men, the response proportions by mailing round were as follows: first round, 47.1 percent ($n = 784$); second round, 29.3 percent ($n = 488$); and third round, 17.2 percent ($n = 286$). Among women, the corresponding figures were: first round, 55.5 percent ($n = 1{,}052$); second round, 25.8 percent ($n = 490$); and third round, 13.2 percent ($n = 251$). Mailing round could not be defined for 6.3 percent of men ($n = 105$) and 5.5 percent of women ($n = 104$) because they did not give the date of questionnaire completion.

The mean age of male respondents was 43.5 years (standard deviation, 16.3), and the median was 41.0 years; the corresponding figures for women were 42.0 years (standard deviation, 15.7) and 39.0 years. Of the respondents, 64.8 percent of men did not report any nocturia; 23.7 percent reported voiding once per night; and 11.5 percent reported voiding twice or more per night. Among women, 58.6 percent did not report any nocturia; 30.0 percent reported voiding once per night; and 11.4 percent reported voiding twice or more per night.

The age-standardized prevalence of obesity (BMI ≥ 30) was 13.5 percent (95 percent confidence interval (CI): 11.7, 15.4) among men and 13.2 percent (95 percent CI: 11.5, 14.9) among women. Among men, the age-standardized prevalence of overweight (BMI 25–29.9) was 45.7 percent (95 percent CI: 42.4, 49.1), and among women it was 30.8 percent (95 percent CI: 28.2, 33.5) (figure 1). The

TABLE 1. Mean body mass index* (BMI) by sex and age group in a random sample of 3,560 people in Finland, 2003–2004

Age group (years)	Men		Women	
	No.	BMI	No.	BMI
18–29	384	24.8 (3.5)†	488	23.2 (4.2)
30–39	421	26.4 (4.0)	478	24.6 (4.9)
40–49	320	26.8 (4.1)	395	25.4 (5.2)
50–59	192	27.2 (3.8)	200	26.0 (4.5)
60–69	213	26.7 (4.0)	221	27.5 (5.4)
70–79	133	26.3 (3.3)	115	26.3 (4.1)
All	1,663	26.2 (3.9)	1,897	25.0 (4.9)
Age-standardized‡		26.3 (3.9)		25.2 (5.2)

* Weight (kg)/height (m)^2.
† Numbers in parentheses, standard deviation.
‡ European standard population (18).

age-standardized mean BMI was 26.3 (standard deviation, 3.9) for men and 25.2 (standard deviation, 5.2) for women (table 1).

Among men, the age-standardized (European standard) prevalence of nocturia (≥1 void/night) was 33.4 percent (95 percent CI: 28.5, 38.3) for the nonoverweight, 35.8 percent (95 percent CI: 31.4, 40.1) for the overweight, and 48.2 percent (95 percent CI: 38.8, 57.6) for the obese (figure 2). For the second criterion (≥2 voids/night), the corresponding figures were 10.2 percent (95 percent CI: 7.48, 12.9) for the nonoverweight, 11.2 percent (95 percent CI: 8.84, 13.6) for the overweight, and 16.6 percent (95 percent CI: 11.6, 21.5) for the obese (figure 3).

Among women, the age-standardized prevalence of nocturia (≥1 void/night) was 37.2 percent (95 percent CI: 33.0, 41.5) for the nonoverweight, 48.3 percent (95 percent CI: 42.5, 54.2) for the overweight, and 53.6 percent (95 percent CI: 43.9, 63.2) for the obese (figure 4). For the second criterion (≥2 voids/night), the corresponding figures were 8.2 percent (95 percent CI: 6.12, 10.3) for the nonoverweight, 14.8 percent (95 percent CI: 11.6, 18.0) for the overweight, and 22.6 percent (95 percent CI: 16.4, 28.9) for the obese (figure 5).

Among men, there was a consistent association between increasing BMI and nocturia across age groups. Nocturia (defined as ≥1 void/night) was more common among obese men than among nonoverweight men in every age group from early adulthood to old age (figure 2). In every age group, the prevalence of nocturia among obese men was approximately 15 percentage points higher than that among nonoverweight men. In the secondary analysis, nocturia (defined as ≥2 voids/night) was also more common among obese men than among nonoverweight men (figure 3).

Among women, premenopausal (aged 18–49 years) obese women had an approximately 18 percentage points' higher prevalence of nocturia (defined as ≥1 void/night) than nonoverweight women. Among menopausal and postmenopausal women (aged 50–69 years), nocturia was more

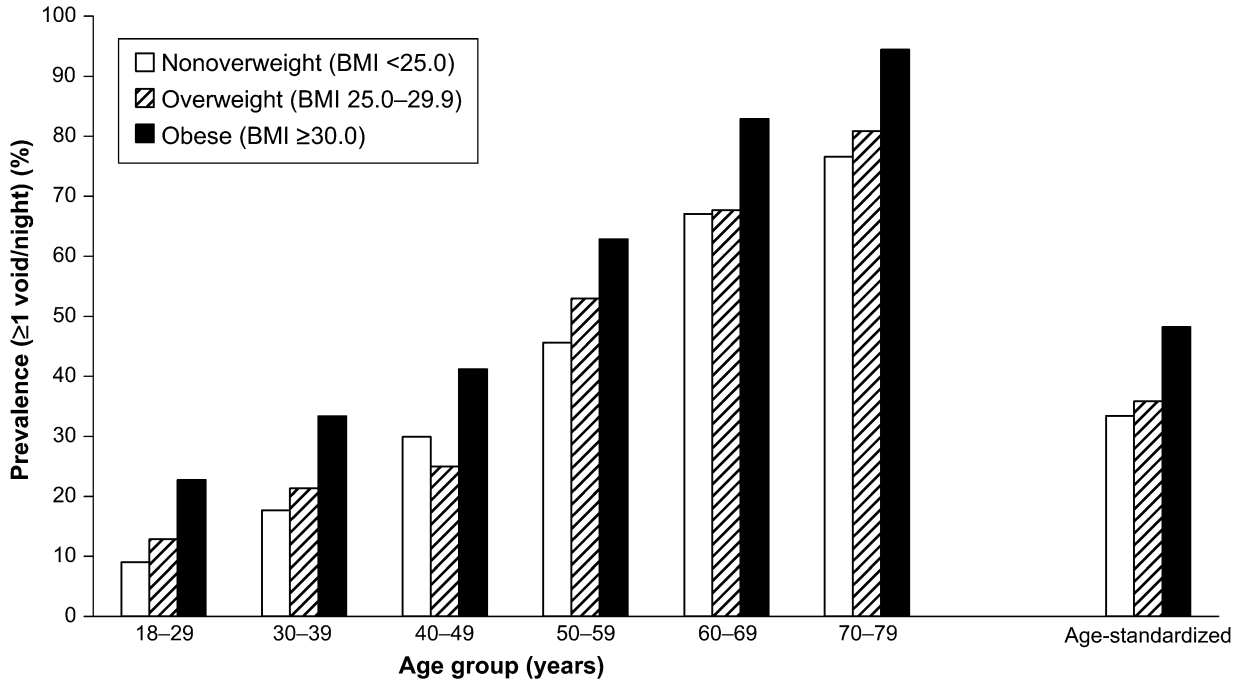

FIGURE 2. Prevalence of nocturia (defined as at least one void per night) in a random sample of 1,663 men in Finland, 2003–2004. The white bars indicate nonoverweight subjects (self-reported body mass index (BMI; weight (kg)/height (m)^2) <25); the bars with diagonal lines indicate overweight subjects (BMI 25–29.9); and the black bars indicate obese subjects (BMI ≥30). Age-standardization was performed using the European standard population (18).

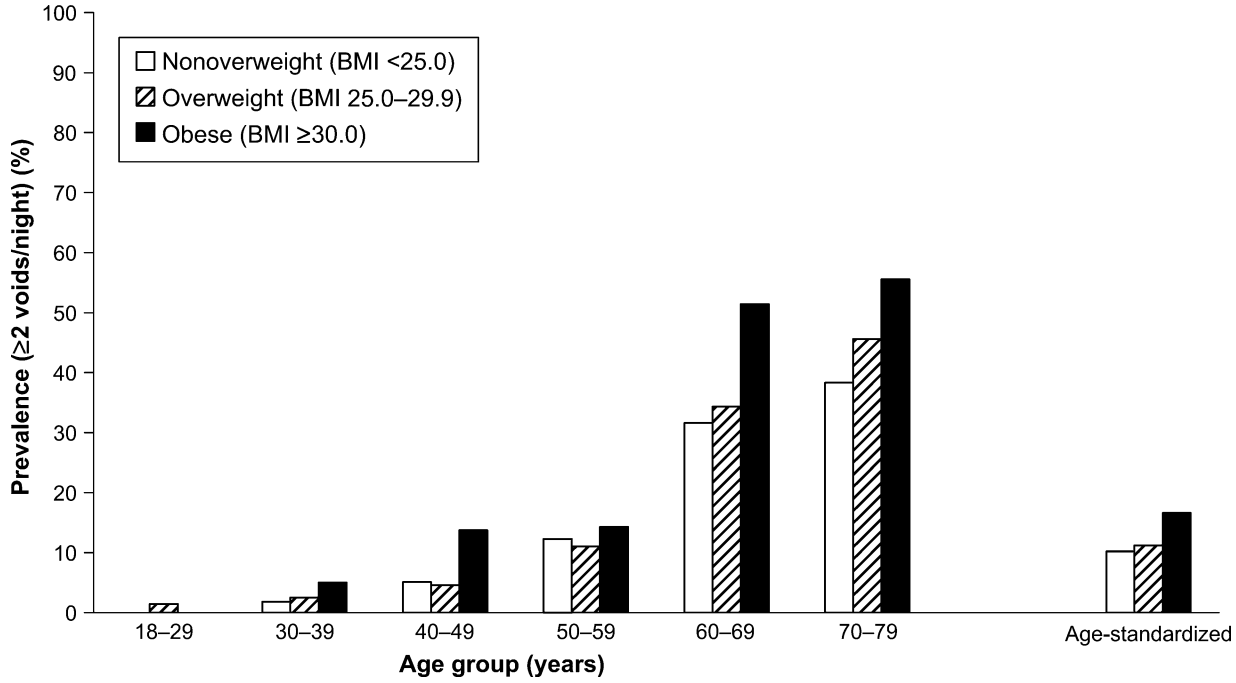

FIGURE 3. Prevalence of nocturia (defined as at least two voids per night) in a random sample of 1,663 men in Finland, 2003–2004. The white bars indicate nonoverweight subjects (self-reported body mass index (BMI; weight (kg)/height $(m)^2$) <25); the bars with diagonal lines indicate overweight subjects (BMI 25–29.9); and the black bars indicate obese subjects (BMI ≥30). Age-standardization was performed using the European standard population (18).

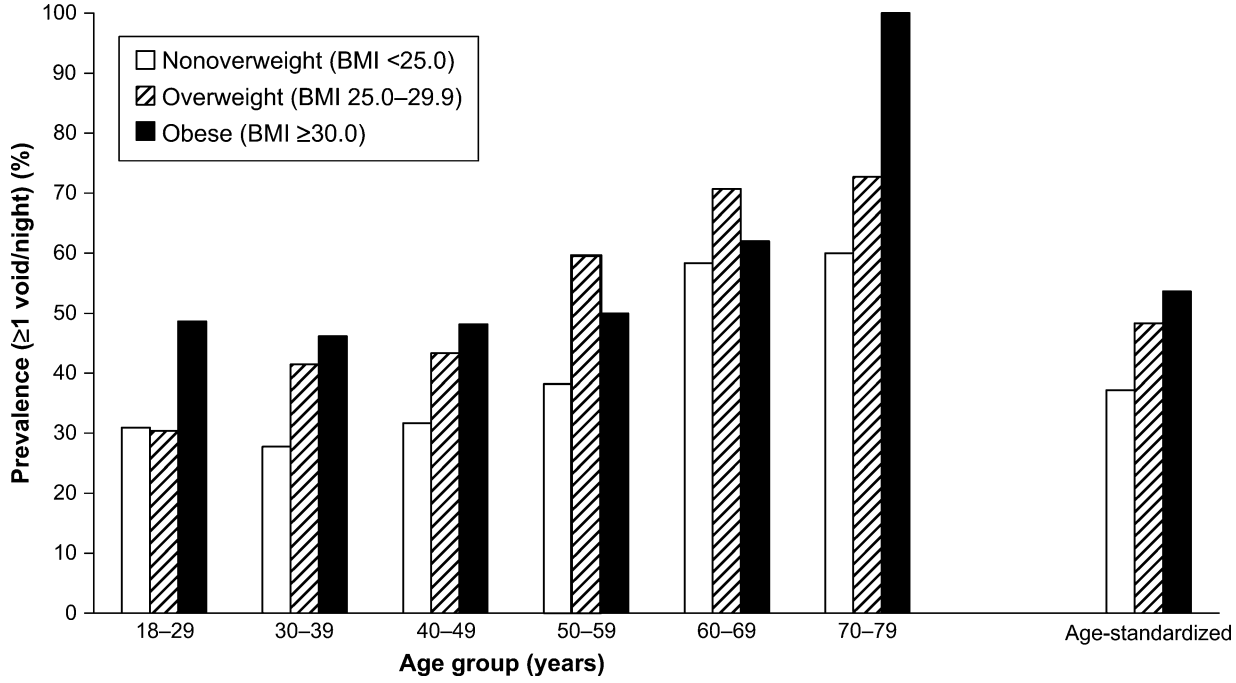

FIGURE 4. Prevalence of nocturia (defined as at least one void per night) in a random sample of 1,897 women in Finland, 2003–2004. The white bars indicate nonoverweight subjects (self-reported body mass index (BMI; weight (kg)/height $(m)^2$) <25); the bars with diagonal lines indicate overweight subjects (BMI 25–29.9); and the black bars indicate obese subjects (BMI ≥30). Age-standardization was performed using the European standard population (18).

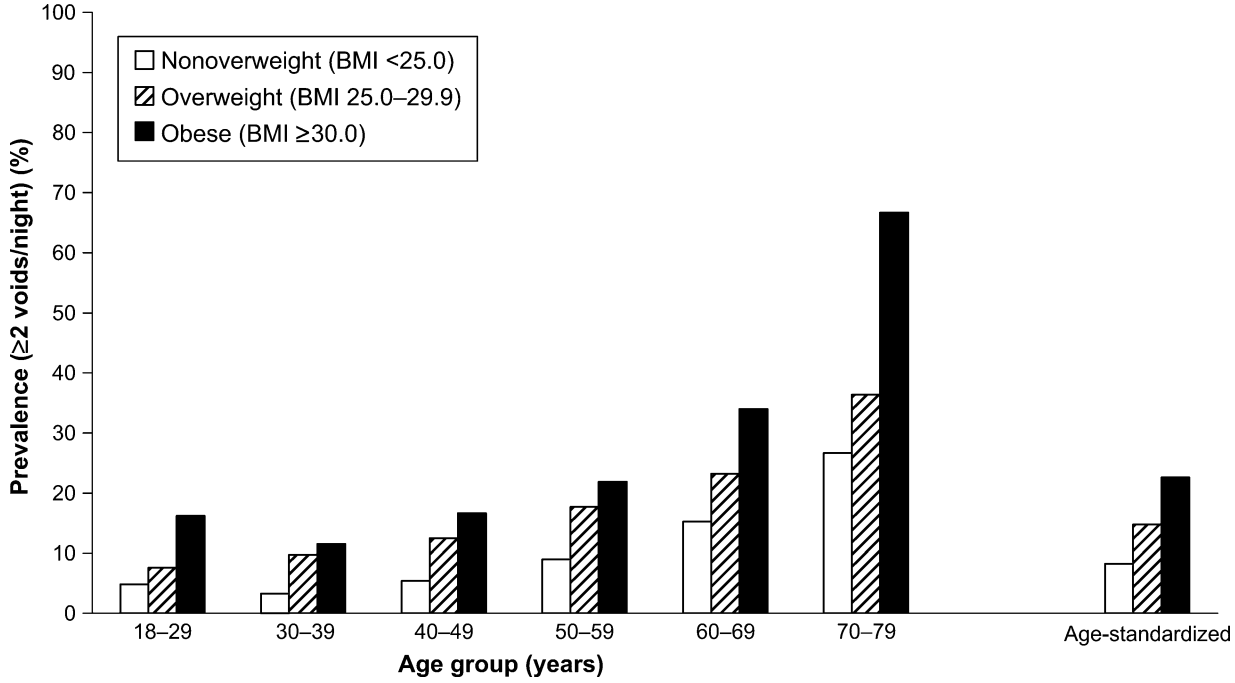

FIGURE 5. Prevalence of nocturia (defined as at least two voids per night) in a random sample of 1,897 women in Finland, 2003–2004. The white bars indicate nonoverweight subjects (self-reported body mass index (BMI; weight (kg)/height $(m)^2$) <25); the bars with diagonal lines indicate overweight subjects (BMI 25–29.9); and the black bars indicate obese subjects (BMI ≥30). Age-standardization was performed using the European standard population (18).

frequent among the overweight than among the obese (figure 4). Using nonoverweight (BMI <25) women as the reference group, nocturia odds ratios for the overweight women were 2.38 (95 percent CI: 1.28, 4.42) and 1.72 (95 percent CI: 0.91, 3.26) for the age groups 50–59 years and 60–69 years, respectively. In these age groups, odds ratios for overweight women in relation to obese women were 1.47 (95 percent CI: 0.64, 3.35) and 1.48 (95 percent CI: 0.72, 3.03), respectively. Thus, overweight women did not report significantly more nocturia than obese women. In every other age group, obese women had more nocturia than other women. In the secondary analysis, the obese subjects had more nocturia (defined as ≥2 voids/night) than the overweight and nonoverweight subjects in each age group. Obese women had nocturia at least twice as often as nonoverweight women in every age group (figure 5).

We also performed multivariate analysis with adjustment for gynecologic, internal, musculoskeletal, neurologic, psychiatric, and urologic diseases. Adjustment for comorbidity did not materially affect the results. The greatest difference between adjusted and unadjusted nocturia odds ratios for different BMI groups was observed among obese men (with nocturia defined as ≥2 voids/night and subjects with BMI <25 used as the reference group). The adjusted odds ratio was 2.42, and the unadjusted odds ratio was 2.25. Thus, there was no substantial confounding.

Overall, subjects with higher BMI had more nocturia. The age-standardized attributable fraction of nocturia in the exposed (the overweight and obese) was 26.8 percent for men and 35.2 percent for women (table 2). The age-standardized attributable fraction in the population was 17.7 percent for men and 18.5 percent for women. After age-standardization, nocturia attributable to overweight and obesity (the attributable number) in the entire study population was 62 per 1,000 men and 77 per 1,000 women.

BMI was a risk factor for nocturia. Increasing BMI predicted nocturia overall for both men and women ($p < 0.001$ for both). There was no statistically significant interaction between BMI and age (with nocturia defined as ≥1 void/night, $p = 0.86$ for men and $p = 0.13$ for women; with nocturia defined as ≥2 voids/night, $p = 0.66$ and $p = 0.62$, respectively). Thus, there was no effect modification. There was no statistically significant departure from linearity in either sex.

DISCUSSION

Overall, in our survey of approximately 3,600 subjects, nocturia increased with increasing age and BMI. Among nonoverweight subjects aged 30–39 years, only one out of 50 men and one out of 30 women reported voiding two or more times per night. Among obese subjects aged 30–39 years, the corresponding figures were one out of 20 for men and one out of nine for women. Among nonoverweight subjects aged 70–79 years, slightly more than every third

TABLE 2. Odds ratios for nocturia (defined as at least one void per night) by body mass index,* sex, and age group and the fraction of nocturia attributable to overweight (BMI ≥25) in a random sample of 3,560 people in Finland, 2003–2004

Age group (years)	Body mass index†				*p* for trend	Attributable fraction in the exposed (%)	Attributable fraction in the population (%)	Attributable number (per 1,000 subjects)
	25–29.9		≥30					
	OR‡	95% CI‡	OR	95% CI				
Men								
18–29	1.49	0.75, 2.93	2.97	0.99, 8.91	0.050	36.5	19.5	22
30–39	1.26	0.75, 2.14	2.33	1.19, 4.55	0.021	26.7	18.2	39
40–49	0.78	0.46, 1.34	1.64	0.83, 3.25	0.342	−2.9	−1.8	−5
50–59	1.34	0.70, 2.58	2.02	0.85, 4.77	0.111	17.9	13.3	70
60–69	1.03	0.55, 1.93	2.37	0.88, 6.42	0.151	6.4	4.1	29
70–79	1.29	0.52, 3.20	5.19	0.62, 43.6	0.132	8.5	5.7	46
All men	1.38	1.11, 1.73	2.61	1.91, 3.56	<0.001	13.5	8.5	31
All men§						26.8	17.7	62
Women								
18–29	0.98	0.57, 1.65	2.12	1.07, 4.18	0.086	14.6	3.9	13
30–39	1.85	1.19, 2.86	2.23	1.23, 4.07	0.001	35.3	16.7	55
40–49	1.64	1.04, 2.61	2.00	1.09, 3.67	0.008	29.3	15.5	58
50–59	2.38	1.28, 4.42	1.62	0.72, 3.65	0.061	32.7	21.2	103
60–69	1.72	0.91, 3.26	1.17	0.56, 2.44	0.537	13.9	9.8	64
70–79	1.78	0.77, 4.12		—¶	0.005	23.6	15.9	113
All women	2.06	1.67, 2.53	2.32	1.75, 3.08	<0.001	25.3	13.9	60
All women§						35.2	18.5	77

* Weight (kg)/height $(m)^2$.
† Reference category: body mass index <25 (nonoverweight).
‡ OR, odds ratio; CI, confidence interval.
§ Age-standardized (European standard population (18)).
¶ All of the subjects had nocturia.

man and approximately every fourth woman reported having at least two voids per night. In this age group, more than half of obese men and two thirds of obese women reported having at least two voids per night. The results were parallel with those obtained when nocturia was defined as at least one void per night.

Nocturia has been considered a multifactorial symptom caused by several urologic and nonurologic factors, such as nocturnal polyuria, low nocturnal bladder capacity, mixed nocturia (nocturnal polyuria and low nocturnal bladder capacity), and polyuria (1). Benign prostatic hyperplasia has been regarded as an underlying factor for a high prevalence of nocturia among men (20), but Bruskewitz et al. (21) reported nocturia in 38 percent of their patients 1 year after transurethral resection of the prostate (nocturia was defined as ≥2 voids/night). High prevalence rates of nocturia among women suggest that other factors are also involved in nocturnal voiding (12, 22, 23). Simple overproduction of urine during the night is a common etiology (24).

Obesity is a multifactorial disease with adverse health consequences such as cardiovascular disease, type 2 diabetes mellitus, hypertension, sleep apnea, and possibly depression (3). All of these diseases may be associated with increased risk of nocturia (2, 25). However, in our study, the impact of obesity on nocturia did not materially change after results were adjusted for comorbidity, indicating lack of confounding.

Few studies have explored the association between nocturia and obesity. In earlier studies of lower urinary tract symptoms, Rohrmann et al. (7) and Haidinger et al. (8) found a positive association between greater waist circumference and lower urinary tract symptoms but not between lower urinary tract symptoms and BMI. Rohrmann et al. (7) reported incomplete emptying, hesitancy, and a weak urine stream in addition to nocturia among US men aged 60 years or more. Subjects with three symptoms out of four were defined as lower urinary tract symptom cases (if they had not undergone prostate surgery). Haidinger et al. (8) also reported on lower urinary tract symptom cases, not nocturia cases. Their study population consisted of Viennese men aged 40 years or more.

Our aim in this study was to obtain a generalizable, unbiased estimate of an association between nocturia and obesity. Therefore, no exclusion criteria (such as pregnancy) were used, and no exclusions were made except for persons with serious disability or disease and persons who had died

or emigrated. The study population was representative of the Finnish population in terms of sociodemographic factors (22, 26, 27).

Self-reported BMI was used as an indicator of obesity. Although the correlation between BMI and body fat adjusted for age is high ($r = 0.82$–0.91) (28), it is not possible to distinguish lean body mass from fat on the basis of BMI. For example, the proportion of body fat is higher among women than among men with a similar BMI. In addition, body fatness has been shown to increase with age; that is, similar BMIs may correspond to a greater body fat content in older subjects compared with younger subjects (29, 30). Despite these limitations, BMI is a simple and useful measure of obesity in adults. A BMI of 30 is a widely recognized cutoff point for obesity, and the cutoff point for overweight (BMI $\geq$25) is recommended by the World Health Organization (17).

Our study population ($n = 3{,}560$) was representative of the Finnish population in terms of BMI in comparison with population surveys carried out by the National Public Health Institute (31). On the other hand, obesity was more common (age-standardized among subjects aged $\geq$30 years, 21.2 percent of men and 23.5 percent of women had a measured BMI $\geq$30) in a recent population-based study of 8,000 persons (32). The former study was comparable to ours in the sense that it was based on self-reported weight and height (31). The difference in comparison with the latter population sample may be due to two facts: First, their study population was older (in our study, obesity prevalence was higher when the age group was restricted to persons aged $\geq$30 years—16.1 percent of men and 14.6 percent of women) (32), and second, obese people tend to underestimate their obesity in questionnaire surveys (33–35). However, regarding nocturia, postal questionnaire responses have been reported to reflect urodynamics better than interview-assisted questionnaire responses (36).

In our study, mean BMIs did not vary markedly by response round. In a previous report (22), we assessed differences between participants and nonparticipants in terms of marital status, education, employment, and urbanity and found no major differences. These findings indicate a lack of selection bias.

In the present study, nocturia was substantially more common among subjects with higher BMIs than among those with lower BMIs. The only exception was perimenopausal women (aged 50–69 years), among whom overweight subjects reported more nocturia (only with the definition of $\geq$1 void/night) than did obese subjects. However, the difference was not statistically significant. This is in accordance with the finding reported by Asplund and Åberg (13). Among perimenopausal women aged 40–64 years, they found more nocturia among subjects with BMI $\geq$30 than among subjects with BMI $<$20. They reported more nocturia among obese women than among overweight women, but the difference was not significant (13). Likewise, among women aged 50–59 years, Teleman et al. (37) reported that overactive bladder was more common in subjects with increased BMI and other risk factors for metabolic syndrome. By contrast, Elia et al. (12) did not find any association between increased BMI and nocturia in their study of 540 female outpatients.

Nocturia is more common in obese men and women than in normal-weight men and women. The etiology of nocturia is still unclear, and the factors underlying an association between nocturia and obesity are even more ambiguous. Nonurologic causes of nocturia are more frequent among obese subjects. Lifestyle-related factors that increase the risk of nocturia may also be more common among the obese than among persons of normal weight. It is possible that nocturia in some obese persons is related to excessive nighttime eating (38) or drinking, especially alcohol drinking (39). However, few studies have addressed this issue.

Nocturia is one of the most bothersome of all urologic symptoms, and obesity is a worldwide epidemic with several associated comorbidities. To our knowledge, this is the first population-based study of the association between nocturia and obesity that included subjects of both sexes and all age groups, ranging from young adults to elderly persons. Age-standardization improves the comparability of these findings with those of other studies, as well as generalizability to other populations. We conclude that obesity accounts for a substantial proportion of nocturia in both sexes. Potentially, preventing obesity may also decrease nocturia, though establishing causality would ideally require an intervention study.

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UROGYNECOLOGY

Reproductive factors associated with nocturia and urinary urgency in women: a population-based study in Finland

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OBJECTIVE: The objective of this study was to evaluate the association of nocturia and urinary urgency with reproductive factors, including parity, the postpartum period, the menopause, hormone replacement therapy, hysterectomy, and surgery for stress urinary incontinence (SUI).

STUDY DESIGN: In 2003-2004, questionnaires eliciting urinary symptoms, reproductive factors, SUI surgery, and potential confounders were mailed to 3000 randomly selected women aged 18-79 years, identified from the Finnish Population Register. Nocturia was defined as 2 or more voids/night. Sudden compelling desire to urinate often or always (scale of never, rarely, often, always) was regarded as urgency. Pregnant and puerperal (6 weeks after delivery) women and those reporting urinary tract infection were excluded.

RESULTS: Responses totaled 2002 (67%). Parity, postpartum (defined as six weeks to one year after delivery) and postmenopausal periods were associated with increased nocturia and SUI surgery with increased urgency (adjusted for age, comorbidity, medication, anthropometric, sociodemographic and lifestyle factors). Hormone therapy and hysterectomy were associated with neither symptom.

CONCLUSION: Reproductive factors associated with nocturia differed from those related to urgency.

Key words: hormone replacement therapy, hysterectomy, menopause, overactive urinary bladder, parity, risk factors

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The International Continence Society defines nocturia as waking at night to void, whereas urinary urgency refers to a sudden compelling desire to pass urine.[1] Both symptoms are part of a symptom complex called overactive bladder syndrome.[1] Besides incontinence, nocturia and urgency are among the most bothersome urinary symptoms.[2] Nocturia is one of the most common reasons for disrupted sleep.[3] Nocturia is associated with impaired mental and somatic health,[4] poorer quality of life[5] and increased mortality.[6] Urgency is related to increased comorbidity[7] and poorer quality of life.[8] These overlapping symptoms are equally or more common among women than men, nocturia (twice per night) affecting every 8th and urgency every 10th woman.[9,10]

Despite substantial recent research interest in these conditions, there are few studies evaluating their risk factors.[11,12] Reproductive factors particularly have received little attention.[11,12] Most earlier reports have focused on 1 or more reproductive factors without adjustment for potential confounders. Risk factors (including diseases, medications, and reproductive factors) of urinary symptoms are often interrelated,[11] emphasizing the importance of appropriate analysis. We compared the effect of reproductive factors and surgery for stress urinary incontinence (SUI) on nocturia and urgency in a population-based study comprising women aged 18-79 years.

Materials and Methods

Between November 2003 and February 2004, questionnaires were mailed to a

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TABLE 1
Nocturia and urinary urgency questions and definitions of the study in Finland, 2003-2004[a]

		Response	
Symptom	**Defining questions**	**Normal**	**Abnormal**
Nocturia	"How many times do you have to void per night?"[13] and "How many times did you most typically get up to urinate from the time you went to bed at night until you got up in the morning?"[14] were combined.	0-1 time(s) per night	2 or more times per night
Urgency	"Do you experience an imperative (strong) urge to urinate?"[13]	Never or rarely	Often or always

[a] To evaluate these criteria, we studied the bother of these symptoms. Women fulfilling criteria for abnormality were significantly more likely to report moderate or major than small or no bother from nocturia or urgency, compared with those with milder symptoms (age-adjusted odds ratio 17 [95% CI 10-28] for nocturia and 76 (95% CI 46-124) for urgency). These findings support the selection of cut points.

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random sample of 3000 women aged 18-79 years identified from the Finnish Population Register. Stratification by age was used in subject selection, with oversampling of the younger age groups to achieve a similar number of subjects with nocturia or urgency in all age groups, regardless of the prevalence of these symptoms. The questionnaires elicited urinary symptoms, reproductive factors, prior surgery for SUI, and potential confounders. More information on procedures has been published.[10] Information on pregnancy was based on the questionnaire and the Finnish Population Register, which also provided information on parity, delivery dates, and urbanity. To ensure responder-friendliness and intelligibility, the questionnaire was pretested in a pilot study. Under the Finnish regulations on questionnaire surveys, exemption from ethical review was granted by the Ethics Committee of the Pirkanmaa Hospital District (Tampere, Finland).

Exclusions and outcomes

We excluded pregnant and puerperal women (6 weeks after delivery) and those reporting urinary tract infection. Responses to nocturia questions from the Danish Prostatic Symptom Score (DAN-PSS) and the American Urological Association Symptom Index (AUA-SI) were combined to assess nocturia.[13,14] Urgency was elicited by the DAN-PSS[13] (Table 1). The DAN-PSS has 4 response options for nocturia (none, 1-2 times, 3-4 times, and 5 times or more [per night]), whereas the AUA-SI has 6 (never, 1, 2, 3, 4, and 5 times or more [per night]). Subjects who did not respond to the AUA-SI were not included in the analyses because of the lack of precise information on the number of nocturnal voids. In the case of conflict between the responses to the 2 questions, the DAN-PSS was regarded as the gold standard so that the DAN-PSS response nearer to the AUA-SI response was chosen. Overall, consistency between the 2 nocturia questions was very good. Kappa for being classified as nocturic by the AUA-SI or the combination of the 2 nocturia responses was 0.978 ($P < .001$). Furthermore, the results remained similar also when only the AUA-SI was used (for instance, age-adjusted odds ratio [OR] was 2.88 for postpartum period and 1.27 for SUI surgery, compared with ORs of 2.97 and 1.29 when the combination of the 2 nocturia responses was used, respectively).

TABLE 2
Classification of women by menopausal status in Finland, 2003-2004

Characteristic	**Definition**
Premenopausal	Nonhysterectomized without hormone replacement therapy for menopause (HRT[a]) who menstruated during the previous year and nonhysterectomized younger than 40 years
Postmenopausal	Nonhysterectomized without HRT who did not menstruate during last year (and at least 40 years old)
Women with HRT	Nonhysterectomized with HRT (and at least 40 years old)
Hysterectomized	Reported prior hysterectomy

[a] Menopausal hormone replacement therapy (included those subjects who reported current use of vaginal or systemic HRT).

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Reproductive and gynecological factors

The Finnish Population Register provided data on parity (but not delivery mode) and time of delivery (for determining the postpartum period, 6 weeks to 1 year after delivery). Information on menstrual history, hormone replacement therapy (HRT), and hysterectomy was elicited using questions modified from those used extensively in earlier studies (the National FINRISK Study by the Finnish National Public Health Institute).[15] We used the following questions: "Did you have periods during the last 12 months?" (yes/no); "have you had a hysterectomy?" (yes/no); "do you use hormone therapy for menopausal symptoms?" (yes/no); and "if you answered yes, do you use vaginal, oral, or transdermal?"

Women were classified as premenopausal, postmenopausal, hysterectomized, or HRT users (Table 2). There was no difference in the prevalence of nocturia (age-standardized 15.9% of

TABLE 3
Reproductive factors among 1728 women in Finland, 2003-2004

Characteristic	n (%)	Age-standardized[a] prevalence (%)	95% CI
Parity (number of children)			
0	623 (36)	30.6	28.1 to 33.2
1	248 (14)	15.5	13.4 to 17.6
2	493 (29)	30.9	27.9 to 33.9
3 or more	364 (21)	23.0	20.4 to 25.6
Postpartum period[b]	53 (3)	2.2	1.6 to 2.8
Menopausal status[c]			
Premenopausal	1159 (67)	52.9	49.8 to 56.0
Postmenopausal	276 (16)	23.8	20.9 to 26.8
Women with HRT	123 (7)	9.8	8.0 to 11.6
Hysterectomized	170 (10)	13.4	11.3 to 15.6
Surgery for SUI	33 (2)	2.5	1.6 to 3.4

[a] Age standardized to the general population of Finland (beginning of 2004) by the Finnish Population Register.[16]

[b] Postpartum period was defined as more than 6 weeks but not more than 1 year after delivery.

[c] Details of classification in Table 2.

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vaginal and 15.5% of systemic HRT users, $P = .51$) or urgency (10.2%, 9.4% and $P = .95$, respectively) between women reporting using vaginal or systemic (oral or transdermal) HRT. Hence, we combined these (Tables 2 and 3). Finally, information on surgery for SUI was assessed by the question, "Have you had surgery for stress urinary incontinence?" (yes/no). Because the laity is probably unfamiliar with the specific medical terminology, no details on surgical procedures were elicited. Even if this information had been collected, sample size would not have allowed subgroup analyses.

Statistical analysis

Logistic regression was used for the analyses, with presence of nocturia/urgency as the outcome. All confidence intervals were likelihood based. Analyses were performed with SPSS program, (version 14.0.1, SPSS, Inc, Chicago, IL). Confidence Interval Analysis 2.0.0 software (Trevor Bryant, University of Southampton, Southampton, UK) was used for calculating age-standardized prevalences. The age structure of Finland (beginning of 2004) was used.[16] Effect modification was assessed according to the statistical significance of the interaction term (parity × age) in a model containing the main effects (parity, age). These analyses were unfeasible for other reproductive factors, given the small number of women in some strata.

Potential confounders

Information on self-reported physician-diagnosed comorbidity (Supplementary Table 1), regular use of prescribed medication (classified according to ATC/DDD classification[17]) (Supplementary Table 2), sociodemographic factors (marital status, education, employment, urbanity), body mass index, smoking (never, former, current), and coffee and alcohol consumption were treated as potential confounders. Information on these variables (except urbanity, which was provided by the Finnish Population Register) was collected by questionnaire using questions modified from earlier studies.[15] Age, body mass index, coffee consumption (cups per day), and alcohol consumption (grams per day) were used as continuous variables.

The Nocturia Confounder Score (NCS) and Urgency Confounder Score (UCS) were calculated based on comorbidity and medication among women responding on both symptoms (in the basic analysis population) (Figure 1). For each comorbidity and medication factor (reported by at least 10 women), we calculated age-adjusted ORs with confidence intervals. All factors respectively associated with nocturia or urgency were used to construct the NCS and UCS formulas:

$$\text{Score} = \sum_{i=1}^{n} (\text{OR}_{\text{rf}} - 1)_{\text{n}} \text{ and only if}$$

$$P < .10 \text{ for } \text{OR}_{\text{rf}}$$

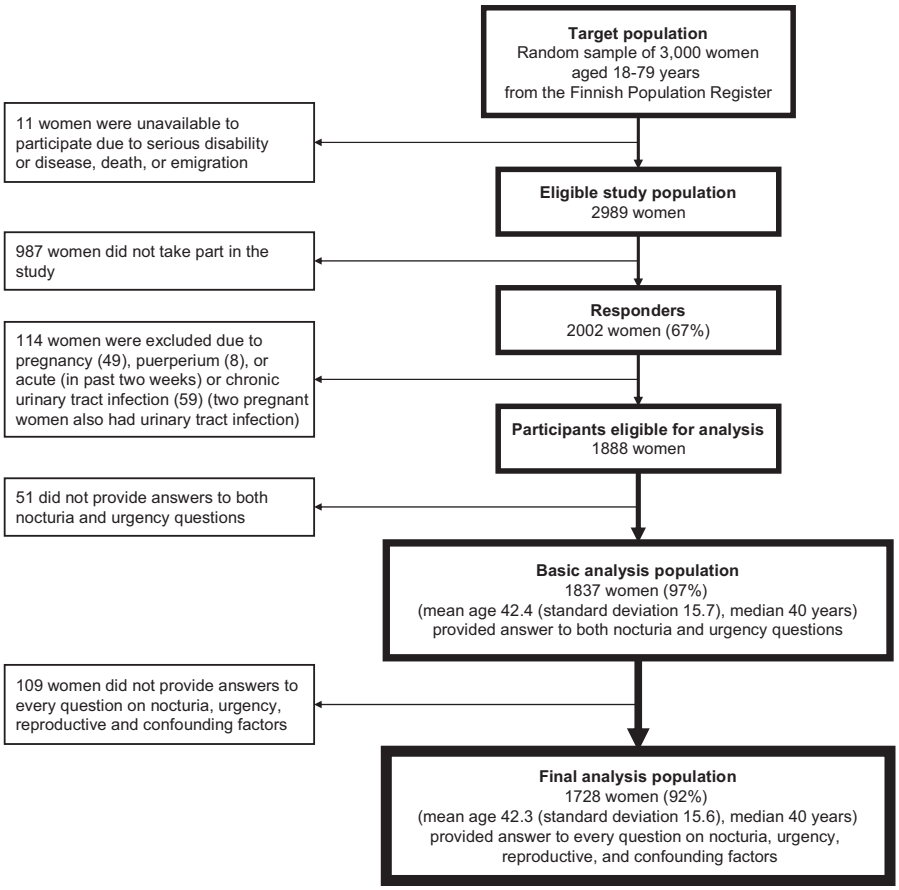
where OR_{rf} is the odds ratio for a risk factor (Supplementary Table 3). Nagelkerke R^2 was 15% for NCS and 13% for UCS; $P < 0.001$ for both.

Information on age, NCS, UCS, body mass index, smoking, coffee consumption, and alcohol consumption was available, respectively, for 100%, 100%, 100%, 97%, 100%, 95%, and 76% of women (basic analysis population). Moreover, information on each sociodemographic factor was available for more than 99% of women. Hence, information on every factor was well reported (except alcohol consumption, which was not significantly associated with either symptom). All factors associated ($P < .10$) with nocturia or urgency in the age-adjusted analysis were entered as potential confounders into multivariate models. Finally, backward elimination techniques were used to select variables for the final model of nocturia and urgency, separately, with likelihood ratio tests used to determine significance. At least 10% change in the estimate (OR) because of the elimination of a potential confounder was deemed confounding. Confounders emerging were NCS and age for nocturia; and UCS, age, smoking, and education for urgency.

Final exclusions and analyses

The final analysis included women answering every question on symptoms, variables, and confounders (Figure 1). The same sample was used for both symptoms (including information on smoking and education as inclusion cri-

FIGURE 1
Flow chart of the study in Finland, 2003-2004



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teria decreased the final analysis population by only 2 subjects), but analyses were performed separately for both symptoms. First, we calculated ORs for all variables with adjustment for age (model 1). Second, we calculated ORs adjusted for age and other confounders (model 2). Finally, multivariate analyses with all variables and confounders were performed (model 3) (Tables 4 and 5).

RESULTS

Of the 3000 women approached for the study, 2002 (67%) participated; 11 were unavailable because of serious disability/disease, death, or emigration (Figure 1). We excluded 114 women because of pregnancy, puerperium, or urinary tract infection. Of the 1888 women included, 97% answered nocturia and urgency questions (basic analysis population for prevalence and potential confounding factors analyses). Finally, 1728 women (92%) responded to every question of nocturia, urgency, reproductive, and confounding factors (final analysis population) (Figure 1). For details of reproductive and gynecological factors, see Table 3.

The age-standardized prevalence was 13.0% (95% confidence interval [CI], 11.1 to 15.0) for nocturia and 10.2% (95% CI, 8.5 to 11.9) for urgency (Figure 2). Both symptoms were reported by 4.2% of the women (95% CI, 3.1 to 5.3), corresponding to 31% and 41% of those women with nocturia and urgency, respectively. Excluding the women not answering every question on reproductive and confounding factors (final analysis population) did not change these estimates.

In the age-adjusted analyses (model 1), parity, the postpartum period, and menopausal status were associated with nocturia (Table 4); the only factor associated with urgency was surgery for SUI (Table 5). Surgery for SUI remained significantly associated with urgency after adjustment for confounders (models 2 and 3). In the analyses adjusted for age and other confounders (model 2), parity, the postpartum and postmenopausal periods were associated with increased prevalence of nocturia (Table 4). In the multivariate analysis (model 3), parity and the postpartum period were associated with nocturia. Furthermore, postmenopausal women reported more nocturia than premenopausal but not more than hysterectomized women (OR, 0.80; 95% CI, 0.48 to 1.33); postmenopausal as reference) or women on HRT (OR, 0.78; 95% CI, 0.44 to 1.40); postmenopausal as reference). However, there was no significant difference in nocturia between premenopausal, HRT, or hysterectomized women (Table 4). Furthermore, no difference between primi- and multiparous women was found in prevalence of nocturia ($P = 0.91$) or urgency ($P = 0.65$).

There was no statistically significant interaction between parity and age, indicating lack of effect modification (nocturia $P = 0.72$, urgency $P = 0.27$). No differences were found in reproductive and gynecological factors between women responding at different mailing rounds (Supplementary Table 4). Among nonparticipants, 62% were parous, which is comparable with 64% among participants (Table 3).

COMMENT

In this large, population-based study, female reproductive factors associated with nocturia differed from those related to urinary urgency. After adjustment for confounders, nocturia was associated with parity and the postpartum and postmenopausal periods, whereas urgency was associated with surgery for SUI. Hysterectomy and HRT use were not associated with nocturia or urgency.

Parous women reported more nocturia than nulliparous women, which contradicts earlier reports of no association between parity and nocturia.[18,19] However, earlier studies used only perimenopausal women.[18,19] Parallel with our

TABLE 4
Odds ratios for nocturia by reproductive factors with and without adjustment for confounders and other reproductive factors among 1728 women in Finland, 2003-2004

Reproductive and gynecological factors	Model 1 (adjusted for age)			Model 2 (adjusted for all confounders)			Model 3 (adjusted for all confounders and mutually for other reproductive factors)		
	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value
Parity (per child)	1.15	1.03 to 1.29	.016	1.14	1.01 to 1.29	.031	1.13	1.00 to 1.28	.047
Postpartum period[a]	2.97	1.21 to 7.31	.018	3.31	1.34 to 8.19	.009	2.83	1.12 to 7.20	.028
Menopausal status[b]									
Premenopausal	1.00			1.00			1.00		
Postmenopausal	2.49	1.33 to 4.67	.004	2.18	1.14 to 4.18	.018	2.31	1.20 to 4.42	.012
Women with HRT	2.06	1.06 to 4.00	.034	1.69	0.85 to 3.37	.137	1.80	0.90 to 3.60	.096
Hysterectomized	2.17	1.14 to 4.13	.018	1.69	0.86 to 3.29	.125	1.84	0.94 to 3.61	.075
Surgery for SUI	1.29	0.54 to 3.12	.568	1.02	0.40 to 2.60	.963	0.93	0.36 to 2.45	.889

[a] Postpartum period was defined as more than 6 weeks but not more than 1 year after giving birth.

[b] Other significant associations were not found when other options (postmenopausal, women with HRT, or hysterectomized) were used as a reference (in any of the models [model 1, 2, or 3]).

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findings, most earlier studies reported no association for parity with urgency[20] or overactive bladder,[7,21] with 2 exceptions.[18,22]

In our study, the postmenopausal period was associated with more nocturia, consistent with a Danish population-based study on 40 to 60 year old women.[18] Two other studies have also reported increased nocturia in the postmenopausal period,[19 23] whereas another attributed this to aging, not to menopausal transition.[24] However, 4 studies demonstrated an association between postmenopausal period and increased urgency or an overactive bladder.[20,22,23,25] But these were either not population based[20,25] or failed to control for age or comorbidities.[22,23]

Surgery for SUI was strongly associated with increased urgency, as reported earlier.[26] Furthermore, we found that the postpartum period (as defined here) was associated with increased nocturia but not with urgency. No earlier investigations of these relations exist.

In our study, hysterectomy was not associated with urgency. The hysterectomized women (premenopausal as reference) had an OR of 1.8 for nocturia with borderline statistical significance. This could be regarded as clinically meaningful, but because of limited statistical power, we

TABLE 5
Odds ratios for urinary urgency by reproductive factors with and without adjustment for confounders and other reproductive factors among 1728 women in Finland, 2003-2004

Reproductive and gynecological factors	Model 1 (adjusted for age)			Model 2 (adjusted for all confounders)			Model 3 (adjusted for all confounders and mutually for other reproductive factors)		
	OR*	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value
Parity (per child)	1.02	0.90 to 1.16	.740	0.99	0.86 to 1.13	.851	0.98	0.85 to 1.13	.983
Postpartum period[a]	0.55	0.13 to 2.28	.406	0.74	0.17 to 3.16	.684	0.77	0.18 to 3.34	.771
Menopausal status[b]									
Premenopausal	1.00			1.00			1.00		
Postmenopausal	1.53	0.79 to 2.98	.209	1.17	0.57 to 2.38	.667	1.15	0.56 to 2.36	.705
Women with HRT	1.15	0.54 to 2.45	.725	0.84	0.38 to 1.87	.668	0.82	0.37 to 1.84	.636
Hysterectomized	1.86	0.96 to 3.61	.065	1.39	0.69 to 2.80	.354	1.29	0.63 to 2.63	.488
Surgery for SUI	3.08	1.38 to 6.85	.006	2.61	1.10 to 6.22	.030	2.53	1.04 to 6.13	.040

[a] Postpartum period was defined as more than 6 weeks but not more than 1 year after giving birth.

[b] Other significant associations were not found when other options (postmenopausal, women with HRT, or hysterectomized) were used as a reference (in any of the models [model 1, 2, or 3]).

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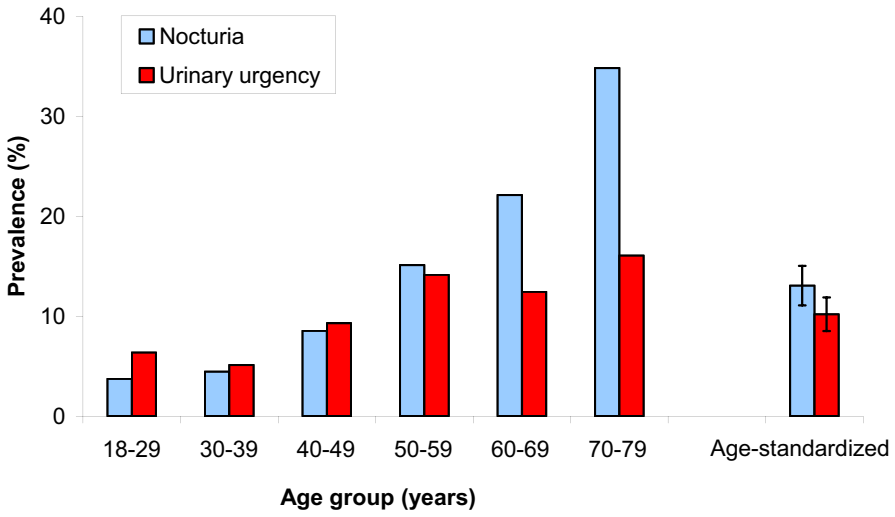
FIGURE 2
Prevalence of nocturia and urinary urgency



The prevalence of nocturia and urinary urgency among 1837 women in Finland, 2003-2004. The *blue bars* indicate women with nocturia and the *red bars* women with urinary urgency. Women in pregnancy or puerperium (defined as 6 weeks after giving birth) or with urinary tract infection were excluded. Age standardization was performed using the age structure of Finland (beginning of 2004).[16]

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could not exclude the possibility that it might be due to chance. Six earlier studies[21,27-31] have found no association for hysterectomy with nocturia and urgency, and our results are consistent with these. However, 2 studies reported less nocturia and urgency,[32,33] and 5 studies reported a decrease of 1 or other symptom after hysterectomy (most with a follow-up period of 1 year or less).[25,34-37] However, a Danish study reported more nocturia and urgency among hysterectomized women.[18] Most studies were neither population-based surveys nor controlled trials.[21,25,27-31,33-35]

HRT use was not related to urgency here. There was some indication of increased nocturia among women with HRT (compared with premenopausal women; OR, 1.8), but the finding was not statistically significant. An effect size of this size could be considered clinically meaningful, but our result could also be due to chance. There are few studies evaluating the effect of HRT on nocturia and urgency. Our finding is consistent with a placebo-controlled trial[38] and a population-based cross-sectional study.[19] Other uncontrolled trials have reported conflicting results.

Our results partly contradict earlier findings.[18-20,22-25,32-37] However, many of the differences can be readily explained by dissimilarities in study samples and procedures. The fact that parity, the postmenopausal period, hysterectomy, and SUI surgery were significantly associated in unadjusted analyses with both nocturia and urgency highlights the importance of controlling for confounders. Given the numerous possible risk factors,[7,11,39-41] we assessed several potential confounders, including comorbidities, medications, body mass index, lifestyle, and sociodemographic and reproductive factors. Earlier epidemiological studies have been limited by having adjusted for limited numbers of potential confounders or none.[7,18-20,22-24] Although results from earlier studies were known, confounder scores were constructed empirically (based on many comorbidities and medications) because of inconsistencies in the literature. Using confounder score, a particular strength of the study, improves statistical efficiency, leading to decreased residual confounding,[42] although there may be a risk for overadjustment by chance correlation.

This study also reduced potential selection bias through the good questionnaire response rate, the information (such as parity) coming from a comprehensive Finnish national database; the study population matched the overall Finnish population in terms of parity, menopausal status, HRT, and number of hysterectomies[15]; parity did not vary between participants and nonparticipants and reproductive factors by response round.

This study sought to evaluate the association of reproductive factors and surgery for SUI with nocturia and urgency in a population-based setting. We excluded pregnancy, puerperium, and urinary tract infection, as obvious reasons for nocturia or urgency. The study population is representative of the Finnish population regarding sociodemographic[9] and anthropometric factors.[43]

In summary, our study benefits from the following factors: (1) a large population-based sample of adult women; (2) a large number of relevant reproductive factors as variables; (3) adjustment for numerous possible confounders using scoring; (4) questions about nocturia and urinary urgency, enabling outcomes consistent with standardized definitions; and (5) an opportunity to compare, within the same study population, differences between reproductive risk factors for nocturia and urgency.

There are also potential limitations. We could not distinguish between delivery modes. There are, however, 4 earlier studies demonstrating no effect of delivery mode on prevalence of urgency, urgency incontinence, or overactive bladder.[20-22,44] The study that did show a higher prevalence of overactive bladder for vaginal delivery than cesarean section (adjusted for parity, obesity, and age) was somewhat limited because of a low response rate (37%) and that those delivering vaginally were significantly older than those having cesarean section.[45] No studies have examined the association between delivery mode and nocturia.

We also had no information on different hysterectomy procedures or the indication for hysterectomy. Because ran-

domized controlled trials found no difference in prevalence of nocturia or urgency postoperatively between subtotal and total hysterectomies for benign indication with 1-year[32,36] or 2-year[37] follow-up, this may not be an important limitation. Because no results from postoperative nocturia and urgency randomized trials comparing vaginal hysterectomy with other techniques are available, current evidence suggests that technique is hardly decisive.[46]

Additionally, no information was obtained regarding type of SUI surgery. Generally, there is a lack of randomized trials comparing these techniques. A Cochrane review found no difference in de novo detrusor overactivity after laparoscopic colposuspension, compared with tension-free vaginal tape.[47] Recent randomized controlled trials reported no difference in de novo urgency incontinence after fascial sling compared to Burch colposuspension[48] or in de novo urgency after suburethral sling procedure by retropubic or transobturator route.[49]

Another study limitation is the factor of no laboratory testing result confirming menopausal status, based here on reported menstruation during the past year. Those reporting hysterectomy or HRT were regarded as separate groups because their natural menopausal status remains unclear. We used an age of 40 years as a cut off point for menopause because amenorrhea is due to other reasons than menopause in most women aged younger than 40 years.[50] In our study, among women aged younger than 40 years, 46 (4%) reported no menstruation in the past year.

In our study, increased nocturia was associated with parity and postpartum and postmenopausal periods, also known to be associated with sleep disturbances.[51,52] It is proposed that the association of nocturia with parity more likely is due to pregnancy itself than physical damage to the urinary tract during delivery.[12] This may be supported by our finding of no difference in nocturia between primi- and multiparous women.

With age, comorbidities associated with increased nocturia increase.[39] In our study, the association of the postmenopausal period with nocturia persisted after adjustment for confounders. This period is often associated with insomnia for several reasons, including hot flashes, mood disorders, and increased sleep-disordered breathing,[51] when nocturia may be secondary.

During the postpartum period, increased nocturia may be secondary to increased number of awakenings and insomnia. Most awakenings are for baby care; however, maternal depressed mood may also play a role.[51]

In our study, SUI was related to increased nocturia and urgency. However, only urgency was associated with surgery for SUI. It is known that SUI surgery may cause de novo urgency, but the underlying mechanism remains unclear.[26] It may be due to the obstructive nature of the procedures; however, bladder outlet obstruction is not the sole cause.[26] Furthermore, people needing SUI surgery may already have more (bothersome) symptoms preoperatively.

In a population-based setting, we evaluated the association of reproductive factors and surgery for SUI with nocturia and urinary urgency among women of all adult ages. Our response rate was high, and the study population was representative of Finnish women. Adjustment for numerous confounders improved the study's validity, highlighting the importance of thorough control for confounding. Parity and the postpartum and postmenopausal periods were positively associated with nocturia, whereas only SUI surgery was related to urgency. The cross-sectional study design precludes conclusions about causality. We conclude that reproductive factors associated with nocturia differ from those related to urgency, suggesting different etiologies for these symptoms. ■

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APPENDIX

SUPPLEMENTARY TABLE 1

Physician-diagnosed diseases and conditions regarded as candidates for the models of Nocturia Confounder Score and Urgency Confounder Score[a]

List of diseases and conditions (in alphabetical order)

Anxiety disorders	Glaucoma	Osteoporosis
Arrhythmia	Gout	Psoriasis
Back pain	Hypersensitivity	Parkinson's disease
Breast neoplasms	Hypertension	Psychotic disorders
Celiac disease	Hyperthyroidism	Restless legs syndrome
Cerebrovascular accident	Hypothyroidism	Rheumatoid arthritis
Contracted bladder[b]	Inflammatory bowel diseases	Rhinitis (nonacute)
Coronary disease[c]	Kidney neoplasms	Sleep apnea syndromes
Dementia	Migraine disorders	Spinal cord injuries
Diabetes mellitus	Mood disorders	Stress urinary incontinence[d]
Dyslipidemias[e]	Multiple sclerosis	Urinary bladder neoplasms
Epilepsy	Narcolepsy	Urinary calculi
Fibromyalgia	Obstructive lung diseases[f]	
Gastroesophageal reflux	Osteoarthritis	

[a] Diseases and conditions were collected from the responses to the question, "Have you ever been diagnosed by a physician with any of the following diseases or conditions?"

[b] Due to, for example, painful bladder syndrome (interstitial cystitis) or radiation.

[c] Including those with heart failure.

[d] Based on response to the stress urinary incontinence question of the Danish Prostatic Symptom Score[13] with response options of never, rarely, often, or always (99% of women responded). Women who reported having SUI often or always (during last 2 weeks) were classified as abnormal.

[e] Including users of lipid-modifying agents (Anatomical Therapeutic Chemical Classification code[17]: C10).

[f] Including those with asthma and/or chronic obstructive pulmonary disease.

Tikkinen. Reproductive factors associated with nocturia and urinary urgency in women. Am J Obstet Gynecol 2008.

SUPPLEMENTARY TABLE 2

Self-reported regular use of prescribed medications classified by the Anatomical Therapeutic Chemical classification[17] regarded as candidates of Nocturia Confounder Score and Urgency Confounder Score

List of medications (classified in alphabetical order of the ATC code[17])

Groups of medication	ATC Code	Groups of medication	ATC Code
Drugs for acid related disorders	A02	Urinary antispasmodics[a]	G04BD
Drugs for functional gastrointestinal disorders	A03	Alpha-adrenoreceptor antagonists[b]	G04CA
Insulins and analogs	A10A	NSAIDs[c]	M01A, M01B
Oral blood glucose-lowering drugs[d]	A10B/X	Muscle relaxants	M03
Cardiac glycosides	C01A	Antigout preparations	M04
Antiarrhythmics, classes I and III	C01B	Opioids	N02A
Cardiac stimulants (excluding cardiac glycosides)	C01C	Antiepileptics	N03
Vasodilators used in cardiac diseases	C01D	Antiparkinson drugs	N04
Diuretics (other than high-ceiling diuretics)[†]	C03A/B/D/E	Antipsychotics[e]	N05AA-AL, N05AX, N06CA
High-ceiling diuretics[b]	C03C	Lithium	N05AN
Beta-blocking agents	C07	Anxiolytics[e,f]	N05B, N06CA, A03CA
Calcium channel blockers	C08	Hypnotics and sedatives	N05C
Agents acting on the renin-angiotensin system	C09	Antidepressants[e]	N06A, N06CA
Contraceptives[g]	G02BB01, G03AA/AB/H	Nasal preparations	R01
Progestin-only contraceptives	G03AC	Drugs for obstructive airway diseases	R03
Hormone replacement therapy for menopause[h]	G03CA03, G03F	Corticosteroids for systemic use, plain	H02A

ATC, Anatomical Therapeutic Chemical; *NSAID*, nonsteroid antiinflammatory drug.

[a] Urinary antispasmodics (synonymously antimuscarinics) were not included in the models of Nocturia Confounder and Urgency Confounder scores because of strong overlapping of medication and symptoms.

[b] High-ceiling diuretics and loop diuretics are used synonymously, likewise alpha-adrenoreceptor antagonists and alpha blockers.

[c] Including nonsteroid antiinflammatory and antirheumatic products (M01A) and antiinflammatory and antirheumatic agents in combination (M01B).

[d] Including oral blood glucose–lowering drugs (A10B) and other drugs used in diabetes (A10X) excluding insulins and analogs (A10A).

[e] Partly including antidepressants in combination with psycholeptics (N06CA).

[f] Partly including synthetic anticholinergic agents in combination with psycholeptics (A03CA).

[g] Contraceptives included progestogens and estrogens, fixed combinations (G03AA); progestogens and estrogens, sequential preparations (G03AB); antiandrogens (G03H); and vaginal ring with progestogen and estrogen (G02BB01).

[h] Those reporting regular use of menopausal HRT (vaginal or systemic) were regarded as HRT users (vaginal or systemic) in the classification of the Menopausal status (Table 2).

Tikkinen. Reproductive factors associated with nocturia and urinary urgency in women. Am J Obstet Gynecol 2008.

SUPPLEMENTARY TABLE 3

Physician-diagnosed diseases/conditions and regular use of prescribed medications (with Anatomical Therapeutic Chemical Classification code[17]) included in the models of Nocturia Confounder score and Urgency Confounder score[a]

Nocturia Confounder Score		Urgency Confounder Score	
Diseases/conditions	**Medication (ATC Code)**	**Diseases/conditions**	**Medication (ATC Code)**
Anxiety disorders	Antipsychotics (N05A)[b]	Anxiety disorders	Antidepressants (N06A)[c]
Coronary disease[d]	Anxiolytics (N05B)[e]	Arrhythmia	Antiepileptics (N03A)
Diabetes mellitus	Calcium channel blockers (C08)	Back pain	Antipsychotics (N05A)[b]
Fibromyalgia	Opioids (N02A)	Breast neoplasms	Hypnotics and sedatives (N05C)
Gastroesophageal reflux		Diabetes mellitus	Loop-diuretics (C03C)[f]
Mood disorders		Epilepsy	
Obstructive lung diseases[g]		Gastroesophageal reflux	
Osteoarthritis		Mood disorders	
Restless legs syndrome		Obstructive lung diseases[g]	
Sleep apnea syndromes		Multiple sclerosis	
Stress urinary incontinence[h]		Restless legs syndrome	
		Sleep apnea syndromes	
		Stress urinary incontinence[h]	

ATC, Anatomical Therapeutic Chemical

[a] All factors (of comorbidity and medications reported by at least 10 women) associated ($P < .10$) with nocturia or urgency (after adjustment for age) were included in the models of Nocturia Confounder Score or Urgency Confounder Score, respectively. With a single indication for a drug, those reporting using it were also taken to have the indication (disease/condition). Furthermore, if both drug and indication were associated with a symptom, we included only the indication in the formula of Nocturia Confounder Score or Urgency Confounder Score.

[b] Antipsychotics (N05AA-AL, N05AX) excluding lithium (N05AN) and partly including antidepressants in combination with psycholeptics (N06CA).

[c] Antidepressants (N06A) and partly including antidepressants in combination with psycholeptics (N06CA).

[d] Including those with heart failure.

[e] Anxiolytics (N05B) and partly including antidepressants in combination with psycholeptics (N06CA) and synthetic anticholinergic agents in combination with psycholeptics (A03CA).

[f] Loop diuretics used as synonym for high-ceiling diuretics (as in ATC classification[17]).

[g] Including those with asthma and/or chronic obstructive pulmonary disease.

[h] Based on response to stress urinary incontinence question of the Danish Prostatic Symptom Score[13] with answer options of never, rarely, often, always (99% of women responded). Women who reported having SUI often or always (during last 2 weeks) were classified as abnormal.

Tikkinen. Reproductive factors associated with nocturia and urinary urgency in women. Am J Obstet Gynecol 2008.

SUPPLEMENTARY TABLE 4

Reproductive factors by mailing rounds (first, second, or third) among 1728 women in Finland, 2003-2004[a]

	First mailing round			Second mailing round			Third mailing round		
	Crude	Age standardized[b]		Crude	Age standardized		Crude	Age standardized	
Characteristic	n (%)	Prevalence	95% CI	n (%)	Prevalence	95% CI	n (%)	Prevalence	95% CI
Parity (number of children)									
0	381 (39)	32	28-35	140 (32)	29	24-34	76 (34)	27	21-34
1	138 (14)	15	12-18	72 (16)	17	13-21	27 (12)	13	8-18
2	269 (28)	32	28-37	134 (30)	31	25-36	62 (28)	32	23-41
3 or more	184 (19)	21	17-24	96 (22)	24	19-29	56 (25)	28	20-36
Postpartum period[c]	32 (3)	2	2-3	14 (3)	2	1-4	7 (3)	2	0-4
Menopausal status									
Premenopausal	680 (70)	53	48-57	285 (64)	53	47-59	153 (69)	52	44-61
Postmenopausal	127 (13)	22	18-27	88 (20)	27	21-33	38 (17)	28	19-36
Women with HRT	72 (7)	10	8-13	30 (7)	9	6-13	11 (5)	8	3-12
Hysterectomized	93 (10)	15	12-18	39 (9)	11	7-14	19 (9)	12	7-18
Surgery for SUI	17 (2)	2	1-3	8 (2)	2	1-4	3 (1)	3	0-5

[a] Mailing round was assessed by date of questionnaire completion that was given by vast majority of the included women (95%).

[b] Age standardization was performed using the age structure of Finland (beginning of 2004).[16]

[c] Postpartum period was defined as more than 6 weeks but not more than 1 year after delivery.

Tikkinen. Reproductive factors associated with nocturia and urinary urgency in women. Am J Obstet Gynecol 2008.

Discussion: 'Reproductive factors associated with nocturia and urgency' by Tikkinen et al

In the roundtable discussion that follows, clinicians discuss a study that is published in this issue of the Journal in light of its methods, relevance to practice, and implications for future research. Article discussed:

Tikkinen KAO, Auvinen A, Tiitinen A, Valpas A, Johnson TM 2nd, Tammela TLJ. Reproductive factors associated with nocturia and urinary urgency in women: a population-based study in Finland. Am J Obstet Gynecol 2008;199:153.e1-153.e12.

DISCUSSION QUESTIONS

- What were the study's objectives?
- What was the study's design?
- What are the benefits of population-based surveys?
- How were nocturia and urinary urgency measured?
- What were the main findings of the study?
- What is effect modification?
- What are the strengths and limitations of this study?
- Does this study alter the way you would counsel patients?

INTRODUCTION

Nocturia and urinary urgency are common among women, yet the symptoms frequently are overlooked. Patients might not mention them, assuming the problems are inevitable and harmless consequences of aging or childbearing. In fact, they can create other concerns, such as fractures that are incurred when hurrying to a bathroom. Yet, despite the prevalence of urinary symptoms, their associations with reproductive characteristics are understood incompletely. Journal Club members discussed a new study that examined the relationship between urinary symptoms and parity, recent pregnancy, menopause status, hormone therapy, hysterectomy, and previous surgery for stress urinary incontinence. The work raises an interesting question about cause. Hopefully, it will generate further investigation.

From the Washington University in St. Louis, School of Medicine, St. Louis, MO:

Moderator

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Discussants

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BACKGROUND

Allsworth: Nocturia and urinary urgency are 2 symptoms of overactive bladder syndrome. In 2005, the European Prospective Investigation into Cancer and Nutrition conducted cross-sectional population-based surveys in Canada, Germany, Italy, Sweden, and the United Kingdom and found that almost 13% of women had overactive bladder.[1] Individual symptoms of overactive bladder were more common: 55% of women reported at least 1 nighttime urination; 24% reported that they urinated ≥2 times per night; and 13% reported urinary urgency. In the United States, a study of >4000 community-dwelling women also reported a 13% prevalence of overactive bladder.[2] The current study by Tikkinen et al describes the prevalence of specific symptoms of overactive bladder among Finnish women and the association of these symptoms with reproductive characteristics.

Allsworth: ***Why are urinary symptoms an important topic?***

Omicioli: Bladder dysfunction, which includes urgency, urinary incontinence, and nocturia, often are underdiagnosed and undertreated. Approximately 50% of women who have symptoms seek treatment. Worldwide, the prevalence of urgency is 16-18%, and one-third of those women who experience urgency have urge incontinence. Among women aged 50-59 years, 50% of women experience intermittent nocturia. Often, symptomatic women do not volunteer information about voiding dysfunction unless specifically asked. Many studies show that incontinence, urgency, and nocturia can affect physical function, sleep, and psychologic wellbeing adversely; as a result, urinary symptoms can be associated with medical comorbidities and, generally, diminished quality of life. For example, in elderly women, nocturia is a significant risk factor for accidental falls. Women usually see their obstetrician-gynecologist annually or semiannually, which provides the practitioner with an opportunity to elicit information about bladder function.

STUDY DESIGN

Allsworth: ***What were the study's objectives? Were these important questions?***

Cunkelman: The study's objectives, according to the authors, were to evaluate the association of nocturia and urinary urgency with reproductive factors that include parity, postpartum period, menopause, hormone replacement therapy, hysterectomy, and surgery for stress urinary incontinence (SUI). Overactive bladder syndrome, of which nocturia and urinary urgency are components, is associated with decreased quality of life and, in the case of nocturia, a decrease in the general level of health. Understanding the associated reproductive factors, if there are any, potentially would allow for modi-

fication of some factors and further our understanding of these disease processes.

Allsworth: ***What was the study's design?***

Homco: The investigators used a cross-sectional, population-based study to assess the association of nocturia and urinary urgency with reproductive factors. With the use of the Finnish Population Register, questionnaires were mailed to 3000 randomly selected women who were 18-79 years old. The investigators oversampled younger groups to achieve a sufficient number of subjects with the outcome in each age group. This provided a cheap and easy way to evaluate reproductive risk factors that are associated with nocturia and urinary urgency among a representative sample of the entire population.

Allsworth: ***What are the benefits of population-based surveys? Was this an appropriate study design for this question?***

Homco: Surveying a group that is representative of the entire population reduces sampling bias that is common to many clinical studies in which recruitment is tied to some health concern, and it allows results to be generalized beyond the study population.

Cross-sectional studies serve as a great tool for gathering preliminary data when an analytic study is being developed. Unfortunately, a cross-sectional study only allows one to assess association; not causality. Cross-sectional studies cannot account for temporality, whether the exposure, in fact, occurred before the outcome. Therefore, it cannot be inferred that the exposure actually caused the outcome. For example, this study does not address whether the subjects experienced nocturia and/or urinary urgency before exposure to any of the reproductive factors, such has having a child. As a follow-up to this study's results, it would be interesting to use a different study design, such as a case-control model, to further investigate risk factors and causes for nocturia and urinary urgency.

Allsworth: ***How were the outcomes of nocturia and urinary urgency measured? Were these appropriate gauges?***

Cunkelman: Respondents' answers to questions from the Danish Prostatic Symptom Score and the American Urological Association Symptom Index were combined to assess nocturia. Urinary urgency was assessed by the Danish Prostatic Symptom Score. Although both tools were designed and validated originally for the evaluation of urinary symptoms in men with benign prostatic hypertrophy, the defining questions that were used to assess nocturia and urgency were gender-neutral and not specific to benign prostatic hypertrophy.

Allsworth: ***The authors excluded women who were pregnant or during the immediate postpartum period and those women who reported urinary tract infections. Do you feel these exclusions were appropriate? Were other conditions included in the sample that could have had an impact on nocturia and urinary urgency?***

Omicioli: Yes, I think they are appropriate, because these conditions are time-limited. Obviously, pregnancy resolves with delivery, and antibiotic therapy usually clears up urinary tract infection. In addition, many women have frequent awakenings well beyond the 6-week immediate postpartum period that are related to infant sleep patterns and disturbed maternal sleep. In assessing nocturia, the study does not discriminate between women who were awakened by the need to void and those who were already awake and decided to void before going back to sleep.

Allsworth: ***Approximately 2000 participants (67%) of the initial sample responded, and 1728 (58%) were in the final analysis sample. What do you think of these rates? What are the potential impacts of response rate on the study's findings and interpretation?***

Homco: There are no specific guidelines on response rate. Obviously, higher response rates provide better samples. Given that participants were asked to respond to a questionnaire by mail, a 70% response rate is reasonable. When response rates are considered, it is important to keep selection bias in mind, because it results in an inaccurate estimate of association. Selection bias may invalidate generalization or conclusions that are drawn from the study. For example, the individuals who did not respond to the questionnaire may differ in some unidentified way from those who did respond. Also, those individuals who respond quickly to a questionnaire may differ from those who take longer to respond. The investigators noted that no reproductive or gynecologic differences were found among participants who responded to different mailing rounds, but this is not to say that the study population differs in some other unknown way from the nonresponders. The investigators might have benefited from looking at alternate means of completing the questionnaire, such as telephone surveys.

CONCLUSIONS

Allsworth: ***What were the main findings of the study? What additional reproductive characteristics would have been of interest in this or future studies?***

Cunkelman: After adjustment for age, confounders (comorbidity, prescription medication use, sociodemographic factors, body mass index, smoking, and alcohol and caffeine consumption), and reproductive factors, nocturia was associated with parity, postpartum period, and postmenopausal status. Surgery for SUI was the only factor to be associated with urgency after adjustment for age, confounders, and reproductive factors. Although nocturia and urgency together constitute overactive bladder syndrome, the findings imply that these are separate disease processes with different causes.

It would have been interesting to stratify data by mode of delivery, type of hysterectomy, and type of surgery for SUI. The current evidence, what exists of it, on the association between these factors and nocturia or urgency is, at best, mixed. Some of these risk factors might be modifiable; thus, an association with nocturia or urgency would be useful information.

Allsworth: ***The authors tested for the presence of effect modification because of an interaction between age and parity. Can you describe effect modification? What assumptions did the authors make in testing for effect modification?***

Homco: Effect modification, also known as statistical interaction, is present when the degree of association between an ex-

posure variable and disease outcome changes according to the value or level of a third variable, which is called the *effect modifier*. Effect modification is a desired observation that allows us to identify subgroups with differing risk. However, a biologically sound or sensible argument is required when a covariate is assessed as a possible effect modifier. The authors tested for the presence of a multiplicative interaction between parity and nocturia/urgency risk. More specifically, the authors looked at whether the relationship between parity and nocturia/urgency risk differs depending on the age group you are assessing.

Allsworth: ***The authors concluded that there was no effect modification attributable to age and parity. Was this conclusion warranted?***

Homco: The investigation into the presence or absence of interaction is equated most often with multiplicative interaction. Frequently, multiplicative interaction is assessed when one looks for causal association, as in this study. Consequently, the authors concluded that, in a model that contained parity and age as the main effects, no multiplicative effect modification that is attributable to these factors exists. The probability values of this interaction term indicated no significant effect was present (nocturia, $P = .72$; urgency, $P = .27$). However, this method only tests for the presence of a multiplicative interaction between parity and age. An additive interaction, which was not examined in this study, may be of greater interest in disease prevention. Future studies should examine for an additive-level interaction in evaluating the association of nocturia and urinary urgency with reproductive factors.

Allsworth: ***This study was conducted among Finnish women. Do you feel that the results will be generalizable to women in the United States?***

Cunkelman: Given the ethnic and racial diversity of the US population relative to that of Finland, these results should not be generalized to the US population without further study.

Allsworth: ***What were the strengths and limitations of this study?***

Omicioli: The strengths of the study were its population-based design, a fairly high response rate, the use of confounder scores, and the sampling methods that ensure a similar number of subjects in all age groups. The limitations of the study included the uncertainty that is related to how data that pertain to women with both urgency and nocturia were analyzed. Similarly, were women who had undergone a hysterectomy and who were taking hormonal therapy included in both categories? In those women who had surgery for SUI, what proportion had mixed incontinence with urgency that may have preceded surgery? It would have been informative to distinguish between postmenopausal women with and without symptoms of menopause to determine whether only symptomatic postmenopausal status was associated with nocturia.

Allsworth: ***Does the information from this study impact how you would counsel patients concerned about either nocturia or urinary urgency?***

Omicioli: It does not; the study was descriptive and not designed to assess causation or therapy. From the data that are presented, it is unclear whether the association of urinary urgency after SUI surgery was due to mixed incontinence before surgery or whether it occurred de novo after the surgery. In addition, SUI surgery frequently has transient urgency that resolves after several months; because temporal factors cannot be assessed, we have no idea at what point in time people were sampled in relationship to the surgery. ■

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Original Contribution

A Systematic Evaluation of Factors Associated With Nocturia—The Population-based FINNO Study

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In a case-control study with prevalence sampling, the authors explored the correlates for nocturia and their population-level impact. In 2003–2004, questionnaires were mailed to 6,000 subjects (aged 18–79 years) randomly identified from the Finnish Population Register (62.4% participated; 53.7% were female). Questionnaires contained items on medical conditions, medications, lifestyle, sociodemographic and reproductive factors, urinary symptoms, and snoring. Nocturia was defined as $\geq$2 voids/night. In age-adjusted analyses, factors associated with nocturia were entered into a multivariate model. Backward elimination was used to select variables for the final model, with adjustment for confounding. Although numerous correlates were identified, none affected $\geq$50% of nocturia cases of both sexes. The factors with the greatest impact at the population level were (urinary) urgency (attributable number/1,000 subjects (AN) = 24), benign prostatic hyperplasia (AN = 19), and snoring (AN = 16) for men and overweight and obesity (AN = 40), urgency (AN = 24), and snoring (AN = 17) for women. Moreover, correlates included prostate cancer and antidepressant use for men, coronary artery disease and diabetes for women, and restless legs syndrome and obesity for both sexes. Although several correlates were identified, none accounted for a substantial proportion of the population burden, highlighting the multifactorial etiology of nocturia.

coronary artery disease; diabetes mellitus; life style; obesity; prostatic hyperplasia; prostatic neoplasms; sleep disorders; urinary bladder, overactive

Abbreviations: BPH, benign prostatic hyperplasia; FINNO, Finnish National Nocturia and Overactive Bladder.

Nocturia (waking at night to urinate) is a common cause of awakenings and may lead to sleep maintenance insomnia (1–3). Nocturia can be bothersome (4) and is associated with impaired mental and somatic health (5), impaired quality of life (4), and even increased mortality (6).

The etiology of nocturia is inadequately understood. Nocturia is frequently attributed to aging or childbirth in women and to benign prostatic hyperplasia (BPH) in men. Other related conditions include overactive bladder syndrome; nocturnal polyuria; obstructive sleep apnea; awakening for other reasons such as anxiety; primary sleep disorders; and use of diuretics, caffeine, or alcohol (7–9). Bedtime fluid intake correlates poorly with nocturia episodes (10).

Nocturia persists frequently following simple prostatectomy (11). In one study, 38% of men reported $\geq$2 voids/night 3 years after transurethral resection of the prostate (12). Several pharmacologic approaches have yielded limited nocturia reductions or significant side effects (7, 13–25).

To our knowledge, no earlier study comprehensively covered the possible associations of medical conditions; medications; lifestyle; and anthropometric, reproductive, and sociodemographic factors with nocturia. We explored correlates for nocturia and assessed their population-level impact in a large population-based study.

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MATERIALS AND METHODS

Finnish National Nocturia and Overactive Bladder (FINNO) Study

In 2003–2004, questionnaires were mailed to 6,000 subjects aged 18–79 years randomly identified from the Population Register Centre. Age stratification was used with oversampling of younger age groups to ensure precise estimates even in age groups experiencing lower nocturia frequency (3, 26). More information on the FINNO Study (including characterization of nonrespondents) has been published previously (3, 26, 27).

Outcome

Nocturia cases were defined as subjects reporting 2 or more voids/night because this frequency involves clinically significant bother (4). All subjects without nocturia were considered controls in unconditional logistic regression analyses. Self-reported nocturia frequency was determined by using a previously described algorithm (27) combining responses to the Danish Prostatic Symptom Score (28) and the American Urological Association Symptom Index (29) (Web Table 1; this information is described in the first of 4 supplementary tables, each referred to as ''Web table'' in the text and posted on the *Journal*'s website (http://aje.oupjournals.org/)).

Correlate assessment

Self-reported information on physician-diagnosed conditions, prescribed medication, specific symptoms, and lifestyle factors was obtained by using questions modified from surveys conducted by the National Public Health Institute (30). Comorbidity indicators were formulated for 36 conditions deemed common or previously hypothesized as determinants of lower urinary tract symptoms (Web Tables 1 and 2). Medication use was classified into 27 groups by using the Anatomical Therapeutic Chemical Classification (31) (Web Tables 1 and 3). Lifestyle factors included body mass index, smoking, and alcohol and coffee consumption (Web Tables 1 and 4). The Danish Prostatic Symptom Score questions were used to evaluate (urinary) urgency and stress urinary incontinence (28) and the Basic Nordic Sleep Questionnaire to evaluate snoring (32) (Web Tables 1 and 4). These symptoms have been specifically shown to be risk factors for nocturia (26, 33, 34).

With the exception of the alcohol consumption question (response rate: men, 86%; women, 76%), data on potential correlates were highly available (men, 97%–100%; women, 95%–100%). Alcohol consumption was not associated with nocturia.

Potential confounders

Age, sociodemographic factors (marital status, education, employment, urbanization) (3), and female reproductive/gynecologic factors (parity, postpartum period, menopausal status, hormone therapy, hysterectomy, stress urinary incontinence surgery) (27) were treated as potential confounders. Data on urbanization, parity, and delivery date(s) were obtained from the population register. Information on each potential confounder was available for at least 99% of subjects.

Statistical analysis

Logistic regression was used for the analyses stratified by sex, with nocturia as the outcome. All potential correlates and confounders associated ($P < 0.10$) with nocturia in the age-adjusted analyses (basic analysis population) were entered into the multivariate model (Web Figure 1, also posted on the *Journal*'s website (http://aje.oupjournals.org/)). In these analyses, potential correlates and confounders numbered 16 and 2 for men and 18 and 6 for women, respectively. Backward elimination techniques were used to select variables for the final model, with likelihood ratio tests used to determine significance ($P < 0.05$). Finally, cofactors that were not actual confounders (they did not change any estimate by $\geq$10%) were eliminated. Confirmed confounders were age for men, menopausal status for women, and employment for both sexes. The final analysis included subjects with information on nocturia, correlates, and confounders (Web Figure 1). For the correlates identified, age-standardized sensitivity, positive predictive value, attributable fraction in the exposed, population attributable fraction, and attributable number were calculated (35).

RESULTS

Of the 6,000 subjects approached, 3,727 (62.4%) participated; 23 were unavailable, and 130 were excluded because of pregnancy, puerperium, or urinary tract infection (Web Figure 1). (The response rate was approximately 32% after the first round, 50% after the second round, and 62.4% after the final, third round.) Of the 3,597 subjects included, 98% provided nocturia information (basic analysis population). The 3,307 subjects (92%) who responded to all nocturia, correlate, and confounder questions formed the final analysis population. Prevalence of nocturia was 12.5% (95% confidence interval: 10.7, 14.3) among men and 12.9% (95% confidence interval: 11.0, 14.9) among women (age standardized to match Finland's age structure (36)). Excluding subjects with missing information on any correlate or confounder (final analysis population) did not change these estimates. For more detail, refer to Table 1 and to Web Tables 2–4. Correlates for nocturia included (urinary) urgency, snoring, restless legs syndrome, and obesity for both sexes; BPH, antidepressant use, and prostate cancer for men; and overweight, diabetes, and coronary artery disease for women (Table 1).

At the population level (Table 2), urgency and snoring (both sexes), BPH (men only), and overweight/obesity (women only) accounted for the largest proportion of nocturia. At the individual level, the strongest correlate for both sexes was urgency, although odds ratio differences between correlates were mainly statistically nonsignificant (Table 1).

No correlate affected 50% or more of men with nocturia (Figure 1): BPH, urgency, and snoring had the highest sensitivity for nocturia (31%–49%). Of the women with nocturia, 71% were overweight or obese; other correlates were reported by 50% or more of women with nocturia (Figure 2).

Table 1. Prevalences (%) and Odds Ratios of Correlates for Nocturia in Multivariate Analyses[a] in the Population-based Finnish National Nocturia and Overactive Bladder Study, Finland, 2003–2004

	Prevalence[b]	95% CI	OR	95% CI
Men				
Urinary urgency	7.5	6.1, 9.0	7.39	4.46, 12.23
Prostate cancer	1.2	0.7, 1.8	5.45	1.74, 17.08
Antidepressant use	2.5	1.7, 3.3	3.16	1.29, 7.73
Restless legs syndrome	3.0	2.1, 4.0	2.91	1.30, 6.52
Benign prostatic hyperplasia	7.8	6.3, 9.3	2.18	1.31, 3.65
Obesity[c]	13.2	11.2, 15.1	2.07	1.17, 3.67
Snoring	35.1	31.9, 38.2	1.49	1.00, 2.22
Women				
Urinary urgency	9.9	8.2, 11.6	4.92	3.15, 7.67
Coronary artery disease	4.5	3.1, 5.8	3.13	1.48, 6.64
Restless legs syndrome	3.6	2.5, 4.8	2.86	1.41, 5.83
Diabetes	4.7	3.4, 5.9	2.68	1.38, 5.20
Obesity[c]	13.3	11.4, 15.3	2.18	1.30, 3.66
Overweight[c]	32.3	29.2, 35.4	1.90	1.25, 2.88
Snoring	18.4	16.1, 20.7	1.76	1.17, 2.64

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Also adjusted for identified confounders (age and employment for men; employment and menopausal status for women).

[b] Age standardization using the age structure of Finland (36).

[c] Normal-weight (body mass index < 25 kg/m^2) subjects were considered the reference (37).

Table 2. Fraction of Nocturia Attributable to Identified Correlates in the Population-based Finnish National Nocturia and Overactive Bladder Study, Finland, 2003–2004[a]

	Attributable Fraction in the Exposed, %[b,c]	Population Attributable Fraction, %[c,d]	Attributable No./1,000 Subjects[c,e]
Men			
Urinary urgency	77.2	24.0	24
Benign prostatic hyperplasia	69.1	13.1	19
Snoring	30.3	14.4	16
Obesity[f]	29.1	5.9	6
Antidepressant use	65.6	4.3	6
Restless legs syndrome	53.1	4.7	4
Prostate cancer	65.8	3.9	3
Women			
Overweight/obesity[f]	51.5	35.4	40
Urinary urgency	71.0	21.3	24
Snoring	46.8	16.4	17
Diabetes	63.3	8.6	9
Restless legs syndrome	63.4	7.4	7
Coronary artery disease	44.9	7.4	4

[a] Age standardization using the age structure of Finland (36).

[b] Attributable fraction in the exposed refers to the proportion by which prevalence of the condition (nocturia) among exposed persons (with the correlate) would be reduced if the exposure (correlate) were eliminated (35).

[c] Regarding formulae of attributable fractions and attributable number, it is assumed that causes other than the one under investigation have similar effects on the exposed and unexposed groups (35).

[d] Population attributable fraction refers to the proportion by which prevalence of the condition (nocturia) in the entire population would be reduced if the exposure (correlate) were eliminated (35).

[e] Attributable number refers to the number of prevalent cases of the condition (nocturia) attributable to the exposure (correlate) (35).

[f] Body mass index (BMI) was classified as a dichotomous variable when calculating attributable fractions because of the dichotomous nature of these measures. Hence, the reference groups were not obese (BMI < 30 kg/m^2) for men and normal weight (BMI < 25 kg/m^2) for women because overweight (BMI 25–30 kg/m^2) was associated with nocturia in women only.

A majority of men with prostate cancer or urgency reported nocturia, yielding positive predictive values of 74% and 59%, respectively. Half of the men with BPH, and a minority of men with other correlates, reported nocturia (Figure 1). Among women, no correlates were associated with a 50% or greater probability of nocturia (Figure 2).

Generally, questionnaire mailing round did not affect correlate prevalence. However, 4 exceptions emerged (age adjusted). First-round responders reported more nocturia and urgency than responders in subsequent rounds (P for trend $=$ 0.01 for both nocturia and urgency; sexes combined). Moreover, first-round male responders reported more antidepressant use (P for trend $=$ 0.04), and first-round female responders were slightly less obese than those in subsequent rounds (P for trend $=$ 0.05). However, the odds ratio estimates for these factors were similar for each round, suggesting absence of systematic error.

DISCUSSION

In this large, population-based study, numerous factors associated with nocturia were identified. However, no single correlate accounted for more than half of the cases of nocturia, highlighting its multifactorial etiology. At the population level, urgency, BPH, and snoring for men and overweight/obesity, urgency, and snoring for women accounted for the largest proportion of nocturia.

Our FINNO Study population is representative of Finnish adults in terms of sociodemographic, anthropometric, and female reproductive factors (3, 27, 37). The frequencies of comorbidities, medications, and lifestyle factors were similar to those in large-scale population surveys conducted by the National Public Health Institute (38–40).

Concordant with earlier reports (26, 41–44), urinary urgency was strongly associated with nocturia in both sexes, yet only 1 in 3 with nocturia reported urgency. Among men,

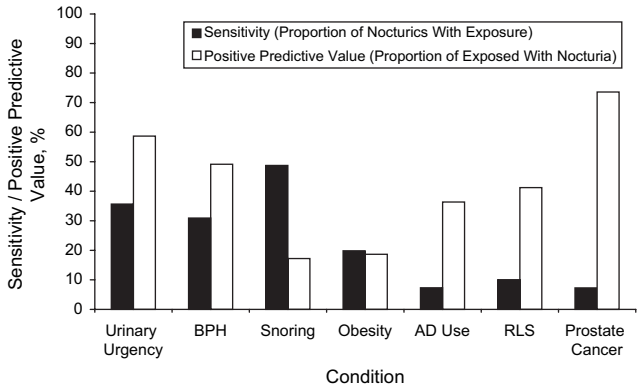

Figure 1. Sensitivity and positive predictive value for correlates of nocturia among men (in order: the correlate with the greatest impact at the population level is given first) in the population-based Finnish National Nocturia and Overactive Bladder Study, Finland, 2003–2004. AD, antidepressant; BPH, benign prostatic hyperplasia; RLS, restless legs syndrome. Body mass index (BMI) was classified as a dichotomous variable when calculating sensitivity and positive predictive value because of the dichotomous nature of these measures. Hence, the reference groups were not obese (BMI $<$ 30 kg/m^2) for men and normal weight (BMI $<$ 25 kg/m^2) for women because overweight (BMI 25–30 kg/m^2) was associated with nocturia in women only.

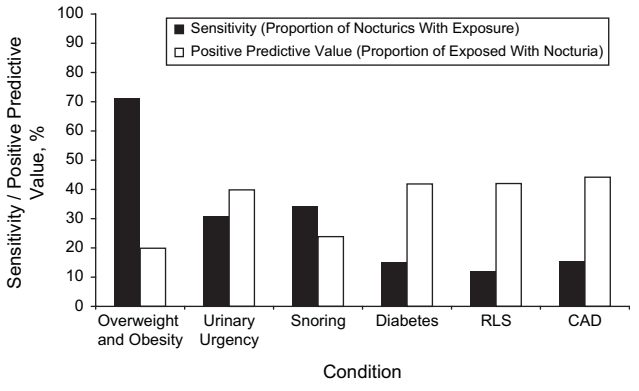

Figure 2. Sensitivity and positive predictive value for correlates of nocturia among women (in order: the correlate with the greatest impact at the population level is given first) in the population-based Finnish National Nocturia and Overactive Bladder Study, Finland, 2003–2004. CAD, coronary artery disease; RLS, restless legs syndrome. Body mass index (BMI) was classified as a dichotomous variable when calculating sensitivity and positive predictive value because of the dichotomous nature of these measures. Hence, the reference groups were not obese (BMI $<$ 30 kg/m^2) for men and normal weight (BMI $<$ 25 kg/m^2) for women because overweight (BMI 25–30 kg/m^2) was associated with nocturia in women only.

BPH had the second highest population impact, but only a third with nocturia reported BPH. Lower urinary tract symptoms suggestive of benign prostatic obstruction constitute a well-recognized risk factor for nocturia (45). However, the impact of BPH may be overestimated. In Japanese studies, nocturia was the lower urinary tract symptom least related to prostatic obstruction, and treatment to relieve obstruction had less of an effect on nocturia than on other symptoms (15, 46). In a lower urinary tract symptoms/BPH study, patients receiving doxazosin experienced very modest reductions in nocturia, whereas finasteride had no effect (23). In the current study, prostate cancer was associated with nocturia. More than 70% of men with prostate cancer reported at least 2 voids/night, yet only 7% of men with nocturia reported prostate cancer.

Concurring with earlier findings (37, 47–49), nocturia was associated with *obesity* in both sexes and, among women, also with *overweight*. Indeed, overweight/obesity had the greatest population impact among women.

Snoring had a strong population impact because of its high prevalence, yet the strength of association was relatively weak (odds ratio = 1.5–1.8). Snoring has been associated with nocturia (34). The severity of obstructive sleep apnea predicted nocturia frequency, and continuous positive airway pressure treatment decreased nocturia (50). In a home sleep study, the prevalence of obstructive sleep apnea was double among urogynecology patients with nocturia compared with those without (51). In our study, reported obstructive sleep apnea was not associated with nocturia after adjustment, which may be due to correlation with snoring (three-quarters of subjects with obstructive sleep apnea reported snoring, and snoring was 10 times more prevalent than obstructive sleep apnea).

To our knowledge, no association has been reported between nocturia and restless legs syndrome. Increased nocturia among patients with restless legs syndrome may reflect sleep disturbance (52). Moreover, such patients use more medications (particularly antidepressants) than controls do (53). Nocturia has previously been linked to (untreated) depression (54, 55) and use of selective serotonin-reuptake inhibitors (54). In our study, only for men was nocturia associated with antidepressant use; depression itself was not associated with nocturia.

Diabetes and coronary artery disease were associated with nocturia in the age-adjusted analyses for both sexes but for only women in multivariate analysis. An association between diabetes and nocturia has been reported sometimes (43, 47, 49, 50, 56–60), but not always (10, 42, 45). In the BACH Survey (47), nocturia was associated with increasing body mass index, diabetes, and cardiac disease, whereas among Danes aged 60–80 years (49), increasing body mass index, diabetes, urinary incontinence, and recurrent cystitis were associated with 2 voids/night. In both surveys (47, 49), sex was used as a covariate, but results were not reported by gender. Some earlier reports (47, 59, 61), but not all (42, 43, 45, 49, 58), found cardiac/coronary disease a correlate for nocturia.

Coffee or alcohol consumption (10, 33, 41, 43, 49, 62, 63) and smoking (33, 49, 61, 63) have been shown elsewhere not to be associated with nocturia. Our findings were the same.

Differences in our results from previous findings may be explained by differences in study procedures and samples (64). Several factors explored here were not assessed in earlier studies (10, 41–43, 45–47, 49–51, 55, 56, 58, 59, 61–63). In addition, several previous studies were not population based (41, 43, 46, 50, 51, 59, 61). The association of numerous factors with nocturia in age-adjusted analyses,

partly differing by gender, highlights the importance of appropriate analysis, including controlling for confounders. Given the multiple possible determinants (7–10, 34, 41–43, 45–51, 54, 56–63), we assessed numerous candidates. Because of inconsistencies in the literature, using existing evidence to choose the potential confounders was not justified. Hence, because of the exploratory nature of this analysis, we used stepwise methods for model building (65).

By our methodology, we avoided selection bias due to treatment seeking (reflecting both severity and health care service use). Our study's strengths include 1) a representative sample of both sexes and all adult ages, 2) a high participation rate and completeness of questionnaire responses, 3) a large number of relevant factors, 4) systematic control for confounding, and 5) assessment of nocturia and related symptoms with validated instruments. Furthermore, determinant prevalences were largely similar by response round, indicating absence of selection bias; any trend in the risk estimates by response round was also lacking.

This study has some limitations. First, the validity of self-report has not been established for all characteristics we considered. Second, alcohol consumption reporting was incomplete, yet nocturia prevalence did not vary by alcohol consumption among those reporting this information. In addition, reported alcohol consumption was comparable with the national statistics (66). Third, we had no information on physical activity, although physical activity has not previously been related to nocturia (41). Finally, these results from the Finnish population may not be directly generalizable to other ethnicities because impact measures generally are context specific. There may be ethnic differences in the prevalence of nocturia. Socioeconomic status attenuated, but did not entirely remove, the effect of race/ethnicity on nocturia (67).

Nocturia has been classified as a symptom caused by 1) nocturnal polyuria, 2) low nocturnal bladder capacity, 3) diminished global bladder capacity, 4) a combination of nocturnal polyuria and low bladder capacity, 5) global polyuria, and/or 6) sleep disorders (7). We found several risk factors that may well cause these pathways and, finally, nocturia. However, the pathways are probably complex, and there may also be numerous other underlying causes for the associations, such as autonomic nervous system hyperactivity and/or metabolic syndrome (68, 69). At the population level, urgency, BPH, and snoring for men and overweight and obesity, urgency, and snoring for women explained the largest proportion of nocturia, whereas obesity, antidepressant use, and prostate cancer in men; diabetes and coronary artery disease in women; and restless legs syndrome in both sexes had less of an impact. Even though numerous correlates for nocturia were identified, none was associated with nocturia in more than half of the affected subjects of both sexes, highlighting the multifactorial etiology.

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K. A. O. T. had full access to all the data used in the study and takes responsibility for the integrity and the accuracy of the data. K. A. O. T., A. A., and T. L. J. T. designed the study. K. A. O. T. collected the data. K. A. O. T. and A. A. performed statistical analysis of the data. All authors contributed to the interpretation of the findings. K. A. O. T. drafted the manuscript. All authors contributed to revising the manuscript.

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