Tampere University

JORI PESONEN

Course and Consequences of Nocturia

Tampere University Dissertations 154

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ACADEMIC DISSERTATION
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Tampere University, Faculty of Medicine and Health Technology
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To *Saija, Anni and Aino*

ABSTRACT

Nocturia (waking from sleep at night to void) is one of the most burdensome lower urinary tract symptoms (LUTS) among middle-aged and older people. The prevalence of nocturia tends to increase with age, due to age-related functional changes of the kidneys and bladder, and due to changes in sleep pattern. Nocturia can also be brought on by various illnesses and lifestyle factors. People with nocturia may be predisposed to further health complications and even mortality. Especially among frail elderly subjects with an increased baseline risk for falls and fall-related injuries, the presence of nocturia may further increase these risks.

Treatment of nocturia is often unsuccessful. For more successful care, treatment decisions and health promotion, a better understanding of the prognosis of nocturia and its associated risks for further morbidity is needed. However, summarising data from previous longitudinal studies is challenging due to variation between study samples, assessment tools, case definitions and analytic strategies. Systematic reviews would clarify the issue, but systematic reviews and meta-analyses of the natural history and prognosis of symptoms are challenging and require methodological knowledge and innovations.

The primary aim of the thesis was to ascertain the natural course of nocturia and associated risks of falls, fractures and mortality. The secondary aim was to further develop methods for systematic reviews and meta-analyses assessing the natural history, prognosis and impact of symptoms, including effect sizes and quality of evidence (certainty in evidence).

The thesis comprises three systematic reviews with accompanying meta-analyses and one population-based cohort study. The systematic reviews were based on a comprehensive search of both published and unpublished reports without language restrictions, and subsequent screening of abstracts and full texts according to predefined eligibility criteria to detect all available observational cohort studies. The quantitative syntheses included random effects meta-analyses addressing the incidence/remission rates of nocturia, and relative risks (RR) of all-cause mortality, falls and fractures. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to rate the quality of evidence for nocturia as a prognostic and causal factor of mortality, falls and fractures.

The longitudinal analysis of Tampere Ageing Male Urologic Study (TAMUS) included a population-based sample of men from Pirkanmaa Region (Finland) initially aged 50, 60, and 70 years. The cohort was followed-up with mail surveys including the assessments of LUTS and comorbidities repeatedly in 1994, 1999, 2004, and 2009, and for mortality through the population registry until the end of 2014. LUTS-associated hazard ratios (HR) were analysed with time-dependent Cox regression adjusted for year of birth and comorbidities using variable values updated every five years.

The pooled estimates of 12 studies demonstrated a strong association of annual incidence of nocturia with age: 0.4% (95% confidence interval 0-0.8%) for adults aged < 40 years; 2.8% (1.9-3.7%) for adults aged 40-59 years; and 11.5% (9.1-14.0%) for adults aged 60 years. Of those with nocturia, each year 12.1% (9.5-14.7%) experienced remission with no significant differences in estimates between age groups.

For association between nocturia and mortality, the pooled estimates of 11 studies demonstrated an RR of 1.27 (95% CI 1.16-1.40, absolute 5-year mortality difference 1.6% in people aged 60 and 4.0% in those aged 75 years). For association between nocturia and falls, five studies demonstrated a pooled RR of 1.20 (95% CI 1.05-1.37, annual risk difference 7.5% among the elderly) and five studies, a pooled RR of fractures of 1.32 (95% CI 0.99-1.76, annual risk difference 1.2%). The quality of evidence was rated moderate for nocturia as a prognostic factor for mortality and very low for nocturia as a cause of mortality. The quality of evidence was rated moderate for nocturia as a prognostic factor for falls, low for fractures and very low for nocturia as a cause of falls or fractures.

An association between nocturia and mortality was also observed in the 21-year follow-up of the TAMUS cohort of 1,332 men: adjusted HR was 1.38 (1.07-1.79).

The available evidence suggests that the onset of nocturia is strongly associated with age, with much higher rates in those over 60 years; remission occurs in approximately 12% each year. Moderate-quality evidence suggests that nocturia is associated with a 1.2-fold risk for falls and low-quality evidence suggests that nocturia is associated with a 1.3-fold risk for fractures. Furthermore, moderate-quality evidence suggests that nocturia is associated with a 1.3-fold risk of death.

The findings of the thesis suggest that greater attention needs to be paid to underlying health conditions in patients with nocturia. Future research should address the impact of treatment for nocturia on falls and fractures with adequately long follow-up to detect further morbidity and mortality.

TIIVISTELMÄ

Yövirtsaaminen (nokturia) on yksi yleisimmistä elämänlaatua heikentävistä virtsaamisoireista. Nokturian esiintyvyys kasvaa iän myötä johtuen ikääntymisen aiheuttamista muutoksista munuaisten ja virtsateiden toiminnassa. Nokturiaa aiheuttavat myös monet sairaudet ja elintavat. Nokturiaan saattaakin liittyä lisääntynyttä sairastavuutta ja jopa kuolleisuutta. Varsinkin hauraiden ikäihmisten kaatumis- ja murtumariskit saattavat kasvaa entisestään nokturian yhteydessä.

Nokturian hoito ei aina ole tehokasta. Parempien hoitotulosten ja hoitopäätösten tueksi tarvitaan lisää tietoa nokturian luonnollisesta kulusta ja oireeseen liittyvien terveyshaittojen riskeistä. Nokturian ennusteen ja terveysvaikutusten selventämiseksi tarvitaankin systemaattisia katsauksia ja näihin pohjautuvia meta-analyysejä. Aiempien tutkimustulosten yhteenveto on kuitenkin haastavaa johtuen tutkimusväestöjen, oirekartoitusmenetelmien, nokturian määritelmien ja analyysimenetelmien vaihtelevaisuudesta ja niinpä luonnollista kulkua ja ennustetta käsittelevien systemaattisten katsausten ja meta-analyysien tekeminen edellyttävät metodologista erikoisosaamista ja innovaatioita.

Väitöstutkimuksen tavoitteena oli selvittää nokturian ilmaantuvuutta ja remissiota väestötasolla, sekä nokturian vaikutusta kaatumisten, murtumien ja ennenaikaisen kuoleman riskiin. Lisäksi tavoitteena oli kehittää oireiden ennustetta tutkivien systemaattisten katsausten ja meta-analyysien menetelmiä.

Väitöskirjakokonaisuus koostui kolmesta meta-analyysin sisältävästä systemaattisesta katsauksesta ja yhdestä väestöpohjaisesta kohorttitutkimuksesta. Systemaattisten katsausten perustana oli laaja-alainen kirjallisuushaku täydennettynä julkaisemattomien konferenssiabstraktien erillisellä haulla. Päävastemuuttujina kvantitatiivisissa analyyseissä olivat nokturian ilmaantuvuus- ja remissioluvut, sekä nokturiaan liittyvät suhteelliset riskit mortaliteetille, kaatumisille ja murtumille. Tutkimusnäytön laatu koskien nokturiaa kaatumisten, murtumien ja mortaliteetin ennusteellisena ja kausaalisena riskitekijänä arvioitiin GRADE-menetelmällä (Grading of Recommendations Assessment, Development and Evaluation).

Nokturian ja mortaliteetin välistä yhteyttä kotimaisessa väestössä selvitettiin pirkanmaalaismiehistä koostuvan TAMUS-kohortin (Tampere Ageing Male Urologic Study) avulla. Käytettävissä oli viiden vuoden välein toistetut haastattelut

50-, 60- ja 70-vuotiaille miehille vuodesta 1994 alkaen ja tiedot kuolemista vuoden 2014 loppuun saakka. Haastattelukierrokset sisälsivät tietoja virtsaamisoireista, sairauksista, lääkityksistä ja elintavoista. Virtsaamisoireiden ja ennenaikaisen kuoleman riskin väliset vaarasuhteet määritettiin aikariippuvaisten Coxin regressioanalyysien avulla vakioituna selittävien muuttujien viiden vuoden välein päivitetyillä arvoilla.

Systemaattisen katsauksen avulla identifioidun kahdentoista tutkimuksen yhdistetyt estimaatit (meta-analyysi) osoittivat nokturian ilmaantuvuuden kasvavan ikääntymisen myötä: nokturian keskimääräinen vuosittainen ilmaantuvuus oli alle 40-vuotiailla aikuisilla 0.4 % (95% luottamusväli 0–0.8%), 40–59-vuotiailla 2.8% (1.9–3.7%) ja yli 60-vuotiailla 11.5 % (9.1–14.0%). Vuosittainen remissio oli 12.1 % (9.5–14.7%). Remissiossa ei ollut merkittäviä eroja ikäryhmien välillä.

Meta-analyysit osoittivat yhteyden nokturian ja ennenaikaisen kuoleman, sekä kaatumisten ja murtumien riskien välillä. Yhdentoista tutkimuksen yhdistetty suhteellinen ennenaikaisen kuoleman riski oli 1.27 (95% LV 1.16-1.40) vastaten 1.6 %:n absoluuttisen riskin kasvua 60-vuotiailla ja 4.0 %:n kasvua 75-vuotiailla viidessä vuodessa. Viiden tutkimuksen yhdistetty suhteellinen kaatumisten riski oli 1.20 (1.05-1.37) ja murtumien riski 1.32 (0.99-1.76), vastaten 7.5% kaatumisten ja 1.2% murtumien absoluuttisen riskin kasvua vanhuksilla vuosittain. Tutkimusnäytön laatu arvioitiin kohtalaiseksi nokturialle mortaliteetin ennusteellisena riskitekijänä ja hyvin heikoksi mortaliteetin kausaalisena riskitekijänä. Tutkimusnäytön laatu arvioitiin kohtalaiseksi nokturialle kaatumisten ennusteellisena riskitekijänä ja heikoksi murtumien ennusteellisena riskitekijänä. Näytön laatu arvioitiin hyvin heikoksi nokturialle kaatumisten ja murtumien kausaalisena riskitekijänä.

Nokturian ja ennenaikaisen kuoleman välinen yhteys havaittiin myös TAMUS-kohortin 1332 miehen 21 vuoden seurannassa: vakioitu HR oli 1.38 (1.07–1.79).

Saatavilla olevan tutkimusnäytön perusteella nokturian ilmaantuvuus liittyy voimakkaasti ikääntymiseen ja kiihtyy erityisesti 60 ikävuoden jälkeen. Oireen spontaania lievenemistä tavataan vuosittain 12 %:lla niistä, joilla on nokturiaa. Kohtalaisen tutkimusnäytön perusteella nokturiaan liittyy 1.2-kertainen kaatumisten ja 1.3-kertainen ennenaikaisen kuoleman riski. Heikon tutkimusnäytön perusteella nokturiaan liittyy lisäksi 1.3-kertainen murtumien riski.

Väitöskirjan havaintojen perusteella nokturiaa selvitellessä on suositeltavaa huomioida potilaan yleisen terveydentilan kartoitus. Tulevaisuudessa tutkimusten odotetaan selvittävän nokturian hoidon vaikutusta kaatumisten ja murtumien riskiin ja pitkällä aikavälillä hoidon vaikutusta sairastavuuteen ja kuolleisuuteen

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LIST OF ORIGINAL PUBLICATIONS

I. Pesonen JS, Cartwright R, Mangera A, Santti H, Griebling TL, Pryalukhin AE, Riikonen J, Tähtinen RM, Agarwal A, Tsui JF, Vaughan CP, Markland AD, Johnson TM 2nd, Fonsell-Annala R, Khoo C, Tammela TL, Aoki Y, Auvinen A, Heels-Ansdell D, Guyatt GH, Tikkinen KA. Incidence and remission of nocturia: a systematic review and meta-analysis. Eur Urol 2016;70:372-81.

II. Pesonen JS, Cartwright R, Vernooij RWM, Aoki Y, Agarwal A, Mangera A, Markland AD, Tsui JF, Santti H, Griebling TL, Pryalukhin AE, Riikonen J, Tähtinen RM, Vaughan CP, Johnson TM 2nd, Auvinen A, Heels-Ansdell D, Guyatt GH, Tikkinen KAO. The impact of nocturia on mortality: a systematic review. J Urol 2019 (https://doi.org/10.1097/JU.0000000000000463) [Epub ahead of print].

III. Pesonen JS, Vernooij RWM, Cartwright R, Aoki Y, Agarwal A, Mangera A, Markland AD, Tsui JF, Santti H, Griebling TL, Pryalukhin AE, Riikonen J, Tähtinen RM, Vaughan CP, Johnson TM 2nd, Auvinen A, Heels-Ansdell D, Guyatt GH, Tikkinen KAO. The impact of nocturia on mortality: a systematic review. J Urol 2019 (https://doi.org/10.1097/JU.0000000000000459) [Epub ahead of print].

IV. Åkerla J, Pesonen JS, Pöyhönen A, Häkkinen J, Koskimäki J, Huhtala H, Tammela TLJ, Auvinen A. Impact of lower urinary tract symptoms on mortality: a 21-year follow-up among middle-aged and elderly Finnish men. Prostate Cancer Prostatic Dis 2019;22:317-23.

ABBREVIATIONS

ADMA	Asymmetric dimethylarginine
ANP	Atrial natriuretic peptide
AUA	American Urological Association
AVP	Arginine vasopressin
BMI	Body mass index
BOO	Bladder outlet obstruction
BP	Blood pressure
BPH	Benign prostatic hyperplasia
CHF	Congestive heart failure
CI	Confidence interval
CKD	Chronic kidney disease
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CVD	Cardiovascular disease
DAN-PSS-1	Danish Prostatic Symptom Score
DM	Diabetes mellitus
EAU	European Association of Urology
EBM	Evidence-based medicine
GFR	Glomerular filtration rate
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Hazard ratio
HTN	Hypertension
ICS	International Continence Society
IPSS	International Prostatic Symptom Score
IUGA	International Urogynecological Association
LUTS	Lower urinary tract symptoms
NO	Nitric oxide
NP	Nocturnal polyuria
OAB	Overactive bladder

OR	Odds ratio
OSA	Obstructive sleep apnea
PN	Pressure natriuresis
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomised controlled trial
RR	Relative risk
RAA	Renin-angiotensin-aldosterone
SDB	Sleep-disordered breathing
TAMUS	Tampere Ageing Male Urologic Study
TURP	Transurethral resection of prostate
QoL	Quality of life

1 INTRODUCTION

Nocturia (waking from sleep at night to void) (Hashim et al. 2019) is one of the most common and bothersome lower urinary tract symptoms (LUTS) (Abrams et al. 2002, Agarwal et al. 2014). The prevalence of nocturia increases markedly with age in both genders (Bosch & Weiss 2010), with normal age-related changes in the bladder and kidneys, and changes in sleep pattern, each contributing to the increase in nocturia. Besides being a major cause of sleep disruption and associated impaired quality of life (QoL), nocturia is often associated with illnesses such as diabetes, hypertension, cardiovascular diseases, chronic respiratory diseases, neurological diseases and malignancies (Tikkinen et al. 2009, Yoshimura 2012, Oelke et al. 2017). The wide range of conditions associated with nocturia suggests a multifactorial aetiology and, importantly, nocturia may also increase the risk of these conditions (Marshall et al. 2015).

Both the multifactorial aetiology and the wide range of associated comorbidities make the treatment of nocturia challenging. Furthermore, the elderly are especially susceptible to adverse effects of medical treatments (Chrischilles et al. 2001, Vaughan et al. 2016). Accurate estimates of progression and remission of nocturia over time would facilitate shared decision-making about the initiation and continuation of therapeutic options between patients and healthcare providers (Blanker et al. 2014). However, the majority of data on age-related changes of nocturia comes from cross-sectional studies (Bosch & Weiss 2010), whereas only few longitudinal studies have assessed the natural course of nocturia, and with highly heterogeneous study settings in terms of assessment tools, case definitions and analytic strategies (Marshall et al. 2015). A systematic review would clarify the issue but, unlike the case with conventional systematic reviews comparing one treatment against another or against a non-treatment control with well-established methods (Higgins & Green 2011), systematic reviews and meta-analyses addressing natural history or prognosis of symptoms are rare, and therefore require methodological innovations.

Due to its close association with several illnesses, nocturia has been proposed to have prognostic importance in predicting further morbidity or even mortality

(Yoshimura 2012). However, as people with nocturia tend to be older and are more likely to have comorbid conditions, the relevance of using nocturia as a risk factor for morbidity and mortality must be considered in light of the effects of various confounding factors. Furthermore, heterogeneity in estimates of previous studies exploring the longitudinal association between various LUTS and comorbidity, such as those exploring male LUTS as an exposure and cardiovascular disease (CVD) as an outcome (Bouwman et al. 2015, Gacci et al. 2016), may be due in part to variation in follow-up times and age distributions as the natural course of LUTS may vary considerably among different populations (Lee et al. 1998, Malmsten et al. 2010). Thus, repeated assessments of LUTS and other time-varying factors are required to establish robust estimates for associations between various symptoms and long-term health-related outcomes in order to differentiate short-term fluctuating symptoms from longer-term patient-important symptoms.

Regarding the links between nocturia, morbidity and mortality, falls and fractures comprise an important entity, especially among elderly population. Although retrospective and cross-sectional studies have shown associations of nocturia with both falls and fractures (Stewart et al. 1992, Kim et al. 2017), there are fewer prospective studies, which are more capable in controlling for confounding when compared to cross-sectional studies. When considering including nocturia as a potentially modifiable risk factor in the health promotion of older adults, accurate estimates of nocturia-related fall, fracture and mortality risks in general population would be highly relevant. Therefore, to guide future research and clinical practice, a critical appraisal of the existing evidence of the consequences of nocturia is warranted.

2 REVIEW OF THE LITERATURE

2.1 Terms and definitions

2.1.1 Evidence-based medicine

Historically and perhaps even in the present day, medical decision-making has been based predominantly on physicians' beliefs and so-called "expert opinion". Only recently has it been acknowledged that determination of the best practice requires supplementing the potentially biased subjective decisions with all available knowledge from the scientific literature. The first considerations based on systematic analyses of evidence took place in the early 1980s, when the American Cancer Society launched the first guidelines for cancer screening (American Cancer Society 1980). This guideline was based on the pioneering work of David Eddy, a physician and mathematician, who introduced the term "evidence-based". The physicians Alvin Feinstein and David Sackett and others subsequently published textbooks incorporating epidemiological methods into clinical decision-making (Feinstein 1985, Sackett et al. 1985). These were the initial steps of clinical epidemiology, the basic science of "evidence-based medicine" (EBM) – the term introduced slightly later, in the early 1990s in medical education at McMaster University by Gordon Guyatt. The evidence-based approach came to broader awareness via a 25-piece series of "Users' Guides to the Medical Literature" published in JAMA: The Journal of the American Medical Association by the Evidence-based Medicine Working Group at McMaster University between 1993 and 2000. The articles taught health care professionals how to interpret clinical and epidemiological research studies to guide their practice following the principles of evidence-based medicine; i.e. to integrate clinical judgment and patient's values with the recommendations from the best available evidence (Guyatt 1992, Sackett et al. 1996).

2.1.2 Summarising and rating the evidence

For a today's health care professional, the rapidly increasing rate of new medical publications makes staying up to date with relevant research a challenging task. Individual studies tend to be heterogeneous in their settings and samples and the results may vary substantially. To bypass the information overload and the challenges in interpreting the findings of individual studies, clinicians often turn to review articles incorporating the topic of interest. Most available review articles represent a narrative approach describing single studies and their results but typically do not apply defined methods to synthesise the data. In contrast, reviews utilising an evidence-based approach – systematic reviews – are conducted using rigorous methods to summarise the data. A systematic review is defined by the Cochrane Handbook, as follows:

"A review of a clearly formulated question that uses systematic and explicit methods to identify, select and critically appraise relevant research, and to collect and analyze data from the studies that are included in the review." (Higgins & Green 2011)

Besides providing a pooled qualitative summary of the analysed data, systematic reviews may include a statistical summary of the results of primary studies, typically a meta-analysis (Table 1). Systematic reviews are therefore able to provide valid, precise and widely applicable answers to clinical questions (Oxman et al. 2005). Furthermore, by summarising large amounts of data, systematic reviews are more likely than any individual trial to describe the true clinical effect of an intervention. Thus, systematic reviews have a crucial role in informing clinical decisions, guidelines and future research.

One of the chief principles of EBM is the hierarchical system of classifying evidence. EBM categorises different types of evidence and rates them according to the probability of bias across studies. Accordingly, when exploring cause-and-effect associations and the effects of treatments, randomised controlled trials (RCT) typically provide the highest quality of evidence, whereas case series or expert opinions typically provide the lowest quality. RCTs have less risk of systematic errors through their approach of randomly allocating subjects to different treatments, and thereby also randomising potential known and unknown confounding factors that may bias results. On the other hand, case series or expert opinions are often biased by the authors' opinions and have no control for confounding factors (Schultz & Grimes 2002, Bhandari et al. 2004, Guyatt et al. 2008c).

Table 1. Differences between narrative reviews and systematic reviews (modified from Cook et al. 1997 and Guyatt et al. 2008a).

Characteristic	Narrative review	Systematic review
Clinical question	Seldom reported, or addresses several general questions	Focused question specifying population, intervention or exposure, and outcome
Search for primary articles	Seldom reported; if reported, not comprehensive	Comprehensive search of several evidence sources
Selection of primary studies	Seldom reported; if reported, often biased sample of studies	Explicit inclusion and exclusion criteria for primary studies
Evaluation of quality of primary articles	Seldom reported; if reported, not usually systematic	Methodologic quality of primary articles is assessed
Summary of results of primary studies	Usually qualitative nonsystematic summary	Synthesis is systematic (qualitative or quantitative; if quantitative, this is often referred as meta-analysis)

In 2000, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group developed a system taking into account more dimensions than just the quality of research. In addition, within the GRADE framework, evaluators are required to consider the impact of different factors on their confidence in the results. The approach grades the quality of evidence (synonymously confidence or certainty in estimates) into four levels (high, moderate, low or very low quality confidence/certainty), according to their confidence in the observed effect (a numerical value) being close to the true effect. The confidence is based on judgements assigned in different domains.

In the GRADE approach to causality, the evidence from RCTs begins as high quality, whereas that from observational studies begins as low quality. Contradictorily, with respect to prognosis – the likelihood of future health outcomes in people with a given disease or health condition or with particular characteristics i.e. not involving comparison of treatments (Iorio et al. 2015), GRADE stipulates that observational studies can often provide trustworthy inferences. Therefore, in the GRADE approach to prognosis, the evidence from observational studies begins as high-quality but may be downgraded in five different domains (Schünemann et al. 2013):

- *Risk of bias.* Is a judgement made on the basis of the chance that bias in the studies included has influenced the estimate of effect?

- *Imprecision.* Is a judgement made on the basis of the chance that the observed estimate of effect could change completely? Occurs when studies have wide confidence intervals, typically because of relatively few patients or events.

- *Indirectness.* Is a judgement made on the basis of the differences in characteristics of how the study was conducted and how the results are actually going to be applied? Indirectness may arise from differences in the population or outcome of interest between the studies included and the studies addressed in the review question. In cases of little evidence with questionable applicability, quality of evidence is rated down for indirectness.

- *Inconsistency.* Is a judgement made on the basis of the variability of results across the studies included? Refers to widely differing estimates (heterogeneity or variability in results) across studies. Variability may arise from differences in populations or methodology. If estimates vary substantially across studies, or if confidence intervals show little or no overlap, quality of evidence is likely to be rated down for inconsistency.

- *Publication bias.* Is a judgement made on the basis of the question whether all the research evidence has been taken to account? Should be suspected when available evidence comes from a number of small studies, most of which have been commercially funded.

Respectively, the quality of evidence can be upgraded in three domains (Schünemann et al. 2013):

- *Large effect.* Observed effect is so large that the probability of it changing completely is less likely.

- *Confounding.* In the presence of a possible confounding factor, expected to reduce the observed effect, the effect estimate still shows significant effect.

- *Dose-response gradient.* Increasing levels of exposure are associated with either an increasing or a decreasing risk of the outcome.

Interpretation of the levels of evidence according to GRADE:

- *High quality evidence.* The authors are very confident that the true effect lies close to the estimate of the effect: there is very low probability of further research completely changing the conclusions presented.

- *Moderate quality evidence.* The authors are moderately confident that the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different: further research may completely change the conclusions presented.

- *Low quality evidence.* The authors' confidence in the effect estimate is limited and the true value may be substantially different from the estimate of the effect: further research is likely to completely change the conclusions presented.

- *Very low quality evidence.* The authors do not have any confidence in the estimate and it is likely that the true value is substantially different from it: new research will most probably completely change the conclusions presented.

The GRADE working group defines "quality of evidence" and "strength of recommendations" based on the quality as two different concepts which are commonly confused with each other (Atkins et al. 2004, Balshem et al. 2011). The strength of recommendation for an intervention can be determined with GRADE approach by evaluating the confidence in the benefits of treatment outweighing the undesirable effects, quality of evidence, variability in values and preferences, and resource use. The recommendations are appraised to be either strong or weak in favour or against treatment (Guyatt et al. 2008b, Andrews et al. 2013).

2.1.3 Lower urinary tract symptoms and nocturia

For fluent communication between healthcare providers and researchers, adequate terminology is essential. In cases of various forms of lower urinary tract dysfunction in which treatment decisions are heavily dependent on patients' subjective perceptions, relevant terminology is especially important. One of the most essential remarks for improved communication between clinicians and patients is the differentiation between "symptoms" and "signs". A symptom refers to a subjective indicator of a disease or change in condition as perceived by the patient, potentially leading him/her to seek care, whereas a sign refers to an observation – typically by a physician – with an instrument such as a frequency volume chart (FVC), pad test or a validated symptom questionnaire, aiming to quantify the intensity of dysfunction. Symptoms may either be volunteered or described during the patient interview. In general, symptoms are usually qualitative and cannot provide a definitive diagnosis. Accordingly, lower urinary tract symptoms (LUTS) refers to a group of symptoms involving the urinary bladder, sphincter, urethra, and, in men, the prostate. Symptoms may also indicate pathologies such as urinary tract infection. Various LUTS can result from dysfunction during bladder filling (storage), emptying (voiding) or post-voiding phase, and often occur in combination (Abrams et al. 2002, Drake 2018).

To facilitate the utilisation of congruent definitions of various LUTS in clinical practice and in research, the standardisation sub-committee of the International Continence Society (ICS) has provided recommendations for terminology beginning from 1988 (Abrams et al. 1988). According to the current ICS definitions, LUTS are broadly divided into three major groups: (1) storage, (2) voiding and (3) post-voiding symptoms (Abrams et al. 2002, Drake 2018). Although the recommendations of ICS are applicable to all patients regardless of gender, increased specificity and complexity of diagnoses has led to a need to update the terminology for lower urinary tract and pelvic floor symptoms and dysfunction using gender-specific approaches (Haylen et al. 2010, D'Ancona et al. 2019).

The symptom discussed in more detail in this thesis, nocturia (waking from sleep at night to void) (Hashim et al. 2019), has recently been recognised as a separate clinical entity, and gained a context-specific terminology report from the ICS (Hashim et al. 2019). Currently, nocturia is defined as follows:

"The number of times urine is passed during the main sleep period. Having woken to pass urine for the first time, each urination must be followed by sleep or the intention to sleep. This should be quantified using a bladder diary." (Hashim et al. 2019)

The new terminology emphasises the importance of clear nocturia case definitions with no attempt to differentiate between the bother and multifactorial causes of nocturia i.e. whether a compelling desire to void at night results from any underlying pathology or whether waking up due to external stimuli leads to subsequent voiding for convenience (Bing et al. 2007, Weiss et al. 2008, Tikkinen et al. 2009). The new definition also takes into account the previous findings that one nocturia episode is a common and usually well-tolerated phenomenon, i.e. not necessarily a "complaint" (Irwin et al. 2006, Tikkinen et al. 2010, Kupelian et al. 2012). Furthermore, the definition also underlines the importance of documenting sleep fragmentation with a bladder diary as sleep disorders are one of the most common reasons for care-seeking among people with nocturia; and sleep disruption is one of the potential mediators between nocturia and further morbidity (Ancoli-Israel et al. 2011).

The assessment of a patient with nocturia should begin from a more detailed characterisation of nocturnal symptoms based on the findings of the bladder diary or alternatively an FVC – providing data on the time of each micturition and the volume voided for at least 24 h. As a distinction to FVC, a bladder diary comprises of a set of more explicit recordings also including fluid intake, pad usage, incontinence episodes and the degree of incontinence and, if necessary, episodes of sensations such as urgency as well as the activities associated with urinary leakage can also be recorded. If supplemented with two or three days of recording, a bladder diary is currently considered the standard tool most likely to provide clinically useful data to guide nocturia treatment (Haylen et al. 2010, Cornu et al. 2012, Oelke et al. 2014, Hashim et al. 2019).

Notably, if a patient with nocturnal symptoms presents with urinary incontinence, it is crucial to differentiate between nocturia and nocturnal enuresis, which refers to a complaint of intermittent incontinence occurring during the main sleep period (Hashim et al. 2019). This distinction is crucial as episodes of incontinence (enuresis) occurring during sleep periods are always an abnormal phenomenon in adults and should prompt investigations for comorbidities (Sakamoto & Blaivas 2001, Wadie 2004, Lee et al. 2018). On the other hand, a more common phenomenon, especially among the frail elderly, is an urgency type of urinary incontinence occurring after waking up and not reaching the toilet before passing urine (Gibson & Wagg 2014).

The cornerstone in the differential diagnostics of nocturia is the consideration of functional bladder capacity and whether any excess fluid intake or urine production (diuresis) is present. Whereas nocturia indicates the number of voids recorded at night, omitting the first morning void not followed by intention to sleep, nocturnal urine volume (NUV) describes the amount of urine produced during the night, also including the first morning void because this urine has been produced during the night. Respectively, 24-hour urine volume refers to the total volume of urine passed during a 24-h period excluding the first morning void of the period (Hashim et al. 2019).

The estimate nocturia index (Ni) indicates the ratio between NUV and maximal voided volume (MVV). If Ni > 1, nocturia occurs because MVV is exceeded by NUV. Respectively, the estimate nocturnal bladder capacity index (NBCi) indicates whether the bladder can store the amount of urine produced at night, corresponding to the actual number of nocturnal voids (Nvoids) minus the predicted number of voids. The predicted number of voids is obtained by subtracting 1 from Ni (NBCi = Nvoids - Ni - 1). Accordingly, NBCi > 0 indicates nocturia at volumes less than MVV, implying bladder storage problems at night (Cornu et al. 2012, Weiss 2012, Oelke et al. 2014, Hashim et al. 2019). The term nocturnal polyuria (NP) refers to an abnormally large urine volume produced during the nighttime. It has been suggested that, for example, Ni > 1.5 and NUV > 10 ml/kg (based on body weight) are indicators of nocturia secondary to NP (Burton et al. 2011, Homma et al. 2000). According to the most commonly used definitions of ICS, the criteria for NP are met if the ratio of NUV and 24-hour urine volume i.e. nocturnal polyuria index (NPi) exceeds >33% in the elderly (aged > 65 years) and 20% in younger individuals (Hofmeester et al. 2015, Hashim et al. 2019). The criteria for 24-h (global) polyuria are considered to be met when overall urine volume is >40 ml/kg per 24 hours (Hashim et al. 2019).

Whereas the term nocturia indicates sleep fragmentation caused by awakenings before voiding and attempts to continue sleeping after voiding, nighttime frequency is the term to be used to describe solely the number of nocturnal voids (Hashim et al. 2019). Accordingly, the vast majority of studies of nocturia have actually assessed nighttime frequency while sleep before or after nighttime voids has been documented only rarely (Oelke et al. 2014). Nocturia has been included in several questionnaires designed to assess the presence of LUTS. In most of these questionnaires, nocturia is included as one of several items, usually summed together to form a total score (Barry et al. 1992, Hansen et al. 1995). After acknowledgment of the multidimensional complexity and distinct characteristics of nocturia,

questionnaires measuring severity of nocturia have been supplemented with assessment tools for QoL and quality of sleep (Abraham et al. 2004, Chartier-Kastler et al. 2007, Kim et al. 2009 & 2011).

The new nocturia definition emphasises the term "main sleep period" instead of "night" because the period from the time of falling asleep to the time of intending to rise may, depending on individual's sleep cycle, take place between sunset and sunrise or during the daylight hours. Therefore, among shift workers, the main sleep period during the daylight hours is considered as "nighttime" and any void during this main sleep period is considered to be nocturia (Hashim et al. 2019).

2.2 Pathophysiology

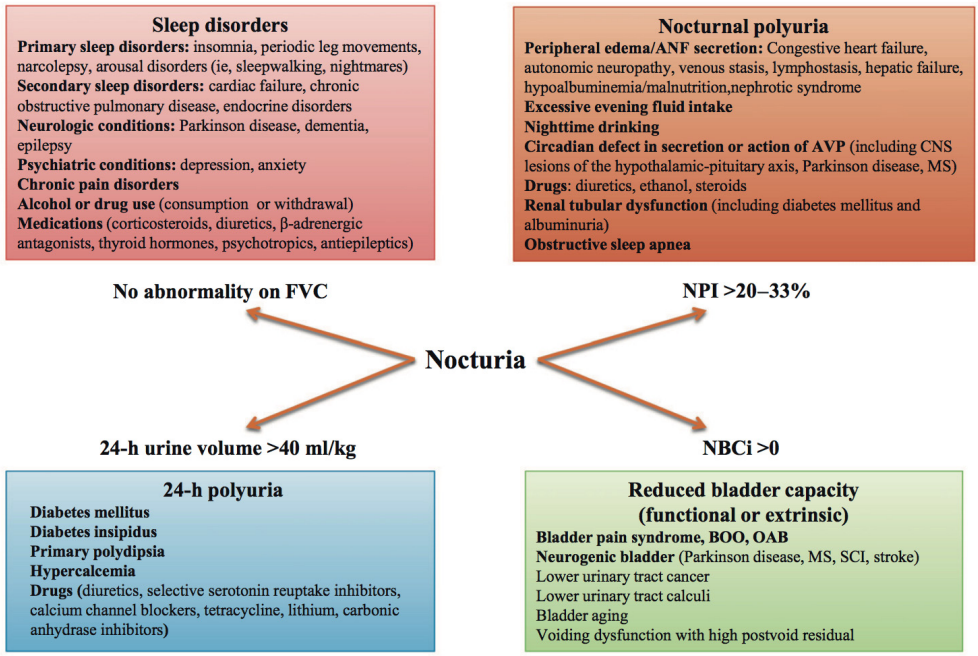
Due to a highly multifactorial aetiology, the treatment of nocturia can be challenging. The pathophysiologic mechanisms of nocturia have been divided into five main categories: reduced bladder capacity, nocturnal polyuria, global polyuria, sleep disorders and circadian clock disorders. Furthermore, multiple pathophysiologic mechanisms are often concomitantly present (Chang et al. 2006, Tikkinen et al. 2009, Cornu et al. 2012, van Kerrebroeck & Andersson 2014, Oelke et al. 2014).

Besides the evaluation of present nocturnal symptoms and associated bother, the approach to a patient with nocturia should include a detailed assessment of symptom history to differentiate between fluctuating and persistent symptoms. Diuresis, lower urinary tract function and sleep quality, as well as perceived bother may vary periodically due to environmental and physiological factors (Yoshimura et al. 2005, Vaughan et al. 2014, Breyer et al. 2013). Nocturnal symptoms may be persistent due to underlying comorbidities as numerous health-impairing conditions can present as nocturia by affecting the urinary system or sleep. Therefore, the approach should include an assessment of the previously diagnosed medical conditions, lifestyle factors, and also risk factors for developing illnesses relevant for each individual (Oelke et al. 2014, Everaert et al. 2019). An overview of some of the common pathophysiologic mechanisms is presented in Fig. 1.

The treatment of nocturia requires understanding of the common age-related functional, anatomical and hormonal changes potentially causing mismatch between nocturnal diuresis and the bladder's capacity to store urine overnight (Boongird et al. 2010). It has been shown that nocturnal bladder capacity and detrusor contractility diminish with age, one reason being an increased collagen to smooth muscle ratio (Kawauchi et al. 2000, Susset et al. 1978). Although both overactive bladder (OAB)

symptoms and urodynamically verified detrusor overactivity (DO) become more common with age in both genders (Drake 2018), the number of muscarinic receptors in the bladder has been demonstrated to decline, also suggesting an increasing tendency for underactive bladder (UAB) symptoms with age (Birder & Andersson 2013, Mansfield et al. 2005, Suskind 2017, Chapple et al. 2018). Besides causing changes in the mucosal (urothelial) and muscle layers of the lower urinary tract and the level of neurotransmitters/receptors, ageing induces inflammation and oxidative stress, potentially further provoking LUTS (Suskind 2017).

Figure 1. Exemplary causes of nocturia, often present in combination (reproduced from Cornu et al. 2012).



ANF = atrial natriuretic factor, AVP = arginine vasopressin, BOO = benign outlet obstruction, CNS = central nervous system, FVC = frequency volume chart, MS = multiple sclerosis, NBCi = nocturnal bladder capacity index, NPI = nocturnal polyuria index, OAB = overactive bladder, SCI = spinal cord injury

The anatomical capacity of the bladder may decrease due to fibrosis and scarring caused by radiotherapy for a malignancy of the lower urinary tract or other pelvic organs, after endoscopic surgery, such as transurethral resection of bladder tumour (TURBT) or after any abdominal surgery involving resection of the bladder.

Impairment of functional bladder capacity and progression of male LUTS are often associated with benign prostatic hyperplasia (BPH), affecting over 50% of men after the age of 50 (Berry et al. 1984, Bosch et al. 2008). Although nocturia in older men is frequently associated with BPH, there are several other urologic conditions that may cause reduction in functional bladder capacity. For example, in cases of a tendency for post-void residual urine, particularly common among older men with BPH, the development of bladder stones may further cause irritative LUTS, including nocturia (Oelke et al. 2017). LUTS may likewise occur in association with a malignant tumour affecting the lower urinary tract. A malignancy particularly often perceived to be related to male LUTS is prostate cancer (pCa) – the most prevalent cancer in men in Western countries. The results of autopsy studies have shown that almost 30% of men over the age of 50 have histological evidence of pCa (Scardino 1989). However, there is no evidence supporting LUTS as risk factors for advanced prostate cancer (Østerø et al. 2018).

Other causes of reduced functional bladder capacity include neurogenic dysfunction related to neurologic illnesses and conditions such as Parkinson's disease, multiple sclerosis (MS), spinal cord injury (SCI), or stroke. Bladder irritation may be caused by chronic inflammatory conditions such as interstitial cystitis or recurrent urinary tract infections (UTI), the latter especially common in older women due to urogenital atrophy associated with estrogen deficiency. Bladder problems may also stem from age-related weakening of the structures supporting the pelvic floor leading to pelvic organ prolapse (Oelke et al. 2017). Furthermore, women with a history of spontaneous vaginal deliveries are at an increased for LUTS among other pelvic floor disorders (Blomquist et al. 2018, Tähtinen et al. 2016, Tikkinen et al. 2008).

Besides age-related physiological changes and illnesses, various lifestyle and environmental factors may affect functional bladder capacity (Coyne et al. 2009, Smith et al. 2014). Theoretically physical activity may protect against LUTS in both genders by decreasing resting sympathetic muscle tone, reducing systemic inflammation and changing certain hormonal factors, particularly those relevant to the metabolic syndrome (Platz et al. 1998, Sea et al. 2009, Parsons et al. 2011, Maserejian et al. 2012, Kim et al. 2017a). Given that body mass index (BMI) and waist circumference are associated with nocturia in both genders, weight maintenance may partly explain the beneficial associations with physical activity (Tikkinen et al. 2006, Kupelian et al. 2009, Shiri et al. 2008, Wolin et al. 2015, Asplund et al. 2004, Wen et al. 2015, Milsom et al. 2017).

Although the nocturia-provoking side effects of various medications are often mediated via nocturnal polyuria, some drugs may directly affect functional bladder capacity. For example, widely used antidepressants, the selective serotonin reuptake inhibitors (SSRIs), have been shown to be associated with a two-fold increased risk for developing urinary incontinence and nocturia. The mechanism accounting for storage LUTS associated with SSRI use is plausibly activation of neuronal 5-HT4 receptors located in the detrusor muscle, thereby potentiating cholinergic neuromuscular transmission and detrusor activation (Cardozo & Robinson 2002, Movig et al. 2002, Asplund et al. 2005, Boongird et al. 2010).

In older people, the pathogenesis of nocturnal polyuria typically comprises altered sodium handling and water conserving mechanisms of the renal system, as well as altered circadian rhythm of glomerular filtration rate (GFR). The concentrating ability of the kidney has been shown to decline with increasing age owing to impaired responsiveness to arginine vasopressin (AVP) i.e. antidiuretic hormone (ADH) (Ouslander et al. 1998, Tian et al. 2004). Among younger healthy individuals, AVP secretion normally has a circadian pattern in which its blood concentration peaks during the night, resulting in a reduction of nocturnal diuresis (Kirkland et al. 1983, Duffy et al. 2016). However, in older people, while the AVP response to volume and osmotic stimuli often remains intact, circadian nocturnal AVP secretion has a tendency to become disrupted, potentially resulting to nocturnal polyuria (Kirkland et al. 1983, Koopman et al. 1989, Ouslander et al. 1998). However, dysregulation of AVP secretion is only one of the factors potentially contributing to nocturnal polyuria among older people as it has been observed that altered circadian rhythm of GFR may also contribute to increased nocturnal urine production and urinary sodium excretion rates with increasing age (Asplund & Aberg 1991, Kikuchi 1995, Tian et al. 2004, Boongird et al. 2010).

Besides taking into account the common age-related changes in the lower urinary tract and renal function, one must consider the different mechanisms of diuresis related to various comorbidities. Water diuresis may result from excess intake of fluids (primary polydipsia). It may also result from a defect in the secretion or action of AVP caused by a hypothalamic or pituitary lesion (central diabetes insipidus), or when the renal capacity to concentrate urine is impaired (nephrogenic diabetes insipidus) caused by conditions such as hypercalcaemia or medications such as lithium – a drug used to treat the manic episodes of bipolar disorder (Goldfarb & Agus 1984, Kishore & Ecelbarger 2013). Osmolarity and volume status are the two greatest factors that affect ADH secretion. However, a variety of other factors promote ADH secretion as well, including pain, nausea, hypoglycaemia, nicotine,

opiates, and certain medications, and a syndrome characterised by an excessive unsuppressible release of AVP – syndrome of inappropriate antidiuretic hormone secretion (SIADH) – can result from conditions that dysregulate ADH secretion in CNS, tumours that secrete ADH, drugs that increase ADH secretion and many others. Respectively, several factors may inhibit the release of AVP, such as caffeine and alcohol (Antunes-Rodrigues et al. 2004, Ellison & Berl 2007).

Osmotic (solute) diuresis may result, for example, from poorly controlled diabetes mellitus (DM) or intentionally after administration of mannitol – a strong diuretic used, for example, to lower increased intracranial pressure. However, the most common type of osmotic diuresis typically occurs in the presence an excess sodium excretion (natriuresis), which is the main mechanism of nocturia in chronic kidney disease (CKD) (Feinfeld & Danovitch 1987, Fukuda et al. 2006, Boongird et al. 2010). Due to a long-established association of CKD with nocturnal polyuria, studies on renal physiology and the regulation of homeostasis in CKD patients have contributed substantially to the identification of the various pathophysiological mechanisms of nocturia (Boongird et al. 2010). Furthermore, due to ageing of populations and also to increasingly common lifestyle-associated comorbidities such as hypertension, diabetes and obesity, the global burden of CKD is increasing from its current prevalence of over 10% (Hill et al. 2016).

Enhanced natriuresis has been found to be associated with a lack of nocturnal blood pressure (BP) fall, a common phenomenon in CKD patients known as nondipping (Agarwal et al. 2009, Fukuda et al. 2006, Boongird et al. 2010). In CKD patients, nocturia-related increased nighttime physical activity has been suggested to contribute to nondipping BP patterns (Agarwal et al. 2009). Furthermore, a potential contributor to increased BP in individuals with CKD is endothelial dysfunction, mediated by elevated serum levels of asymmetric dimethylarginine (ADMA) (Vallance et al. 1992), also hypothetically associated with nocturia via nitric oxide (NO) pathway: it has been suggested that LUTS, secondary to BOO, could be caused by the lack of NO bioactivity at the bladder outlet (Andersson & Persson 1994, Mumtaz et al. 2000, Aizawa et al. 2011). ADMA is a major endogenous competitive inhibitor of NO synthase (Valtonen et al. 2008). The cells of the inner layer of blood vessels (endothelial cells) are responsible for the continuous basal production of nitric oxide (NO), which serves to counteract the neural vasoconstrictor tone and to regulate blood flow and BP (Stamler et al. 1994). Accordingly, elevated ADMA levels have been observed in association with DM, arterial hypertension (HTN), pre-eclampsia, dyslipidemia and CVD (Chan & Chan 2002), as well as in patients with

exaggerated blood pressure response to exercise (EBPR), a suggested predictor of future HTN and CVD (Kayrak et al. 2010, Singh et al. 1999, Kurl et al. 2001).

Previous observations suggest an independent association between nocturnal polyuria and nondipping BP among community-dwelling older people after adjustments for various factors including physical activity, serum levels of ADMA and suspected sleep-disordered breathing (SDB) (Obayashi et al. 2015). Although the association between nondipping BP and nocturnal polyuria seems robust, the mechanisms between nocturia and hypertension have not been fully explained. The relationship between the rate of blood flowing to the renal system (perfusion) and sodium excretion, i.e. the pressure natriuresis (PN) response, has long been regarded as the core mechanism to determine BP homeostasis. In hypertension, higher levels of BP are required to excrete the same amount of sodium and accordingly, PN response is abnormal in most, if not all, models of hypertension (Feldstein 2013, Goessaert et al. 2014, Ivy & Bailey 2014). It has been hypothesised that nocturia-associated defects in the NO pathway may lead to the resetting of the PN relationship in the kidney, leading to sodium retention and compensatory nocturnal natriuresis. This suggestion is consistent with evidence that ageing and hypertension are both associated with defects in the NO pathway (McKeigue & Reynard 2000, Boongird et al. 2010).

Besides age-related changes in the kidney, there are multiple alterations in the hormonal systems governing water and sodium regulation that may occur with ageing. The renin-angiotensin-aldosterone (RAA) system is of major importance in maintaining blood pressure and fluid volume. It exerts this function through regulation of renal blood flow and solute reabsorption, thereby affecting urine production (Carey & Siragy 2003). Atrial natriuretic peptide (ANP) i.e. atrial natriuretic factor (ANF) is a natriuretic peptide hormone secreted from the cardiac atrial myocytes in response to atrial distension and sympathetic stimulation. The main function of ANP is to cause a reduction in expanded extracellular fluid volume by increasing renal sodium excretion through its direct natriuretic effect and suppression of renal renin and aldosterone secretion. Furthermore, ANP inhibits AVP secretion, in part by inhibiting angiotensin II-induced stimulation of AVP secretion (Matsukawa & Miyamoto 2011). With advanced age, the baseline ANP level has been shown to be 3- to 5-fold higher than in younger adults (Ouslander et al. 1998, Asplund & Aberg 1991). Moreover, plasma renin and aldosterone activities also tend to decrease with age. As a consequence, the aforementioned hormonal changes promote diuresis via natriuresis (Boongird et al. 2010, Goessaert et al. 2014).

In cases of non-dipping BP and associated nocturnal polyuria, the diminished renal sodium excretory capability is related to low plasma renin activity and normal aldosterone levels. The relative aldosterone excess with sodium retention during daytime leads to enhanced natriuresis during nighttime (Satoh et al. 2011, Goessaert et al. 2014). Sleep deprivation is known to further induce diuresis and natriuresis by altering the circadian rhythm of the RAA system as well as attenuating nocturnal BP dipping (Kamperis et al. 2010). The non-dipping pattern of BP is also found in subjects with sodium sensitive hypertension, in whom a significant rise in BP occurs as a response to sodium intake. While the pathophysiology of this type of hypertension remains unclear, older age, female sex, as well as several genetic and environmental factors have been suggested as potential aetiologic factors. Lower renin and aldosterone levels are found in these subjects, together with a decreased number of beta2 receptors – one binding site of catecholamines in the activation of the sympathetic nervous system (SNS) (Goessaert et al. 2014, Giner et al. 2000).

In patients with oedema-forming conditions, such as congestive heart failure (CHF), CKD, hypoalbuminaemia, or use of certain medications such as nonsteroidal anti-inflammatory drugs (NSAID) or calcium channel blockers, fluid accumulated in the lower extremities while standing during the day may become mobilised into the circulatory systems at night, inducing ANP release. Enhanced ANP secretion because of medical conditions can also cause nocturnal polyuria. ANP is released by atrial myocytes in response to atrial distension and sympathetic stimulation. It affects the kidneys by increasing GFR and filtration fraction, which in turn produces natriuresis and diuresis. Similarly, respiratory diseases associated with increased airway resistance, typically different types of sleep-disordered breathing and particularly obstructive sleep apnea (OSA), stimulate ANP secretion through hypoxic-induced vasoconstriction causing increased right atrial pressure (Boongird et al. 2010, Yalkut et al. 1996).

Besides AVP, ANP and other natriuretic peptides, studies have also addressed other hormones related to nocturia. Previous findings have suggested that the brain renin-angiotensin system may modulate the synthesis of melatonin – a hormone with a well-established role in regulating circadian rhythms (Campos et al. 2013). In post-menopausal women, oestrogen has been shown to have a stimulatory effect on AVP while progesterone antagonises this effect, also reducing the nocturnal rise in AVP (Bossmar et al. 1995, Graugaard-Jensen et al. 2008).

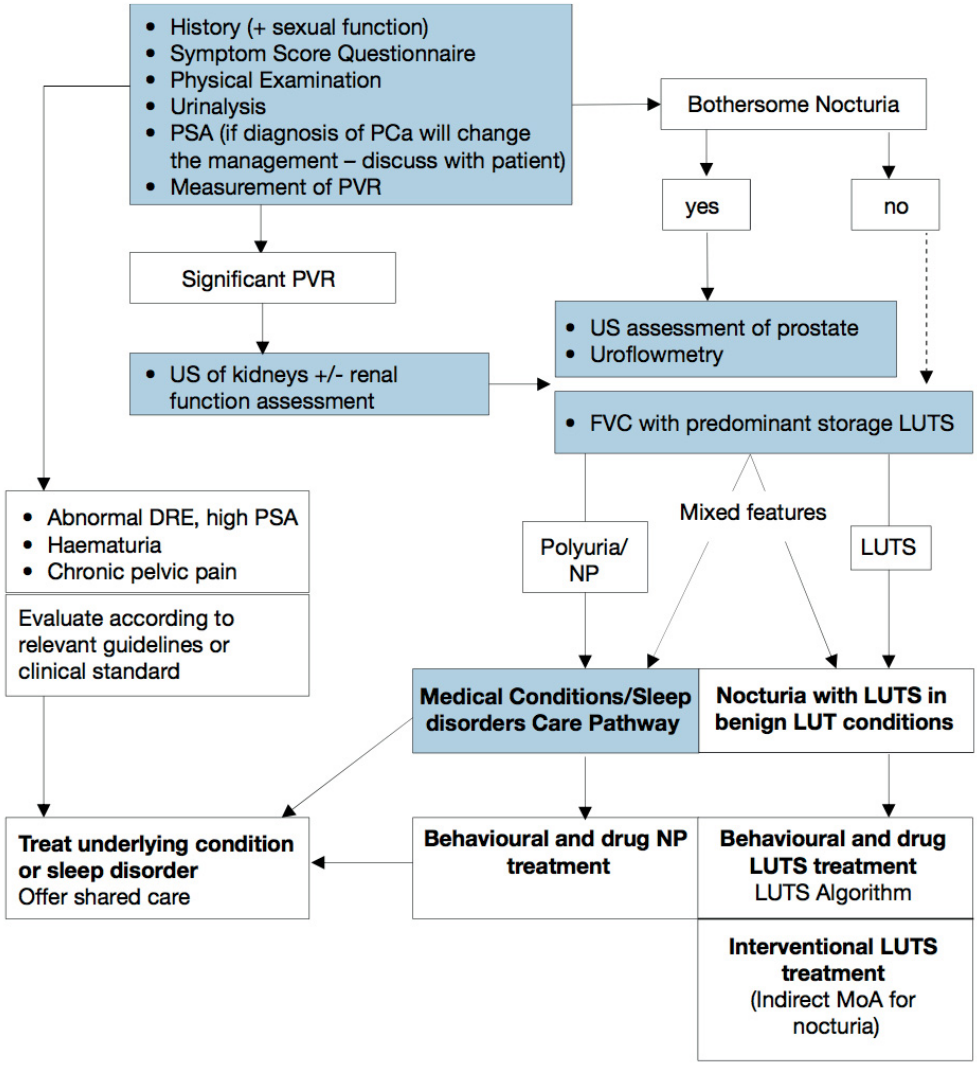
In addition to OSA, primary sleep disorders such as insomnia, restless leg syndrome, narcolepsy and arousal disorders, such as sleepwalking and nightmares, can cause nocturia. Various conditions such as CHF, chronic obstructive pulmonary

disease (COPD), endocrine disorders, as well as several neurologic conditions may cause sleep disorders and subsequent nocturia. Other factors that may result in sleep disturbances and associated nocturia are psychiatric conditions such as depression and anxiety, chronic pain, alcoholism or drug use, and medications such as corticosteroids, beta-blockers, thyroid hormones and various drugs acting on a CNS (Cornu et al. 2012, van Kerrebroeck & Andersson 2014). Furthermore, although there is an evident cause-and-effect association between wakefulness and nocturia, acute sleep deprivation is also a potential inducer of natriuresis and nocturnal polyuria (Ancoli-Israel et al. 2011, Kamperis et al. 2010). Sleep deprivation can also cause nocturnal polyuria and reduced bladder capacity by altering the endogenous circadian rhythm i.e. leading to circadian clock disorders (Negoro et al. 2013, Kim 2016).

2.3 Assessment

According to the European Association of Urology Guideline on Management of Non-neurogenic Male LUTS, in addition to the bladder diary, the basic assessment of a patient with bothersome nocturia should include a detailed symptom history with a validated symptom questionnaire, documentation of previously diagnosed medical conditions and a physical investigation (Gravas et al. 2019). Basic investigations also include urinalysis, measurement of post-void residual volume and uroflowmetry. Additional tests on an individual basis may include urodynamic studies, cystoscopy and blood analyses for comorbidities (Oelke et al. 2017, Everaert et al. 2019, Gravas et al. 2019) (Fig. 2). In case of suspicion of underlying comorbidities, referral to another specialist such as a pulmonologist, nephrologist, or cardiologist may also be necessary. Recognition of the complex aetiology of nocturia has led to the development of specific tools to screen for potential contributing factors in addition to other LUTS, including cardiovascular and metabolic risk factors, sleep variables, mental health and wellbeing (Bower et al. 2017).

Figure 2. Evaluation of Nocturia in non-neurogenic Male LUTS (reproduced from Gravas et al. 2019).



FVC = frequency volume chart, DRE = digital rectal examination, NP = nocturnal polyuria, MoA = mechanism of action, PVR = post-void residual, PSA = prostate-specific antigen, US = ultrasound

2.4 Treatment

Before deciding on interventions, it is necessary to define the treatment goals. For patients with bothersome nocturia, besides aiming at any decrease in nocturnal voiding frequency, regression of nocturia to less than two episodes per night, prolongation of undisturbed sleep for up to at least four hours, feeling rested after awakening and the improvement of QoL are likely to be patient-important outcomes (Abraham et al. 2004, Chartier-Kastler et al. 2007, Cornu et al. 2012, Oelke et al. 2014). Although there are specific treatments available targeted at several hypothesised pathophysiologic mechanisms of nocturia, behavioural treatments and lifestyle modifications should nonetheless be included in every treatment strategy, as they appear to be beneficial in the majority of cases despite differences in the underlying pathophysiology (Oelke et al. 2014). Furthermore, behavioural treatments and lifestyle modifications likely have very few or no side effects, may also benefit the treatment of other conditions and are often very inexpensive or free. Interventional studies have shown that walking exercises, fluid restriction in the evening, reduction of salt intake and a combination of lifestyle changes, including refraining from excess hours in bed and keeping warm in bed, may alleviate nocturia in the majority of cases (Sugaya et al. 2007, Tani et al. 2014, Matsuo et al. 2019, Soda et al. 2010). Furthermore, restriction of caffeinated or alcoholic beverages, emptying the bladder before sleep and elevating legs in the presence of lower limb oedema, can be suggested as potential behavioural treatments if considered appropriate to the individual (Oelke et al. 2014, Everaert et al. 2019). Especially in cases of frail elderly individuals and those with multiple illnesses, lifestyle changes may even be the only possible treatment for nocturia due to lowered tolerability to medications, i.e. treatments manipulating diuresis, sleep or lower urinary tract function, and other interventions (Chrischilles et al. 2001, Vaughan et al. 2016).

Earlier studies have indicated nocturnal polyuria as a major contributing factor in nocturia among men and women of all ages, and particularly in the elderly in up to 85% of nocturia cases (Weiss et al. 2011, Rembratt et al. 2003). Although the association between nocturnal polyuria and nocturia is clear, according to a recent meta-analysis, many people with nocturnal polyuria do not, however, have nocturia, and therefore, the clinical importance of this association appears to be less obvious than previously suggested (Hofmeester et al. 2014). Accordingly, some patients with nocturnal polyuria may have a bladder capable of storing large volumes of urine without presenting as nocturia, whereas patients with a low bladder storage capacity may report nocturia in the absence of nocturnal polyuria. Therefore, in the

assessment of a patient with nocturia, it is advisable to explore whether concomitant LUTS are present and set as the primary goal in treatment the alleviation of the most bothersome symptom (Agarwal et al. 2014). For example, among adult male patients presenting with nocturia and nocturnal polyuria, diurnal symptoms of decreased functional bladder capacity, such as those suggestive of BPH, are often also present (Chang et al. 2006, Oelke et al. 2014).

Pharmacological therapies are indicated after failure of lifestyle modifications and behavioural treatments which, however, should be continued together with the drugs (Oelke et al. 2017). Currently, the only drug approved by the U.S. Food and Drug Administration (FDA) for the treatment of nocturia due to nocturnal polyuria is desmopressin – a synthetic analogue of AVP (FDA 2017 & 2018). Compared to endogenous AVP, desmopressin has a pronounced antidiuretic effect, with no blood pressure-enhancing (vasopressor) effect (Cvetković & Plosker 2005). Desmopressin has been shown to decrease nocturnal diuresis and to prolong the first uninterrupted sleep period (Chang et al. 2007, Juul et al. 2013). The risk of a potential adverse effect, hyponatremia, has to be taken into account, especially among older patients and in women, who seem to be more prone to this effect (Rembratt et al. 2006, Juul et al. 2011, Goessaert et al. 2014). The first formulation of desmopressin approved by FDA for the treatment of nocturia, was a low-dose intranasal formulation with recommended doses of 0.83 ug for patients over 65 years and 1.66 ug for those under 65 years (FDA 2017). Subsequently, a sublingual low-dose formulation was approved with recommended doses of 25 μg for women and 50 μg for men (FDA 2018). The benefits of both low dose formulations include a rapid absorption, a high bioavailability and a limited duration of action (4-6 hours for intranasal and 3-5 hours for sublingual formulation) with reduced risk of hyponatremia (Kaminetsky et al. 2018, Sand et al. 2013, Weiss et al. 2013). However, the results of available RCTs have shown only modest benefits for desmopressin over placebo (Han et al. 2017). For example, in 3-month RCTs, treatment of a mixed-gender population with intranasal formulation led to a reduction of 1.4 nocturia episodes with a dosage of 0.83 ug and of 1.5 episodes with dosage of 1.66 ug vs 1.2 episodes with placebo (Kaminetsky et al. 2018). Similarly, in 3-month RCTs, treatment of women with sublingual formulation with a dosage of 25 ug led to a reduction of 1.5 episodes vs. 1.2 episodes with placebo (Sand et al. 2013), whereas treatment of men with a dosage of 50 ug led to a reduction of 1.3 episodes vs. 0.9 episodes with placebo (Weiss et al. 2013). Overall, the current quality of evidence of the outcomes of treatment of nocturia with various formulations and doses of desmopressin has been rated low

due to the limitations of the previous studies providing data only for small samples with short-term follow-up of three months or less (Han et al. 2017).

Medical treatment of male LUTS with α1-adrenergic antagonists, 5α-reductase inhibitors, phosphodiesterase type 5 inhibitors, antimuscarinics, β3-agonist mirabegrone, and phytotherapy have generally not proven superior to placebo for nocturia-related outcomes in previous RCTs (Sakalis et al. 2017). The reduction of nocturia episodes with LUTS/BPH drugs is only modest compared to placebo or active comparator with a difference of approximately 0.2 voids per night, regardless of the drug class (Oelke et al. 2014). Combination therapies have not proven consistently superior to monotherapy with desmopressin in men affected by nocturnal polyuria and LUTS (Sakalis et al. 2017, Han et al. 2017). Similarly, in mixed-gender samples of patients affected by OAB, previous RCTs on the impact onabotulinumtoxinA injections have shown only modest improvements in nocturia over placebo with a mean reduction of 0.5 nocturia episodes vs. 0.2-0.3 episodes at three months (Chapple et al. 2013, Nitti et al. 2017). Similarly, regarding the targeted treatments for BOO in men in whom medical therapy is unsuccessful, surgical procedures, such as transurethral resection of the prostate (TURP) may alleviate nocturia among other LUTS, although surgery should not be considered in men whose isolated complaint is nocturia, i.e. in the absence of other bothersome LUTS (Marshall et al. 2015). In a single-centre study randomising 66 men with LUTS to receive TURP or tamsulosin 0.4 mg, a significant mean difference of approximately 0.8 voids/night was observed in favour of TURP over Tamsulosin at one year. Duration of undisturbed sleep period was also prolonged in both groups without any statistically significant difference between the two groups (Simaioforidis et al. 2011).

Taking into account the complex etiology of nocturia, efficient treatment of underlying comorbidities is generally considered to be one of the most important aspects (Bower et al. 2017, Evereaert et al. 2019, Gravas et al. 2019). For example, treatment of hypertension may have a substantial effect on nocturia. Diuretic use is associated with an up to twofold increase in nocturia and the risk of nocturia is increased especially if diuretics are administered in the evening (Hall et al. 2012, Park et al. 2013, Oelke et al. 2017). However, changing the timing of the diuretic to late afternoon may help to resolve nocturnal polyuria and nocturia (Asplund 2007, Oelke et al. 2017, Everaert et al. 2019). Calcium channel blockers, which lower blood pressure by increasing natriuresis, may cause leg oedema during daytime and potentially nocturia when the oedema fluid is resorbed during the night (Everaert et al. 2019). In these cases, changing to a different type of antihypertensive medication

may be helpful. Angiotensin II type 1 receptor blockers administered in the morning seem to restore the circadian rhythms of blood pressure and natriuresis from nocturnal non-dipping to dipping patterns in patients with CKD. This, however, is not only due to inhibition of the renin-andiotensin-aldosterone system itself, but mainly to enhanced renal sodium excretion during daytime (Fukuda et al. 2011). This is similar to the effect of diuretics on nocturnal polyuria (Reynard et al. 1998, Goessaert et al. 2014). It has been suggested that treatment of nondipping blood pressure may improve nocturnal polyuria (Takayama et al. 2019).

In patients with OSA and treated with continuous positive airway pressure (CPAP) or surgery (uvulopalatopharyngoplasty), nocturia has been shown to improve (Wang et al. 2015, Park et al. 2016). The treatment of OSA may be beneficial in reducing nocturia in several ways. First, after the reduction of apneic episodes via treatments, the awakenings and subsequent bathroom trips in order to void may resolve. In addition, other biochemical mechanisms may also be involved. For example, OSA is known to be associated with decreased nocturnal plasma renin and aldosterone secretion, and treatment with CPAP reverses these effects, potentially leading to decreased nocturnal natriuresis. Furthermore, as nocturnal diuresis seems to be also partially mediated through enhanced release of ANP and elevated sympathetic tone, the reversing effect of CPAP on these pathways may also play a central role in reducing nocturnal polyuria (Ancoli-Israel et al. 2011). In patients with OSA, observational studies have consistently indicated a reduction in the number of nocturia episodes to be associated with treatment with CPAP, albeit with substantial variation in their estimates (Wang et al. 2015). A recent systematic review and meta-analysis of five studies (of which four were observational) showed an average reduction of 2.3 nocturia episodes and a mean decrease of 180 ml in nocturnal urine to be associated with treatment with CPAP (Wang et al. 2015). The single RCT included in the review – a multi-centre trial including 278 patients aged over 65 years with recently diagnosed OSA randomised to receive either CPAP and best supportive care (BSB) in combination or BSB alone – showed a mean reduction of 0.3 nocturia episodes at one year but no differences between the two groups (McMillan et al. 2014). In a single-centre study including 66 patients undergoing surgery for OSA, successful treatment showed a decrease of nocturia episodes from 1.9 to 0.7 (Park et al. 2016).

While the evidence supports the treatment of OSA in sleep disorders and nocturia, there is only little evidence supporting other sleep-promoting therapies, such as pharmacological or behavioural sleep aids, in the treatment of nocturia (Denys et al. 2018, Everaert et al. 2019). There is some evidence that taking 2 mg of

melatonin at bedtime may improve nocturia in men with BPH: in an RCT of 20 men with bladder outflow obstruction and nocturia (mean 3.1 episodes/night), a reduction of approximately 0.3 nocturia episodes was observed in the melatonin group and 0.1 episodes in the placebo group (Drake et al. 2004). In an RCT of 26 patients with nocturia secondary to multiple sclerosis, no significant difference in the reduction of nocturia episodes was observed between the melatonin and placebo groups (Drake et al. 2018). As an advisable behavioural treatment, patients with insomnia symptoms should avoid spending excess hours in bed, which may make their sleep shallower, leading to a worsening of their nocturia: the longer patients stay in bed, the more likely they are to need to urinate (Spielman et al. 1987, Yoshimura & Terai 2005). Furthermore, patients should be advised to try to go to bed at the same time each day in order to prevent the development of irregular sleep-wake rhythm type circadian rhythm sleep disorders (Zee & Vitiello 2009).

2.5 Natural course

Knowledge about the patterns of progression, remission and fluctuation of nocturia over time would facilitate shared decision-making about the initiation and continuation of therapeutic options between patients and healthcare providers (Blanker et al. 2014). To date, only a little is known about the natural history of nocturia as the majority of the data on the epidemiology of nocturia is based on cross-sectional studies, whereas only few longitudinal studies are available (Marshall et al. 2015, Milsom et al. 2017).

The prevalence of nocturia varies depending on the nocturia case definition (≥1, ≥2, ≥3 voids per night etc.) (Tikkinen et al. 2006, Bosch & Weiss 2010, Milsom et al. 2017). Estimates of the prevalence of nocturia, stratified by different nocturia case definitions, have shown substantial variation, suggesting that several factors in the study characteristics, including the comparability of the sample to general population, recruitment methods, participation rate and symptom assessment tools are likely to affect the estimates. Accordingly, for men aged 20-40 years studies have indicated a prevalence range of 11-35% for nocturia defined as ≥1 episodes and 2-17% for nocturia defined as ≥2 episodes/night, and for women in the same age group, a range of 20-44% for ≥1 episode and 4-18% for ≥2 episodes/night. For men aged over 70 years studies have indicated a prevalence range of 69-93% for ≥1 episodes and 29-59% for ≥2 episodes/night, and for women in the same age group a range of 74-77% for ≥1 episodes and 28-62% for ≥2 episodes/night (Bosch &

Weiss 2010). Overall, there is no great difference between genders in the prevalence of nocturia. Nocturia may be more common among women at a younger age but the differences disappear by middle age, while in the elderly nocturia may be more frequent among men (Tikkinen et al. 2006, Milsom et al. 2017).

For accurate estimates of the prognosis of nocturia, a summary of observational cohort studies would shed light on the issue. However, taking into account the substantial variation between symptom assessment tools, nocturia case definitions and analytic strategies, summarising the data is expected to be challenging. Furthermore, while a number of studies have explored the epidemiology of nocturia, only few have critically discussed the potential sources of bias (Marshall et al. 2015). A systematic review would elucidate the issue but, unlike the case with conventional systematic reviews comparing one treatment against another or against a non-treatment control with well-established methods (Higgins & Green 2011), systematic reviews and meta-analyses addressing natural history or prognosis require methodological innovations, and are therefore rare (Milsom et al. 2017).

2.6 Health consequences of nocturia

Whereas the estimates on the natural course of symptoms are important for shared decision-making between clinicians and patients, it should also be clear that it is equally important to estimate the risks of nocturia if the symptom is left untreated. While we earlier discussed the impact of comorbidities on nocturia, such as diabetes, cardiovascular diseases, chronic respiratory diseases, neurological diseases and malignancies (Mitropoulos et al. 2002, Tikkinen et al. 2009, Johnson et al. 2005, Marshall et al. 2015), in many cases the association may stem from bidirectional causality. Even if nocturia is not a direct cause of other diseases, it may be an important prognostic marker of disease, as in the suggested case of CKD and progressing kidney injury (Hsu et al. 2009, Krol et al. 2009, Boongird et al. 2010). Furthermore, especially among frail elderly subjects with increased baseline risk for falls and fall-related injuries, nocturia has been suggested to further increase these risks (Stewart et al. 1992, Kim et al. 2007b). Suggesting a number of possible causal pathways, some authors have postulated that nocturia may increase the risk of death (Yoshimura et al. 2012).

One of the major contributing factors to the health consequences of nocturia is believed to be sleep fragmentation. Besides the impairing effects of sleep disruption on the patient's vitality, concentration and mood, nocturia may also increase the

patient's risk of accidents at work, on the road, and at home (Chartier-Kastler et al. 2007). Observational studies have shown a clear association between sleep deprivation and metabolic disorders, including obesity, type 2 DM and hypertension, each of these is also linked to nocturia (Oelke et al. 2017). In men, an indication of the beneficial effect of nocturia treatment on hypogonadism has been observed – an effect possibly mediated by prolongation of the first period of uninterrupted sleep (Schmid et al. 2012, Luboshitzky et al. 2001, Kim et al. 2014, Shigehara et al. 2017). In a single-centre observational study of 62 men with late-onset hypogonadism, treatment with desmopressin had no significant effect on baseline testosterone levels in the whole cohort although the treatment was associated with a mean reduction of 1.2 nocturia episodes at three months. However, in the subgroup of 27 men with particularly low testosterone levels (<3.5 ng/mL), treatment resulted in a mean increase of approximately 2.9 ng/ml in testosterone levels in the presence of a decrease of approximately one nocturia episode per night at three months (Kim et al. 2014). Furthermore, sleep deprivation has also been associated with reduced natural immune responses and cytokine levels in the blood, resulting in an increased risk of infections (Irwin et al. 1996, Chartier-Kastler et al. 2007).

In addition to the health-impairing effects of nocturia-related sleep fragmentation, another hypothesised factor mediating nocturia-related morbidity and even mortality, is the potentially increased risk of falls and fractures. These comprise an important entity, especially among elderly population as older adults are at increased risk of falling due to age-related deterioration in balance and gait, which is exacerbated by illness and medications (Kannus et al. 2005, Deandrea et al. 2010). Over 30% of people aged over 65 years and living at home fall at least once per year (Deandrea et al. 2010, Morrison et al. 2013). Although only a minority of falls leads to fractures (Morrison et al. 2013), injuries due to falls are common and, among older adults, are associated with substantial healthcare costs, long-term functional impairment and a high risk of institutionalisation (Burns et al. 2016, Tinetti et al. 1997). Furthermore, falls account for the largest percentage of deaths related to unintentional injuries among older people (Burns et al. 2018). Therefore, developing multifactorial fall prevention programmes is a major focus in geriatric research (Gillespie et al. 2012).

The relationship between nocturia and falls and fractures is complex as they are all associated with multiple comorbidities that could confound or mediate associations. Common factors associated with both nocturia and falls include older age, diabetes, cardiovascular diseases, depression and physical inactivity (Fitzgerald et al. 2007, Tikkinen et al. 2009, Gibson et al. 2018). Some risk factors, such as

obesity, however, may increase nocturia but decrease fractures (Tikkinen et al. 2006a, De Laet et al. 2005). Furthermore, the postulations regarding the relationship between nocturia and falls and fractures are based mainly on cross-sectional studies which in spite of finding a consistent association of nocturia with falls (Stewart et al. 1992, Kim et al. 2007b) have less consistently supported the association with fractures (Stewart et al. 1992, Asplund 2006). Hence, given that in cross-sectional studies one can never be sure of the temporal relation between exposure and outcome, longitudinal studies are required to ascertain the association between nocturia and falls/fractures.

2.7 Mortality

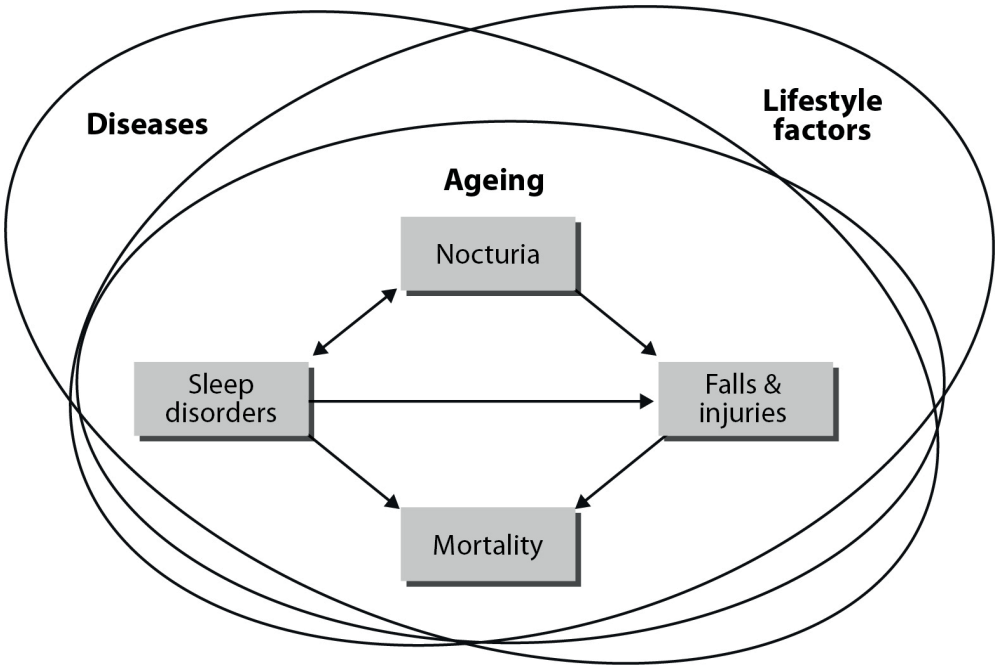
Premature deaths occur before the average age of death in a certain population and are of interest since these are often deemed to be preventable through reduced exposure to behavioural risk factors and timely and effective treatment. According to recent European statistics from 2017, CVD and cancer remain the most common causes of premature death. Annually, CVD contributes to 35% of deaths in people under 75 years and 29% of deaths in those under 65 years. For cancer, the corresponding proportions are 29% and 27% (Timmis et al. 2018). Among working age adults, excessive alcohol consumption remains a leading cause of premature death, being responsible for one in ten deaths among working age adults (Stahre et al. 2014, Timmis et al. 2018).

As people with nocturia tend to be older and are more likely to have comorbid conditions, the relevance of using nocturia as a mortality risk factor must take note of the effect of various confounders on the association between nocturia and mortality (Fig. 3). To optimally assess the impact of nocturia on mortality, one must also take into account fluctuation of nocturia, as well as follow-up time (time interval after initial assessment) (Vaughan et al. 2013). Furthermore, investigators should use a validated nocturia assessment method, and, to further minimise the risk of bias, reliably register all deaths during follow-up.

When interpreting the findings of population-level studies of associations and prognosis, one must consider the validity of the estimates and their applicability to real-world practice. Summarising the data of observational studies on nocturia seems a challenging task due to substantial variation in study methods and populations. Therefore, to guide future research and clinical practice for people with nocturia,

there is an increasing need for systematic reviews and meta-analyses supplemented with assessments of the quality of evidence.

Figure 3. Directed acyclic graph of potential confounders and mediators between nocturia and associated mortality.



NOTE: The ovals represent the potential confounders (ageing, diseases and lifestyle factors) on the association between nocturia and mortality. The arrows demonstrate the directions of the mediators (sleep disorders and falls/injuries) on the causal pathway between nocturia and mortality.

3 AIMS OF THE STUDY

The aims of this thesis are broadly divided in two major topics. First, the work aims to describe the natural course of nocturia and its associated risks of falls, fractures and mortality. Second, the work aims to further develop methods for systematic reviews and meta-analyses assessing natural history and prognosis of symptoms. The detailed objectives are the following:

1. To explore and compare, using different analytical methods and definitions, the average annual cumulative incidence and remission of nocturia, and separately, the progression of nocturia.

2. To establish the risk of bias criteria for systematic reviews assessing prognosis by developing a tool to assess the risk of bias in longitudinal symptom research studies aimed at the general population.

3. To contribute to the methodology of meta-analyses of the natural course of symptoms by comprehensively extracting data from individual studies and converting the measures to the same effect size metric to pool incidence and remission rates of nocturia.

4. To evaluate the association of nocturia with mortality, both as a prognostic and causal risk factor, by performing a systematic review and meta-analysis, including assessment of the quality of evidence (certainty in estimates).

5. To evaluate the association of nocturia with falls and fractures, both as a prognostic and causal risk factor, by conducting a systematic review and meta-analysis, including assessment of the quality of evidence (certainty in estimates).

6. To estimate the association of nocturia, daytime urinary frequency, and urinary urgency with mortality in a population-based cohort of middle-aged and elderly Finnish men.

4 MATERIALS AND METHODS

4.1 Systematic reviews and meta-analyses

4.1.1 Data sources and searches

The three systematic reviews included in the thesis (Studies I, II and III) were based on the same, comprehensive literature search, updated regularly in order to provide up-to-date estimates. Accordingly, for Study I, the literature search was performed up to 31 August 2015 and for Studies II and III, up to 31 December 2018.

An experienced research librarian (M.A.) collaborated in planning the search strategy, in PubMed (from 1946 to present), Scopus (1995 to present), and Cumulative Index of Nursing and Allied Health Literature (CINAHL, 1960 to present) without search limits or language restrictions. As increasing evidence suggests the benefits of including "grey" literature in the systematic reviews (Montori et al. 2008), we also searched abstracts published in the annual meetings of the American Urological Association (AUA), the European Association of Urology (EAU), the International Continence Society (ICS), and the International Urogynecological Association (IUGA) from 2005 until 2015 for Study I and until 2018 for Studies II and III for ongoing and unpublished studies. Appendix 1 provides the search strategy. We also manually searched reference lists of all included articles.

4.1.2 Study selection and data extraction

We screened the studies identified by the literature search according to their titles and abstracts and further included them in the full-text article screening phase if they complied with each of the following criteria: (1) a longitudinal study with a follow-up of at least three months, (2) a study assessing urinary symptoms at baseline, (3) a study sample consisting of 95% adults, and (4) a study examining the effect of any

intervention, including those with untreated control arms. We retrieved full text articles if the reviewers answered "yes" or "unclear" to all selection criteria.

As an additional selection criterion in Study I, taking into account the interaction between nocturia and several comorbidities, and therefore, to avoid potential selection bias, we excluded studies assessing lower urinary tract symptoms (LUTS) in patients with any specific health disorder, such as obstructive sleep apnea, diabetes or post stroke. Furthermore, to rule out the potentially biasing effect of recent delivery to LUTS, we excluded studies assessing the impact of pregnancy or delivery on LUTS if the baseline LUTS assessment was carried out either during pregnancy or in the first post-partum year.

The screening of full text articles was accomplished with more specific eligibility criteria based on the research question of each review. Accordingly, for the systematic review of incidence and remission of nocturia (Study I), we included observational cohort studies providing data on either incident or remittent cases of nocturia or periodic prevalences of nocturia in a sample of community-dwelling individuals not primarily seeking treatment for LUTS or sleep problems. For the systematic reviews of the impact of nocturia on mortality and falls/fractures (Studies II and III), we included observational cohort studies providing relative measures of association of nocturia as an exposure and mortality or falls/fractures as an outcome.

We developed standardised, pilot-tested forms together with detailed instructions for the screening of abstracts and full texts, risk of bias assessments, and data extraction. The reviewers conducted pilot screening and data extraction exercises to achieve a high level of agreement. Pairs of reviewers, independently and in duplicate, screened study reports for eligibility, assessed risk of bias and collected data from each eligible study. Reviewers resolved disagreements through discussions; one of two adjudicators resolved remaining disagreements.

When more than one report provided data from the same study, we used the most complete report, and additionally combined data from less complete reports where possible. We recorded the country/source of the study sample, age and sex distribution, exclusion criteria used in individual studies, assessment tools used for nocturia, follow-up time, sample size including response rate and the data for desired outcomes for each review i.e. incidence and remission of nocturia and relative measures of association of nocturia with mortality and falls/fractures as well as variables used in adjustments of the reported estimates.

4.1.3 Risk of bias and quality of evidence assessment

One challenge for a systematic review assessing prognosis (Study I) is that risk of bias criteria, as well as criteria for overall certainty in estimates, although well established for reviews of therapeutic trials, are controversial in observational studies (Guyatt et al. 2011). Through iterative discussion and consensus building, and informed by the existing literature (Hayden et al. 2013, Kim et al. 2013), we developed a novel instrument to categorise studies as carrying either low or high risk of bias, evaluating the representativeness of the source populations, accuracy of the outcome assessment and the proportion of missing data (Appendix 2) (Tikkinen et al. 2012). In Study I we categorised the overall risk of bias as low if the study met criteria for low risk of bias in each of the three domains of the assessment (Appendix 2).

Furthermore, not only the methods of studies assessing prognosis, but generally the methods of all observational cohort studies require development regarding their risk of bias evaluation (Guyatt et al. 2011). Motivated by the shortcomings of the methodology available and taking the existing literature into account (Tähtinen et al. 2016, Hayden et al. 2013, Kim et al. 2013), we developed instruments for observational cohort studies examining nocturia as exposure and mortality (Study II) and falls/fractures (Study III) as outcome. This includes the features of the studies included that could potentially bias the estimates: the comparability of source populations, confidence in the assessments of both exposure (nocturia) and outcome (separately for mortality, falls and fractures), proportion of missing data and adjustments for important potential confounders/risk factors for each outcome. In Studies II and III we categorised the overall risk of bias as low if the study met the criteria for low risk of bias in each of the five domains of the assessment (Appendices 3 and 4).

According to the GRADE framework, for assessments of prognosis, a body of observational studies begins as high-quality evidence. Several categories of limitations may, however, impair evidence quality, including risk of bias, imprecision, inconsistency and indirectness (Iorio et al. 2015). In contrast, in the GRADE approach for studies of interventions, a body of observational studies begins as low-quality evidence, and may be rated down to "very low" by the same limitations as in intervention studies, but may also be rated up by factors such as a large effect size or dose-response gradient (Guyatt et al. 2008c). Therefore, in this thesis, which includes only observational studies, the evidence can provide trustworthy inferences about prognosis (i.e. if nocturia is associated with mortality, falls or fractures) but

not causation (i.e. if nocturia causes mortality, falls or fractures). To formally compare the certainty of the pooled estimates for nocturia both as a prognostic factor (synonymous with risk factor) and as a cause of mortality, falls and fractures, we assessed the quality of evidence with the GRADE framework for both prognostic and intervention research (Iorio et al. 2015, Guyatt et al. 2008c).

4.1.4 Data synthesis and analysis

For Study I, we used three different analytic definitions to assess the incidence of nocturia: (1) any new case of nocturia (≥1 voids/night) at follow-up for individuals without nocturia at baseline, (2) any new case of ≥2 voids/night for individuals with no or one void per night at baseline, and (3) any new case of ≥3 voids/night for individuals with two or less voids per night at baseline. Similarly, we used three analytic definitions for nocturia remission: (1) one or more voids per night resolving to no nocturia, (2) two or more nocturia episodes resolving to no or one void per night, and (3) three or more nocturia episodes resolving to two or fewer voids per night. Epidemiological studies have suggested that a difference of at least one void per night is often patient-important (Tikkinen et al. 2010, Kupelian et al. 2012).

For cumulative incidence and remission rates, person-years were calculated by multiplying the number of individuals without/with nocturia (for incidence and remission respectively) at follow-up by follow-up time (simple cumulative incidence methodology). Standard errors and 95% confidence intervals (CI) were calculated for natural logarithms of incidence/remission rates per 1000 person- years of follow-up. In the case of zero events, a correction of 0.5 was added to observed events and person-years to enable calculation of confidence intervals.

We calculated pooled rates of incidence and remission of nocturia using the DerSimonian–Laird random effects inverse variance method. Rates were expressed as observed events per 1000 person-years of follow-up. If a study provided more than one definition for incidence/remission of nocturia, when pooling data, we preferred nocturia estimates using a definition of two or more voids/night. Finally, we also used actuarial cumulative incidence methodology for sensitivity analyses (Appendix 5).

For the pooled analyses in Studies II and III, we extracted hazard ratios (HR), or alternatively relative risks (RR) to be used interchangeably with HRs. From the regression models reported, we selected the estimates with the highest level of adjustments to minimise the effect of confounding.

Although the proportional hazards model utilising time-to-event data is superior to the logistic regression model in the analyses of longitudinal data by incorporating more information, in cases of relatively short follow-up periods, as is typically the case with observational studies of nocturia, where distribution of events and therefore, censoring, is concentrated at the end of follow-up, the loss of statistical power is known to be weak, even in cases of moderate values of survival function (Annesi et al. 1989). Therefore, in cases of outcomes of rare events, estimates for proportions at follow-up provided by adjusted regression models, i.e. odds ratios (OR) and RRs, are probably close approximates to HRs (Annesi et al. 1989). Accordingly, as the baseline risk of deaths and fractures is typically low, we considered the interchangeable use of HRs and RRs justified (for easier interpretation, we converted ORs to RRs).

Regarding outcomes of common events (such as falls in the elderly), where the majority of events occur within a short time period, the effects of censoring and competing risks (such as deaths) are less significant and therefore HRs are seldom reported. Taking into account the typically high baseline risk of falls, conversion to the same effect size metric is required, hence, if a study reported only an odds ratio (OR) instead of RR, we converted the OR into RR using the following formula:

$$RR = OR / (1 - p + (p \times OR))$$

in which p represents the baseline risk i.e. the risk of the outcome (death or falls/fractures) in people without nocturia at baseline (Sinclair & Bracken 1994). We calculated the pooled RRs using the DerSimonian–Laird random effects inverse variance method. When raw data were available, to take account of the effect of potential confounders including age and comorbidities, we derived adjusted RRs from multivariable logistic regression models.

4.1.5 Additional analyses

In each meta-analysis, we tested effect modification with subgroup analyses, stratified by at least with following covariables: (1) Mean age (2) gender distribution (3) length of follow-up, (4) nocturia case definition, and (5) risk of bias. Pre-specified hypotheses were employed to examine heterogeneity between the estimates using meta-regression analysis weighted by the inverse of the variance in a random effects model. We set a threshold of *p*-value less than 0.05 as a minimum criterion for a credible subgroup effect.

The subgroup analyses of Study I were stratified into three age groups (18–39, 40–59 and 60 years and over) as earlier research suggest substantial differences in prevalence of nocturia between individuals in young adulthood, middle age and in older age (Bosch & Weiss 2010). We moreover stratified the analyses by gender and across the three nocturia case definitions (defined as ≥1, ≥2 or ≥3 voids/night). Separately for each nocturia case definition (≥1, ≥2 or ≥3 voids/night), we examined the following variables as potential sources of heterogeneity: (1) mean age, (2) sex distribution, (3) length of follow-up and (4) risk of bias. For incidence, we had pre-specified hypotheses that effect estimates would be higher for: (1) older age, (2) higher proportion of male population, (3) shorter follow-up time and (4) lower risk of bias. For remission, we had pre-specified hypotheses that effect estimates would be higher for: (1) younger age, (2) higher proportion of female population, (3) shorter follow-up time and (4) lower risk of bias.

The subgroup analyses of Study II were stratified by three age groups (18-49, 50-69 and ≥70 years) to address the effect of age and the natural history of nocturia on the relative measures of association between nocturia and mortality. We moreover stratified the analyses by gender, follow-up time (<10 vs. ≥10 years), risk of bias, study region and across varying nocturia case definitions in terms of a binary variable (≥2 vs. 0-1; and ≥3 vs. 0-2 voids/night) and a three-value categorical variable (2 vs. 0-1 and ≥3 vs. 0-1 voids/night), using the latter to explore exposure-response relationship of nocturia with mortality. In meta-regression we examined the following variables as potential sources of heterogeneity: (1) gender, (2) age, (3) length of follow-up, (4) nocturia case definition and (5) risk of bias. We pre-specified hypotheses that the effect of nocturia on mortality would be higher for: (1) male vs. female or mixed gender, (2) younger age (<70 vs. ≥70 years), (3) shorter follow-up time (<10 vs. ≥10 years), (4) higher nocturia case definition (≥3 vs. ≥2 voids/night) and (5) high vs. low risk of bias.

The subgroup analyses of Study III were stratified by age, gender, follow-up time, risk of bias and across varying nocturia case definitions in terms of a binary variable (≥2 vs. 0-1 and ≥3 vs. 0-2 voids/night) and a three-value categorical variable (2-3 vs. 0-1 and ≥4 vs. 0-1 voids/night), using the latter to explore the exposure-response relationship of nocturia with falls and fractures. Additional subgroup-analyses with similar stratifications were conducted for studies reporting recurrent falls as an outcome. Due to the paucity of included estimates, conducting a meta-regression analysis to detect any interactions between variables was not considered relevant in Study III.

In Study I, to facilitate the understanding of the natural course of nocturia, we visually demonstrated the relationship between annual incidence, remission and prevalence of nocturia by the three nocturia case definitions (≥1, ≥2 and ≥3 episodes/night). For this illustration, we estimated the baseline prevalence of nocturia separately for each nocturia case definition using an existing comprehensive systematic review (Bosch & Weiss 2010).

For better communication and knowledge translation regarding the consequences of nocturia, considering that optimal decision-making requires estimates of both relative and absolute effects, we illustrated the difference in the absolute risks of the assessed outcomes between individuals with and without nocturia. Accordingly, in Studies II and III we reported the association of nocturia with mortality and falls/fractures in terms of both relative and absolute estimates, presenting five-year absolute risks of death and annual risks of falls and fall-related fractures in people of two exemplary age groups over 60 years – an age group commonly affected by nocturia (Bosch & Weiss 2010).

In Study II, when calculating the baseline risks of death, we first estimated the average five-year death rates from the reported annual death rates for people aged 55-64 and 75-84 years in the USA (Centers for Disease Control and Prevention 2016). Then, for the average estimates of the prevalence of nocturia of two or more voids per night (Tikkinen et al. 2010) in the desired age groups, we extracted the reported prevalences from studies included in an earlier comprehensive systematic review (Bosch et al. 2010), calculated the 95% confidence intervals (CI) for the natural logarithms of prevalences per 100 people and pooled the estimates in a random-effects meta-analysis (Appendix 6). Finally, to derive the baseline risks in the absence and presence of nocturia, we divided the average death rates into proportions based on the prevalence of nocturia and pooled relative risks for the desired age groups.

In Study III, to assess the average risks of falls and fractures in general elderly population, the annual number of people with ≥1 falls/year and the proportion of those who fell and sustained a fracture were extracted from prospective Western population-based studies included in a previous systematic review (Morrison et al. 2013). After calculating the 95% confidence intervals for the natural logarithms of incidence rates of fallers per 100 person-years and the proportions of individuals with a fall-related fracture per 100 fallers, the estimates were pooled in random-effects meta-analyses (Appendices 7 and 8). To stratify the pooled estimates of average annual fall and fall-related fracture rates by age, we used coefficients from another systematic review assessing various risk factors for falls (Deandrea et al.

2010). Finally, to derive the baseline risks in the absence and presence of nocturia, we divided the average annual fall and fracture rates in proportions based on prevalence of nocturia (Appendix 6) and pooled relative risks for the desired age groups. Statistical analyses were performed using metan and metareg in Stata 12.1 (StataCorp, College Station, TX, USA) (Harris et al. 2008).

4.2 The Tampere Ageing Male Urologic Study

A population-based cohort study focusing on urological symptoms and sexual functioning among middle-aged and elderly men was launched in Pirkanmaa Region, Finland in 1994, with repeat rounds in 1999, 2004, and 2009. Details have been published previously (Koskimäki et al. 1998, Häkkinen et al. 2006). Briefly, a sample of 3143 men, living in Pirkanmaa Region, was identified from the Finnish Population Register in 1994, comprising all men born in 1924, 1934, or 1944 residing in the study area at baseline. Self-administered questionnaires were mailed to the men in the study population at all rounds. Non-responders were reminded with a second mailing after three months. The questionnaire comprised items on frequency and bother of LUTS, major health conditions and medications, as well as sociodemographic, anthropometric, and lifestyle factors (Appendix 9).

We assessed the frequencies of LUTS using the Danish Prostatic Symptom Score (DAN-PSS-1) (Hansen et al. 1995), consistent with the International Continence Society definitions (Abrams et al. 2002). An exception was made in 1994 in the assessment of urgency, where a modified question backtranslated from Finnish to English was as follows: "Is your need to urinate so urgent that it is difficult to hold it back until you reach the toilet?", which was since modified and used at sub-sequent the rounds in 1999, 2004, and 2009 as "Do you experience an imperative (strong) urge to urinate?". The response options were never, rarely, often, always. The question concerning daytime frequency was "What is the longest interval between each voiding, from when you wake up until you go to bed?" with response options of more than 3 h, 2-3 h, 1-2 h, less than 1 h. The question concerning nocturia was "How many times do you have to urinate per night?" with response alternatives of none, 1 or 2 times, 3 or 4 times, 5 times or more. The preceding 4-week period was used as the reference time frame for the questions.

As only moderate and severe LUTS are typically patient-important, we compared these with symptoms of milder intensity, after recoding each symptom into a binary variable (O'Leary 2005). Accordingly, we categorised urgency as "often or always"

vs. "never or rarely" and daytime frequency as nine or more vs. eight or fewer voids/day. Based on the response alternatives for nocturia question in DAN-PSS, we considered the case definition of three or more vs. two or less voids per night to most adequately detect patient-important cases with best comparability to the generally acknowledged case definition for significant nocturia of two or more voids/night (Tikkinen et al. 2010, Kupelian et al. 2012). For the analysis, we recoded each symptom into a binary variable: no or mild vs. moderate or severe symptoms (the first two versus the two latter options). We followed up the men for mortality through the population registry until the end of 2014. We obtained information on times and causes of death by a deterministic linkage with the unique personal identification number as the key.

For analyses of mortality, we included men who had answered LUTS questions at every survey in 1994-2009 (while alive) and for comorbidities at least in the 1994 survey. To adjust the analyses for confounders, we selected variables with well-established prognostic importance for regression analyses. These variables, of which many are also known to be associated with LUTS, included age, marital status (married or cohabiting versus single or widowed), body mass index (BMI, ≤25 versus >25 kg/m^2), current smoking (yes/no), alcohol consumption (≤150 g/week vs. >150g/week), previous diagnosis of diabetes, hypertension, cardiac disease, pulmonary disease, cerebrovascular disease, cancer and neurological disease.

We performed univariate Cox regression analyses for each urinary symptom and potential prognostic variable. Independently of their effects in unadjusted analyses, we included each potential prognostic variable in multivariable-adjusted regression models of the three assessed LUTS. Each characteristic was treated as a time-dependent categorical variable. We used the "last observation carried forward" method (Little & Rubin 2002) for comorbidities with missing values in the following rounds. We performed parallel analyses for each three urinary symptoms to provide time-varying HRs using variable values updated every five years (time-dependent analysis). To further examine the effect of fluctuation of LUTS and associated comorbidities, and for easier comparison to earlier studies, we conducted sensitivity analyses using values of all variables fixed to the baseline assessment (1994) and used Kaplan-Meier curves to graphically represent these associations. We moreover evaluated interaction terms in the regression models of the association of each urinary symptom with mortality and conducted subgroup analyses for the variables with a significant interaction. For all statistical analyses in Study IV, we used the Statistical Package for the Social Sciences (SPSS) version 23.

4.3 Ethical considerations

Our studies comply with the Declaration of Helsinki. In accordance with the Finnish regulations on questionnaire surveys, we were granted an exemption from ethical review by the ethics committee of the Pirkanmaa Hospital District for the Tampere Ageing Male Urologic Study (Study IV: tracking number 99050). In the three systematic reviews included in the thesis (Studies I-III), we registered the protocols in an international prospective register of systematic reviews, PROSPERO (CRD42012001985, Pesonen et al. 2014; CRD42016051132, Pesonen et al. 2016a; CRD42016051525, Pesonen et al. 2016b) and followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidance (Moher et al. 2009).

5 RESULTS

5.1 Incidence and remission of nocturia – a systematic review and meta-analysis (Study I)

We screened 4165 abstracts and retrieved 74 full texts and two eligible conference abstracts (Fig. 4). Sixteen studies provided usable data from 15 142 men and 18 726 women (Table 2). Of these 16 studies, two provided proportional measures of progression and remission of nocturia among all persons in follow-up but did not report actual numbers of incident or remitting cases (Lee et al. 1998, Temml et al. 2003). Similarly, one study provided only periodic prevalences of nocturia but not data on incident or remitting cases (Malmsten et al. 2010). We were therefore able to include 13 studies (114 964 person-years) in the meta-analyses of incidence and remission rates of nocturia.

Table 2 provides a description of the 16 studies. Ten (62%) were conducted in Europe, three (19%) in North America, and three (19%) in Asia. The studies varied widely, including gender and age distributions, as well as in follow-up times (median 4.5 years; range, from 6 months to 16 years). Fifteen studies (94%) used symptom questionnaires and one (6%) used frequency-volume charts.

Figure 4. Flow chart – Study I.

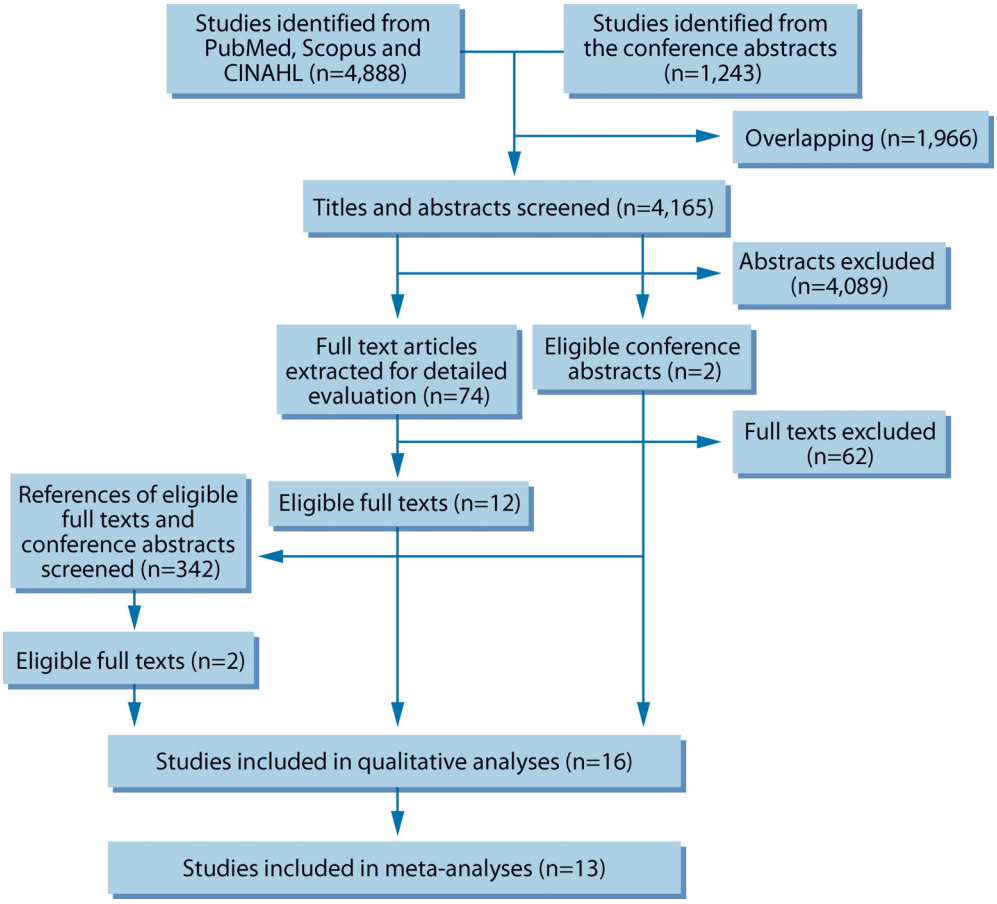


Table 2. Characteristics of the studies included in qualitative analyses – Study I.

Study	Country	Source of sample	Population characteristics [a]	Exclusion criteria	Assessment tool for nocturia	Follow-up time in years	Number of contacted at the baseline	No. of eligible respondents	
								Baseline	Follow-up
Bulpitt 1976	England	GP registry	Both genders, 38% men, mean age 53 (range 32-69)	Hypertension	A Symptom Questionnaire for Hypertensive Patients (validated)	0.8	173	88 (51%)	55 (63%)
Lee 1998 [b]	Scotland	GP registries	Men, mean age 56 years (range 40-79)	Treatment/disease affecting lower urinary tract	AUA-SI	5	3094	1994 (64%)	1159 (58%)
Møller 2000	Denmark	Civil registry	Women, mean age 50 (range 40-60)	None	BFLUTS	1	4000	2860 (72%)	2284 (80%)
Temml 2003 [b]	Austria	Health screening	Men, mean age 55 (range 40-84)	Treatment affecting lower urinary tract	IPSS	5	2096	854 (41%)	456 (53.4%)
Johnson 2005	USA	Marketing list vendor	Both genders, 40.7% men, mean age 71 (range 60+)	Institutionalised	MESA questionnaire (validated)	1	1956	1632 (83%)	1105 (68%)
Häkkinen 2006	Finland	Civil registry	Men, mean age 62 (range 50-70)	None	DAN-PSS	5	3143	2198 (70%)	1683 (77%)
Chen 2007	Taiwan	Health screening	Women, mean age 60 (range 40-79)	None	Unvalidated questionnaire	2	1149	862 (75%)	314 (36%)
Viktrup 2008	Denmark	Department of obstetrics	Primiparous women, mean age 35 (range 17-41) [c]	None	A questionnaire in accordance with definitions by ICS (validated)	7	Unclear	305	226

Wennberg 2009	Sweden	Civil registry	Women, mean age 56 (range 20-98)	None	IPSS	16	2911	2248 (77%)	1081 (37%)
Malmsten 2010 [b]	Sweden	Civil registry	Men, mean age 62 (45-99)	None	IPSS	11	10458	7763 (74%)	3257 (42%)
Heidler 2011	Austria	Health screening	Women, mean age 57 (range 21-81)	Urinary tract infection, surgery for urinary incontinence	BFLUTS	6.5	1166	925 (79%)	386 (42%)
Van Doorn 2011	The Netherlands	Civil registry	Men, mean age 62 (range 50-78)	Surgery/condition affecting lower urinary tract, poor health	FVC (frequency-volume chart)	2.1	3398	1122 (33%)	698 (62%)
Aoki 2012	Japan	Health screening	Both genders, 30.8% men, mean age 68 (range 23-95)	None	Unvalidated questionnaire	4	Unclear	23 126	13 536
Hunter 2012	USA	Home support registries	Women receiving home support, mean age 84 (range 70-103)	Poor health	ICIQ-FLUTS	0.5	203	100 (49%)	75 (75%)
Hirayama 2013	Japan	Health screening	Both genders, 50.7% men, mean age 73 (range 65-93)	Poor health, institutionalised	IPSS	1	4427	3915 (88%)	3685 (94%)
Araujo 2014	USA	Street lists	Both genders, 38.9% men, mean age 52 (range 30-79)	Poor health	AUA-SI	5	9602	5502 (57%)	4144 (75%)

[a] Mean age at the midpoint of the follow-up; to estimate the mean age at the moment of nocturia incidence/remission in the study population, half of the duration of the follow-up time was added to the mean age at the baseline.
[b] Three studies were not included in the meta-analyses.
[c] Age information at the time of delivery. We used data from nocturia observations that were collected between the 7th and 12th postpartum years.

Of the 16 studies included, 14 (88%) accurately assessed nocturia both at baseline and at follow-up, nine (56%) had a little missing data in the follow-up and eight (50%) used representative source populations. Of these studies, 10 (62%) were judged to have high and six (38%) low risk of bias (Fig. 5).

Figure 5. Risk of bias of the included studies – Study I.

Reference	Risk of bias criteria			Overall risk of bias
	Representativity of the source population	Assessment of the outcome	Missing data	
Bulpitt 1976	−	+	−	High
Lee 1998	+	+	−	High
Møller 2000	+	+	+	**Low**
Temml 2003	−	+	−	High
Johnson 2005	+	+	+	**Low**
Häkkinen 2006	+	+	+	**Low**
Chen 2007	−	−	−	High
Viktrup 2008	+	+	+	**Low**
Wennberg 2009	+	+	+	**Low**
Malmsten 2010	+	+	+	**Low**
Heidler 2011	−	+	−	High
Van Doorn 2011	+	+	−	High
Aoki 2012	−	−	+	High
Hunter 2012	−	+	−	High
Hirayama 2013	−	+	+	High
Araujo 2014	−	+	+	High

In the meta-analyses of the incidence rates of nocturia (12 studies, five low and seven high risk of bias), the pooled average annual cumulative incidence was 4.9% (95% confidence interval 4.1-5.8, I^2=98.6%; no difference between simple and actuarial cumulative incidence methodology) (Fig. 6, Appendix 5). With age stratification, annual incidence increased with increasing age: 0.4% (0-0.8%, I^2=65.1%) for adults aged < 40 years, 2.8% (1.9-3.7%, I^2=98.1%) for adults aged 40-59 years, and 11.5% (9.1-14.0%, I^2=98.8%) for adults aged ≥60 years (Fig. 6). Pooled incidence rates did not significantly differ by nocturia case definition (4.1% (3.0-5.2%) for ≥1 episodes per night, 4.4% (3.6-5.2%) for ≥2 episodes per night, and 3.7% (2.4-5.1%) for ≥3 episodes per night (Appendix 10).

In multivariable meta-regression, (borderline) significant predictor for higher incidence was older age (4.7% increase/decade for ≥1 voids/night, -1.4 to 10.8, p=0.12, 2.5% increase/decade for ≥2 voids/night, 0.1-4.9, p=0.04; and 2.6% increase/decade for ≥3 voids/night, -0.2 to 5.4, p=0.06). Follow-up time, sex distribution, or risk of bias were not strongly suggestive of higher or lower incidence of nocturia (Appendix 11).

In the meta-analyses of remission rates of nocturia (12 studies, five low and seven high risk of bias), the pooled average annual cumulative remission was 12.1% (9.5–14.7%, I^2=97.8%; no difference between simple and actuarial cumulative remission methodology) (Fig. 7, Appendix 5). With age stratification, annual remission rates did not differ by age: 11.1% (3.7–18.5%, I^2=0.0%) for adults aged <40 years, 9.4% (6.2–12.6%, I^2=94.1%) for adults aged 40–59 years, and 13.9% (9.0–18.8%, I^2=98.8%) for adults aged ≥60 years (Fig. 7). Pooled remission rates for nocturia increased with higher nocturia case definition: 6.7% (4.5–8.9%) for ≥1 voids/night, 15.5% (10.4–20.6%) for ≥2 voids/night, and 22.3% (13.2–31.3%) for ≥3 voids/night (Appendix 10).

In multivariable meta-regression, age, sex distribution, follow-up time, or risk of bias were not consistently suggestive of higher or lower remission of nocturia (Appendix 12).

Figure 6. Forest plot of incidence rates of nocturia per 1000 person-years of follow-up – Study I.

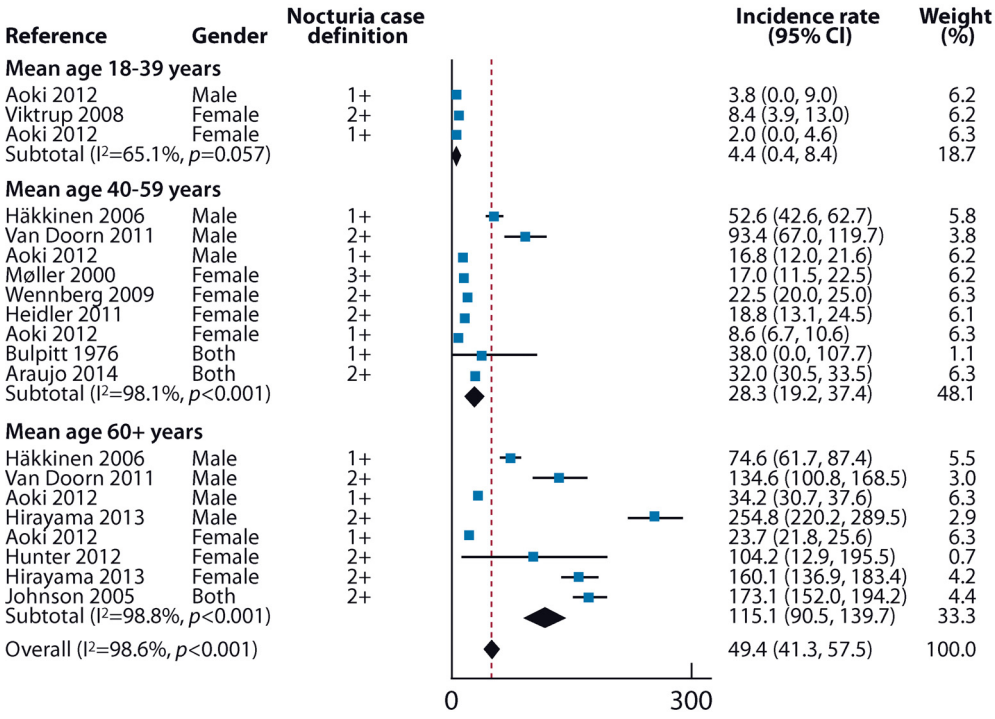


Figure 7. Forest plot of remission rates of nocturia per 1000 person-years of follow-up – Study I.

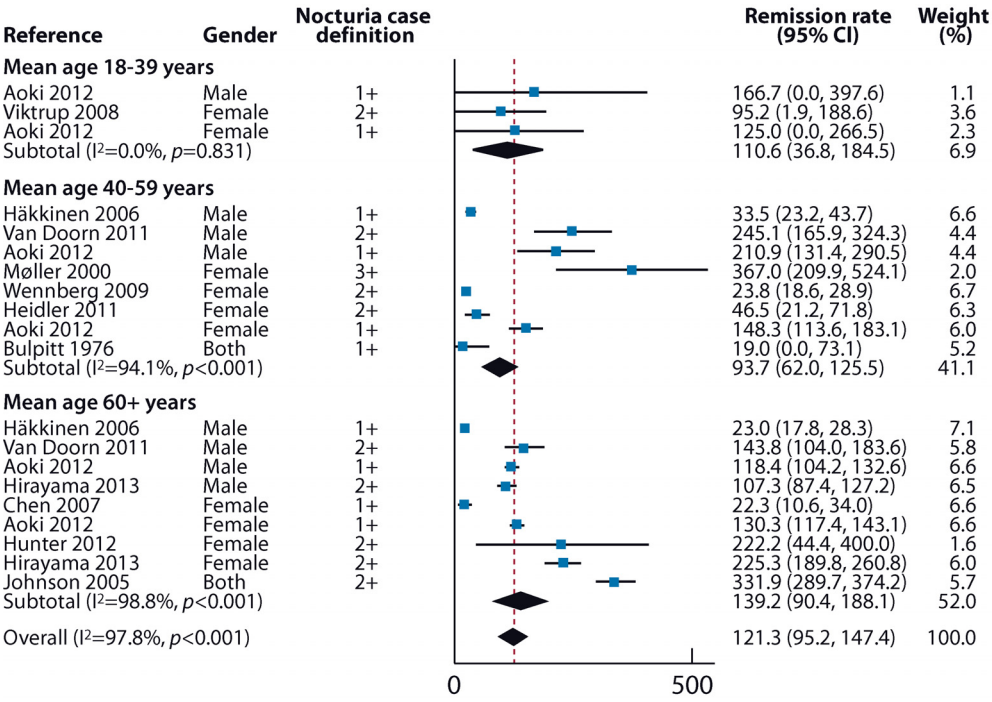
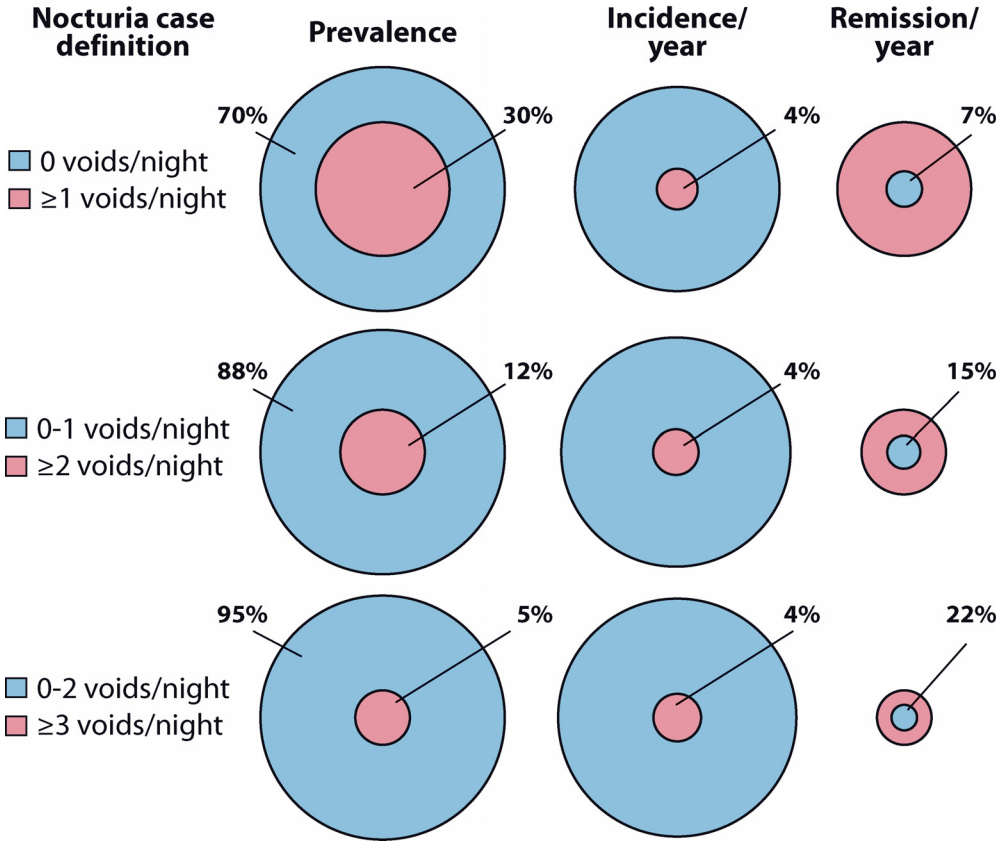


Figure 8 illustrates the relation of baseline prevalence (of having or not having nocturia) with (average annual) cumulative incidence and remission. For instance, baseline prevalence is 5% for ≥3 nocturia episodes. Therefore, 5% of population are "at risk" of nocturia remission and 95% are "at risk" of nocturia incidence. According to our meta-analyses (Appendix 10), cumulative incidence is 3.7% (2.4–5.1%) and cumulative remission is 22.3% (13.2–31.3%) for ≥3 nocturia episodes. However, due to the baseline prevalence, indeed more incident than remittent nocturia cases emerge annually and the prevalence therefore increases with age.

Figure 8. Relation of annual incidence and remission rates of nocturia to baseline prevalence of at least one void per night (30%), at least two voids per night (12%), and at least three voids per night (5%) – Study I.



Three studies provided proportional measures for progression/remission of nocturia (Lee et al. 1998, Temml et al. 2003, Heidler et al. 2011). In a Scottish study conducted among middle-aged and elderly men (Lee et al. 1998), progression of nocturia occurred in 40% and remission in 10%, whereas in 50% of men nocturia remained unchanged after 5-year follow-up. In an Austrian study also conducted among middle-aged and elderly men (Temml et al. 2003), progression occurred in 28%, remission in 27%, while in 45% of men nocturia symptoms were unchanged. An Austrian study conducted among women of all adult ages (Heidler et al. 2011), reported after 6.5-year follow-up, progression from one void to at least two voids per night occurred in 21% of women with one void per night at baseline, and remission to one void per night in 23% of women with at least two voids per night at baseline.

5.2 Impact of nocturia on mortality – a systematic review and meta-analysis (Study II)

We screened 5230 abstracts and retrieved 132 potentially eligible full text reports and 22 conference abstracts (Fig. 9). Ten original full text articles and one conference abstract provided data on nocturia-associated death, including 19 590 men and 14 241 women with a total follow-up of 297 379 person-years (Table 3). Five (45%) of the 11 authors confirmed the accuracy of our data extraction; two (18%) corrected some errors or provided additional information and four (36%) were unable respond to our requests for data checks and clarifications.

Studies were conducted on three continents, in male and mixed gender populations that varied widely in their age distributions and follow-up times (Table 5). Nocturia was defined as ≥2 episodes per night in six (55%), and as ≥3 episodes per night in five (45%) studies. Reflecting the differences in study populations, as well as variations in symptom assessment methods, the baseline prevalence of nocturia in the study populations varied widely, with ranges of 8-34% based on a case definition of ≥2 (vs. 0-1 voids/night) and 2.5-35% with a case definition of ≥3 (vs. 0-2 voids/night) in adults aged <70 years; in adults aged ≥70 years, the range was 35-49% in the broader case definition and 8-38% in the more restrictive (Appendix 13).

Figure 9. Flow chart – Study II.

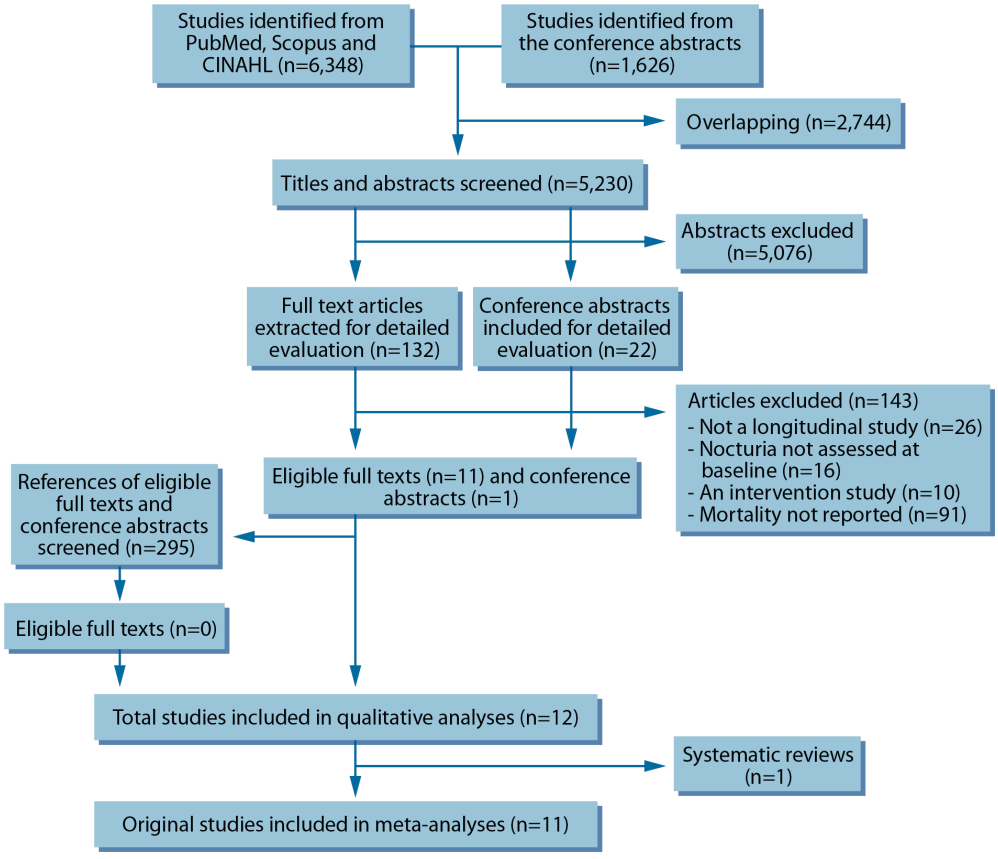


Table 3. Characteristics of the studies included in qualitative analyses – Study II.

Study	Country	Source of sample	Population characteristics	Exclusion criteria	Assessment of nocturia	Assessment of mortality	Median follow-up time	No. of contacted at baseline	No. of eligible respondents
Asplund 1999	Sweden	Pensioners' association registry	Both sex, 40% men, mean age 73 yr (range 53-92 yr) [a]	None	Unvalidated	National death registry	4.5 yr	10216	6143 (60%)
Bursztyn 2006	Israel	Electoral records	Both sex, 55% men, all aged 70 yr	None	Unvalidated	National death registry	12 yr	759	456 (60%)
Fitzgerald 2009 [b]	Puerto Rico	Various public registries	Men, mean age 71 yr (range 60-99 yr)	Institutionalised	Unvalidated	National death registry	2 yr	1736	1480 (85%)
Nakagawa 2010	Japan	Civil registry	Both sex, 46% men, mean age 76 yr (range 70-97 yr)	Non-members of NHI system	In accordance with IPSS/AUA-SI	NHI registry	5 yr	2925	784 (27%)
Kupelian 2011	USA	Various public registries	Both sex, 47% men, mean age 49 yr (range 20-90 yr)	Institutionalised	In accordance with IPSS/AUA-SI	NHCS Linked Mortality Files	8.8 yr	39695	15988 (69%)
Galizia 2012	Italy	Electoral rolls	Both sex, 45% men, mean age 74 yr (range 65+ yr)	None	In accordance with IPSS/AUA-SI	GP registries, death certificates	12 yr	1780	1288 (72%)

Lightner 2012	USA	Medical records from various health care units	Men, mean age 54 yr (range 40-79 yr)	Surgery/condition affecting lower urinary tract	AUA-SI (assessed every 2 yrs)	Multiple sources incl. death certificates and autopsy reports	17 yr	3874	2115 (55%) [c]
Van Doorn 2012	The Netherlands	Civil registry	Men, mean age 61 yr (range 50-78 yr)	Surgery/condition affecting lower urinary tract, poor health	FVC (frequency-volume chart)	GP registries	13.4 yr	3398	1114 (33%)
Chung 2014	Taiwan	Hospital diabetic clinic	Both sex, 52% men, mean age 63 yr (range 32-94 yr) [a]	Treatment for type 2 diabetes for less than 1 yr	OABSS	National death registry	2.5 yr	1715	1301 (76%)
Endeshaw 2016	USA	Medicare beneficiares, designated zip code areas	Men, mean age 74 yr (range 70-79 yr)	None	IPSS	Clinic visits, telephone contacts, death certificates	9 yr	Unclear	1478
Åkerla 2019	Finland	Civil registry	Men, mean age 58 yr (range 50-70 yr)	None	DAN-PSS (assessed every five yrs)	National death registry	21 yr	3143	1332 (42%) [d]

AUA-SI = American Urological Association Symptom Index, DAN-PSS = Danish Prostatic Symptom Score, GP = general practice, IPSS = International Prostate Symptom Score, LUTS = lower urinary tract symptoms, NHCS = National Center for Health Statistics, NHI = National Health Insurance, OABSS = Overactive Bladder Symptom Score

[a] Age range approximated by using the reported standard deviation (SD) for mean age (mean age ± 3SD).

[b] Previously unpublished analyses based on the study raw data.

[c] To replace men who either died or dropped out, additional 332 men were recruited during the first four years of follow-up.

[d] Response available for every assessment of LUTS (while alive).

To identify eligible individuals, two studies used electoral rolls, two household registries, and three civil registries. One study used a combination of hospital and primary care registries, one recruited patients from a hospital's diabetes clinic and one used primary care registries for White and zip code lists for Black participants. We considered the cohorts of seven studies to adequately represent general populations with a satisfactory participation rate (Fig. 10, Table 3). For assessment of nocturia at baseline, ten studies used symptom questionnaires and one used frequency-volume charts. We considered eight studies (73%) to have assessed nocturia accurately (Fig. 10, Table 3). Five studies (45%) collected mortality data from a national death registry, and five (45%) used linkage to registries of different health care institutions. We considered that ten studies (91%) assessed mortality accurately through registry data. Eight studies (73%) had little missing data. Six studies (55%) adequately performed adjustments for their estimates (Fig. 10, Table 3, Appendix 13). The overall risk of bias was judged as high in nine studies (82%), and as low in two studies (18%) (Fig. 10).

Figure 10. Risk of bias of the included studies – Study II.

Reference	Risk of bias criteria					Overall risk of bias
	Representativity of the source population	Assessment of nocturia	Assessment of mortality	Missing data	Adjustment	
Asplund 1999	+	−	+	−	−	High
Bursztyn 2006	+	−	+	+	+	High
Fitzgerald 2009	+	−	+	−	−	High
Nakagawa 2010	−	+	+	+	+	High
Kupelian 2011	+	+	+	+	+	**Low**
Galizia 2012	+	+	+	+	−	High
Lightner 2012	+	+	+	+	−	High
Van Doorn 2012	−	+	+	+	+	High
Chung 2014	−	+	+	−	−	High
Endeshaw 2016	−	+	−	+	−	High
Åkerla 2018	+	+	+	+	+	**Low**

The pooled relative risk of death in 11 studies (2 low and 9 high risk of bias) proved higher in people with nocturia compared to those without nocturia (RR 1.27; 95% CI 1.16-1.40; heterogeneity: I^2=48.3%; moderate quality evidence for prognosis and very low quality evidence for causality) (Figure 11, Table 4).

In subgroup meta-analyses, the pooled estimates for association between nocturia and mortality did not differ significantly for samples stratified by age, gender, follow-up time, nocturia case definition, risk of bias, or study region (Appendices 13-15). This was also true for the multivariable-adjusted meta-regression analyses (Appendix 16).

Based on the mean death rates in the USA among people aged 60 and 75 years with respective age-specific prevalences of nocturia (≥2 episodes per night) of approximately 20% and 40% (Appendix 6), the nocturia-associated increase in the overall five-year absolute death risk were 1.6% and 4.0% among people aged 60 and 75 years respectively (Figure 12, Appendix 17).

We rated down the quality of evidence due to high risk of bias (to which the majority of the included studies were susceptible). We therefore rated the quality of evidence (synonymously confidence or certainty in estimates) as moderate for nocturia as a prognostic risk factor for mortality, and as very low quality for nocturia as a causal factor for mortality (Table 4).

Figure 11. Forest plot of the relative risks of death in people with nocturia – Study II.

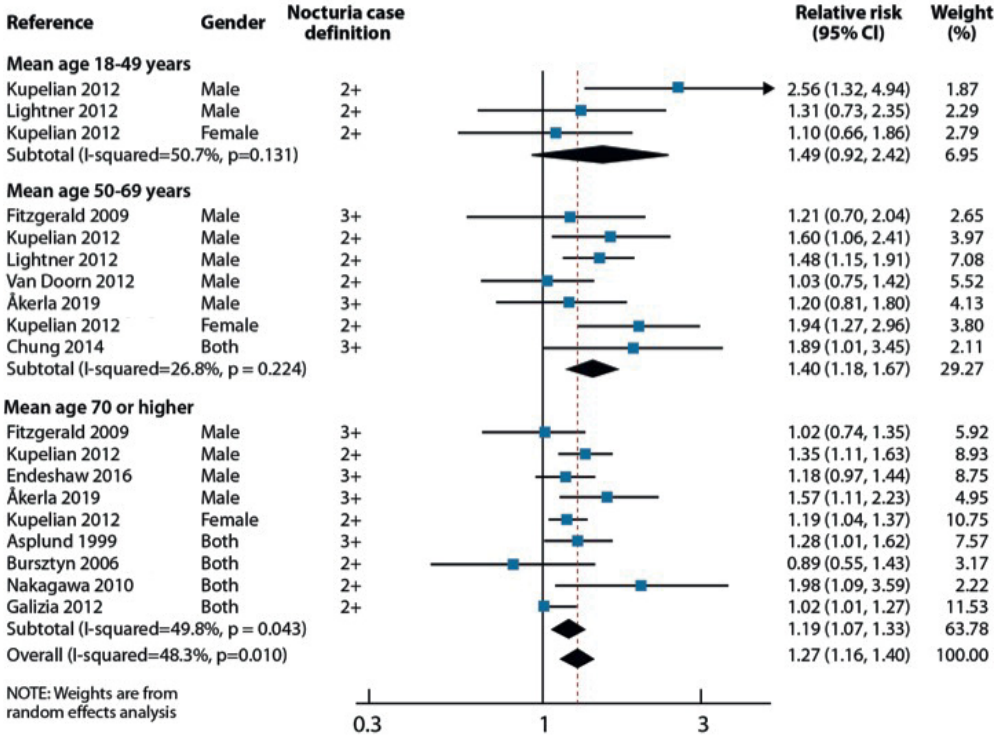


Table 4. Evidence profile: nocturia as a prognostic factor for mortality versus as a cause of mortality – Study II.

		Summary of findings			Prognosis vs. causation [b]	Quality assessment					
No. of studies (design)	**No. of participants [a]**		**Relative risk (95% CI)**	**Absolute risk difference**		**Starting quality**	**Risk of bias [c]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Certainty in estimates**
	No nocturia	**Nocturia**									
11 (observational cohort)	26763	7048	1.27 (1.16-1.40)	Age 60 yr: 1.6% per 5 yr Age 75 yr: 4% per 5 yr	**Prognosis**	High	Serious limitations	No serious limitations	No serious limitations	No serious limitations	Moderate
					Causation	Low	Serious limitations	No serious limitations	No serious limitations	No serious limitations	Very low

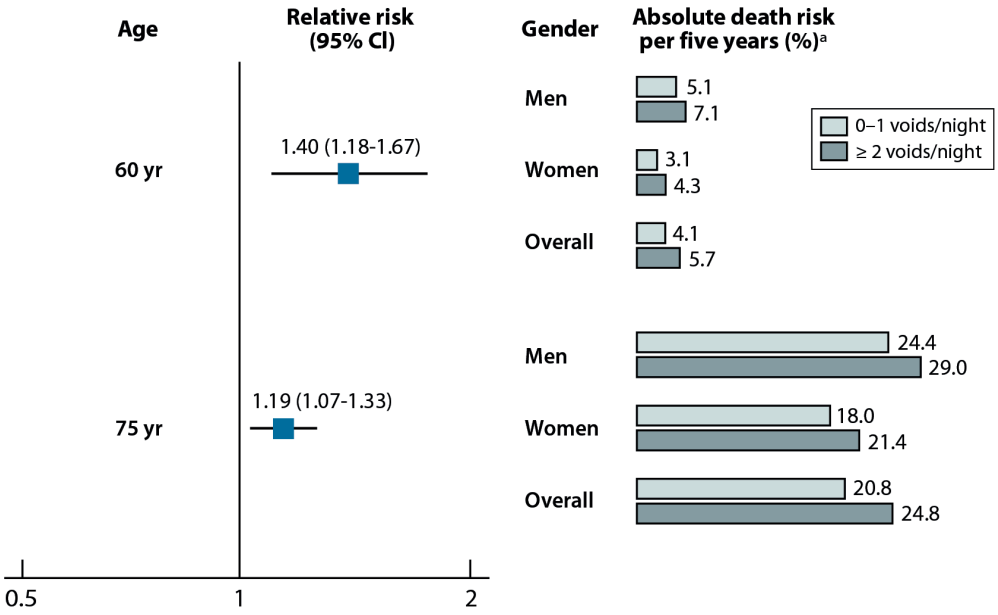
GRADE = Grades of Recommendation, Assessment, Development, and Evaluation

[a] Some studies reported the number of exposed participants for several nocturia case definitions. In these cases, the number of participants with ≥ 2 and 0-1 voids/night was included in the total count of exposed and unexposed participants.

[b] Assessment based on the principles of the GRADE framework where the body of observational evidence begins as high quality when used for prognosis research and as low quality when used for intervention research.

[c] Assessment described in Appendix 3 and Fig. 10.

Figure 12. Relative and absolute risk of death in five years between people with and without nocturia – Study II.



5.3 Impact of nocturia on falls and fractures – a systematic review and meta-analysis (Study III)

We screened 5230 abstracts and retrieved 132 potentially eligible full text articles and 22 conference abstracts (Fig. 13). Five studies provided data on the association between nocturia and falls and five on nocturia and fractures (Table 5).

Of the five studies assessing falls, three were conducted in North America, one in Europe and one in Australia. Of the five studies assessing fractures, two were conducted in North America, two in Europe and one in Eastern Asia. The studies included mainly older people in their seventies and predominantly men, with follow-up times varying from one to six years for studies of falls and four to nine years for studies of fractures (Table 5). Two studies were conducted on the same base population of older men with separate reports on falls and non-spine fractures with varying follow-up times. We identified one conference abstract (Fitzgerald et al. 2009), which reported only death as an endpoint (was included in Study II) but access to the study raw data provided assessments also for both falls and fractures (Palloni et al. 2013) (Appendix 18). We were therefore able to include five studies in the meta-

analysis of falls with a total follow-up of 23 678 person-years and five studies in the meta-analysis of fractures with a total follow-up of 87 973 person-years.

Figure 13. Flow chart – Study III.

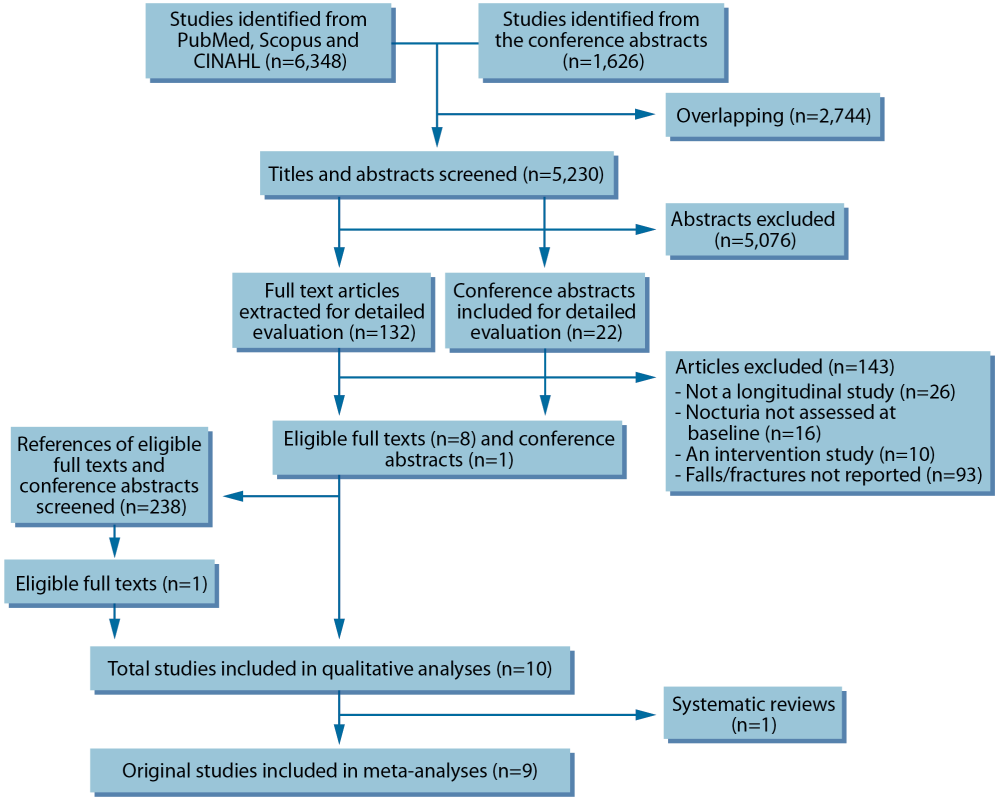


Table 5. Characteristics of the studies included in qualitative analyses – Study III.

Study	Country	Source of sample	Population characteristics	Exclusion criteria	Assessment of nocturia at baseline	Assessment of falls/fractures in follow-up	Median follow-up time	No. of contacted at baseline	No. of eligible respondents
Fitzgerald 2009 [a]	Puerto Rico	Various public registries	Men, mean age 70 yr (range 60-99 yr)	Institutionalised	Unvalidated questionnaire	Falls and fractures via an interview, recall period of 1 yr	4 yr	1736	Baseline:1332 (77%), follow-up:1011 (58%)
Parsons 2009 [b]	USA	Various public registries	Men, mean age 74 yr (range 65-100 yr)	Physical or cognitive disability, terminal illness, bilateral hip replacement	AUA-SI	Falls assessed via repeated telephone contacts every 4 months	1 yr	Unclear	5872
Temml 2009	Austria	Health screening	Men, mean age 52 yr (range 41-80 yr)	None	IPSS	Hip fractures via hospital registries	5 yr	Unclear	1820
Frost 2010	Denmark	Civil registry	Men, mean age 65 yr (range 60-75 yr)	None	Unvalidated questionnaire [c]	All fractures via hospital registries	5 yr	9314	4696 (50%)
Nakagawa 2010	Japan	Civil registry	Both sex, 46% men, mean age 76 yr (range 70-97 yr)	Non-members of NHI system	Questionnaire in accordance with definitions by ICS	All fractures via NHI registry	5 yr	2925	784 (27%)

Vaughan 2010	USA	National social insurance program registry (Medicare)	Both sex, 52% men, mean age 75 yr (range 65-106 yr)	Poor co-operation, institutionalized, history of falls (1 yr prior to the baseline assessment)	Questionnaire in accordance with definitions by ICS	Falls assessed via repeated telephone contacts every 6 months	3 yr	2188	Baseline:1000 (46%), follow-up: 692 (69%)
Stenhagen 2013	Sweden	Civil registry	Both sex, 46% men, mean age 71 yr (range 60-93 yr)	Inability to speak Swedish, history of falls (6 mo prior the baseline assessment)	Unclear	Falls via an interview, recall period of 6 months	6 yr	5370	Baseline: 2535 (47%), follow-up: 1720 (32%)
Marshall 2016 [b]	USA	Various public registries	Men, mean age 74 yr (range 65-100 yr)	Physical or cognitive disability, terminal illness, bilateral hip replacement	AUA-SI (assessed every 2 yrs)	Nonspine fractures via post/telephone and medical record assessments, repeated every 4 months	8.6 yr	Unclear	5989
Noguchi 2016	Australia	Electoral roll	Men, mean age 76 yr (range 70-99 yr)	Institutionalised, dementia, neurological disease, poor mobility	IPSS	Falls assessed via repeated telephone contacts every 4 months	1 yr	3821	1366 (36%)

AUA-SI = American Urological Association Symptom Index, GP = general practice, ICS = International Continence Society, IPSS = International Prostate Symptom Score, NHI = National Health Insurance, NHS = National Health Service, OABSS = Overactive Bladder Symptom Score

[a] Previously unpublished analyses based on the study raw data.

[b] Osteoporotic Fractures in Men Study (MrOS) cohort.

[c] Nocturia registered only for men specifying the symptom in the assessment of symptoms/diseases related to urinary tract.

Of the five studies assessing falls, three used representative source populations, three conducted the baseline assessments of nocturia and follow-up assessments of falls accurately, three had little missing data at the follow-up, and three adequately adjusted their estimates for important prognostic risk factors for falls. We judged three studies, of those assessing impact on falls, to be at overall high risk of bias (Fig. 14, Table 5, Appendix 19).

Of the five studies assessing fractures, three used representative source populations, three assessed nocturia accurately, four assessed fractures accurately, three had little missing data at follow-up, and two adequately adjusted their estimates for important prognostic risk factors for fractures. We therefore considered four studies, of those assessing impact on factures, to be at overall high risk of bias (Fig. 14, Table 5, Appendix 19).

Figure 14. Risk of bias of the included studies – Study III.

Reference - Falls	Risk of bias criteria - Falls					Overall risk of bias
	Representativity of the source population	Assessment of nocturia	Assessment of falls	Missing data	Adjustment	
1. Fitzgerald 2009	+	−	−	−	+	High
2. Parsons 2009	+	+	+	+	+	**Low**
3. Vaughan 2010	+	+	+	+	+	**Low**
4. Stenhagen 2013	+	−	−	−	−	High
5. Noguchi 2016	−	+	+	+	−	High
Reference - Fractures	**Risk of bias criteria - Fractures**					**Overall risk of bias**
	Representativity of the source population	Assessment of nocturia	Assessment of fractures	Missing data	Adjustment	
1. Fitzgerald 2009	+	−	−	−	+	High
2. Temml 2009	−	+	+	−	−	High
3. Frost 2010	+	−	+	+	−	High
4. Nakagawa 2010	−	+	+	+	−	High
5. Marshall 2016	+	+	+	+	+	**Low**

In the meta-analysis of estimates of the association between nocturia and falls, adjusted at least for age and gender (5 studies: 2 low and 3 high risk of bias), the pooled relative risk of falling at least once in follow-up was higher in people with nocturia than in those without nocturia at baseline (RR 1.20; 95% CI 1.05-1.37; heterogeneity: I^2=52%; moderate-quality evidence for prognosis and very low quality for causality) (Fig. 15, Table 6). In the subgroup analyses, the estimates did not differ by age, gender, follow-up time, nocturia case definition or risk of bias (Appendix 20).

In the additional analysis of studies reporting recurrent falls as an outcome (3 studies: 1 low and 2 high risk of bias), the pooled, adjusted relative risk was 38% higher in people with nocturia at baseline (RR 1.38; 95% CI 1.11-1.71; I^2=54.7%). The estimates were only available for men and did not differ by age, follow-up time, nocturia case definition, or risk of bias (Appendix 21).

The absolute risk of falling at least once a year was 5.5% higher among people aged 65 years with nocturia (defined as ≥2 voids/night) than among people without nocturia (defined as 0-1 voids/night), and 7.5% higher in people aged 80 years with nocturia than among people without (Fig. 17, Appendix 23).

In the meta-analysis of estimates on the association between nocturia and fractures, adjusted at least for age and gender (5 studies: 1 low and 4 high risk of bias), the pooled relative risk of having a fracture at follow-up was 32% higher in people with nocturia than in those without nocturia at baseline (RR 1.32; 95% CI 0.99-1.76; heterogeneity: I^2=57.5%; low-quality evidence for prognosis and very low-quality for causality) (Fig. 16, Table 6). In the subgroup analyses, the estimates did not differ significantly by age, gender, follow-up time, nocturia case definition or risk of bias (Appendix 22).

Regarding assessments of the association between nocturia and different types of fractures, only one estimate was available for each specific association with RRs of 1.36 (95% CI 1.03-1.79) for hip fractures in men, 1.00 (95% CI 0.90-1.20) for non-spine fractures in men, 1.37 (95% CI 0.19-9.86) for osteoporotic fractures in men, and 2.20 (95% CI 1.04-4.68) for specifically fall-related fractures in a mixed gender population respectively (Appendix 19).

The absolute annual risk of fractures was 0.9% higher in people with nocturia than in people without among those aged 65 years. The absolute difference in annual fracture risk among people aged 80 years was 1.2% between people with and without nocturia (Fig. 17, Appendix 23).

Figure 15. Forest plot of the relative risks of falls in people with nocturia – Study III.

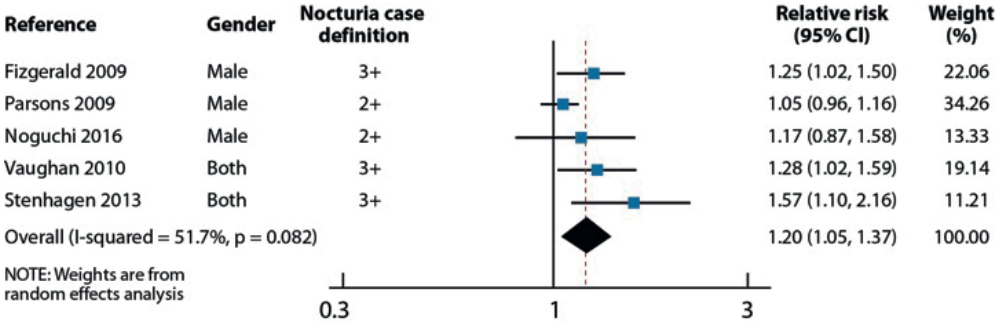


Figure 16. Forest plot of the relative risks of fractures in people with nocturia – Study III.

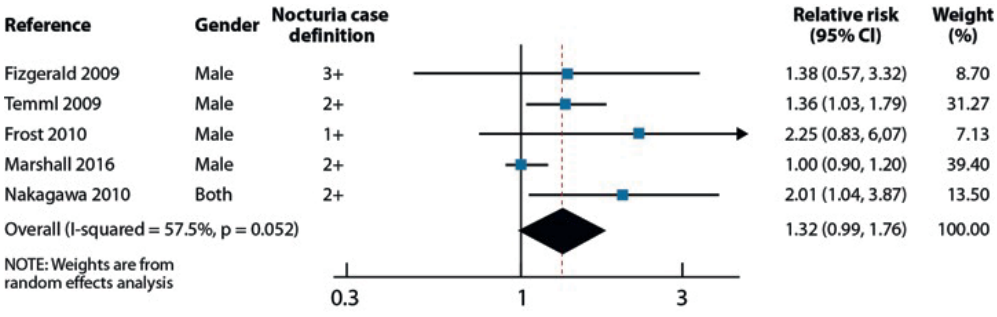
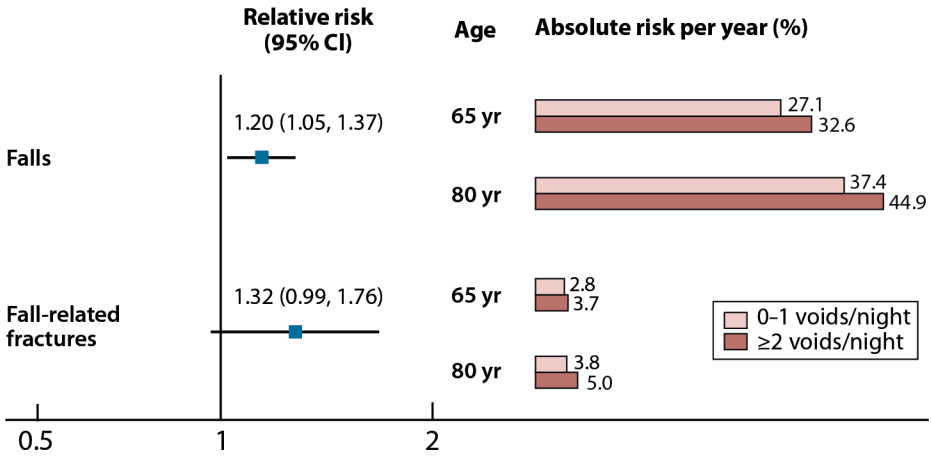


Figure 17. Absolute risk of falls and fall-related fractures between older people with and without nocturia – Study III.



Of the five studies assessing falls, three had high and two had low risk of bias (Fig. 14). We rated down the quality of evidence due to high risk of bias (to which the majority of the studies included were susceptible). We therefore rated the quality of evidence as moderate for nocturia as a prognostic risk factor and as very low quality for nocturia as a causal factor for falls (Table 6). Of the five studies assessing fractures, four had high and one low risk of bias. We therefore rated down for risk of bias. We also rated down for imprecision (confidence interval crossed no effect). We therefore rated the quality of evidence as low for nocturia as a prognostic risk factor for fractures, and as very low quality for nocturia as a causal factor of fractures (Table 6).

Table 6. Evidence profile: nocturia as a prognostic factor for falls and fractures versus as a cause of falls and fractures – Study III.

	Summary of findings				Prognosis vs. causation [b]	Quality assessment					
No. of studies (design)	**No. of partici-pants**		**Relative risk (95% CI)**	**Absolute risk difference per year**		**Starting quality**	**Risk of bias [c]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Certainty in estimates**
	No nocturia	**Nocturia [a]**					**Falls**				
5 (observational cohort)	5931	4730	1.20 (1.05-1.37)	Age 65 yr: 5.5% Age 80 yr: 7.5%	**Prognosis**	High	Serious limitations	No serious limitations	No serious limitations	No serious limitations	Moderate
					Causation	Low	Serious limitations	No serious limitations	No serious limitations	No serious limitations	Very low
							Fractures				
5 (observational cohort)	9767	4533	1.32 (0.99-1.76)	Age 65 yr: 0.9% Age 80 yr: 1.2%	**Prognosis**	High	Serious limitations	No serious limitations	No serious limitations	Serious limitations	Low
					Causation	Low	Serious limitations	No serious limitations	No serious limitations	Serious limitations	Very low

GRADE = Grades of Recommendation, Assessment, Development, and Evaluation

[a] Nocturia case definitions varied across the studies.

[b] Assessment based on the principles of the GRADE framework where the body of observational evidence begins as high quality when used for prognosis research and as low quality when used for intervention research.

[c] Assessment described in Appendix 4 and Fig. 14

5.4 Impact of nocturia, daytime frequency and urinary urgency on mortality among middle-aged and elderly Finnish men – (Study IV)

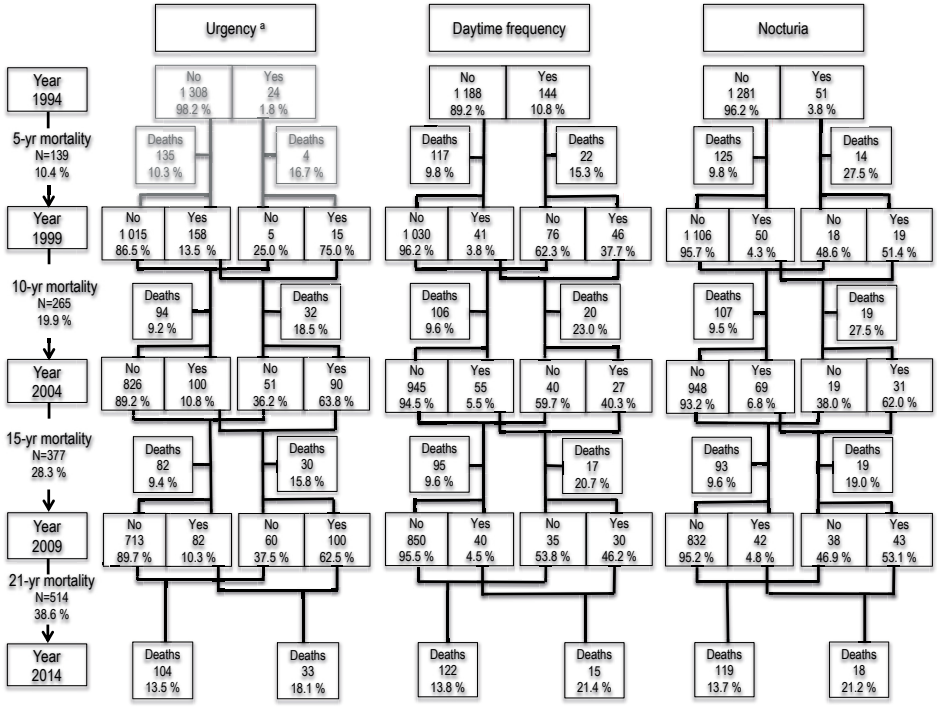
A total of 2198 questionnaires (70 %) were returned in 1994, 2133 (75%) in 1999, 1905 (76%) in 2004 and 1424 (66%) in 2009, of which 1332 were eligible for the study in that they provided sufficient data for the analyses, i.e. they included responses to questions regarding LUTS at every survey round (while alive). Regarding the age distribution of the men included, the respective proportions were 41%, 36% and 23% for men aged 50, 60 and 70 at baseline. Men with LUTS were generally older than those without LUTS and virtually all medical conditions were more frequent among men with LUTS (Table 7, Appendix 24).

Table 7. Characteristics of men with and without urgency, daytime frequency and nocturia at follow-up midpoint (2004) – Study IV.

	Urgency				Daytime frequency				Nocturia			
	Yes		No		Yes		No		Yes		No	
	n	%	n	%	n	%	n	%	n	%	n	%
Number of men	190		877		82		985		100		967	
Year of birth												
1944	66	34.7	432	49.5	34	41.5	464	47.1	25	25.0	473	48.9
1934	84	44.2	328	37.4	33	40.2	379	38.5	44	44.0	368	38.1
1924	40	21.1	117	13.3	15	18.3	142	14.4	31	31.0	126	13.0
Marital status												
Married/cohabiting	148	77.9	717	81.8	63	76.8	802	81.4	81	81.0	784	81.1
Single/divorced	33	17.4	111	12.7	15	18.3	129	13.1	15	15.0	129	13.3
Widowed	9	4.7	49	5.6	4	4.9	54	5.5	4	4.0	54	5.6
BMI												
≤25	60	31.6	289	33.0	21	25.6	328	33.3	36	36.0	313	32.4
25-30	89	46.8	431	49.1	39	47.6	481	48.8	51	51.0	469	48.5
>30	41	21.6	157	17.9	22	26.8	176	17.9	13	13.0	185	19.1
Current smoking	28	14.7	121	13.8	9	11.0	140	14.2	12	12.0	137	14.2
Alcohol intake >150 g/week	38	20	134	15.3	8	9.8	164	16.6	8	8.0	164	17.0
Medical conditions												
Diabetes	35	18.4	93	10.6	15	18.3	113	11.5	15	15.0	113	11.7
Hypertension	101	53.2	391	44.6	47	57.3	445	45.2	46	46.0	446	46.1
Cardiac disease	60	31.6	188	21.4	26	31.7	222	22.5	32	32.0	216	22.3
Pulmonary disease	27	14.2	99	11.3	8	9.8	118	12.0	19	19.0	107	11.1
Cerebrovascular disease	16	8.4	48	5.5	9	11.0	55	5.6	8	8.0	56	5.8
Cancer	22	11.6	79	9.0	8	9.8	93	9.4	18	18.0	83	8.6
Neurological disease	13	6.8	27	3.1	5	6.1	35	3.6	6	6.0	34	3.5

The symptoms showed substantial fluctuation with a decreasing trend for daytime frequency with a prevalence of 10.8% at baseline and 7.3% at 15 years and an increasing trend for nocturia with a prevalence of 3.8% at baseline and 8.9% at 15 years. Reflecting the modified question in the assessment of urgency in 1994, its prevalence was materially lower at baseline (1.8%) than in subsequent rounds (14.5% at five, 17.8% at 10 and 19.1% at 15 years) (Fig. 18).

Figure 18. Flow chart of mortality rates of men in relation to baseline prevalences and periodic incidence and remission rates of urinary urgency, frequency and nocturia – Study IV.



[a] Assessed with a modified question in 1994.

During the 21-year follow-up, 514 men died, of whom 139 during the first, 126 during the second and 112 during the third 5-year period and 137 during the last period of six years. The overall mortality was 10.4% at five years, 19.9% at 10 years, 28.3% at 15 years and 38.6% at 21 years (this means that 61.4% survived the whole follow-up). Mortality was higher among men with LUTS at every stage of follow-up (Fig. 18). In unadjusted time-dependent analyses, each of the storage symptoms studied was strongly associated with an increased risk of death: HR was 1.71 (95% CI 1.36-2.14) for urgency, 1.95 (1.52-2.49) for daytime frequency and 2.31 (1.79-2.98) for nocturia (Table 8). In unadjusted analyses with fixed baseline characteristics, daytime frequency and nocturia were significantly associated with increased risk of death, while urgency showed no significant association: HR 1.43 (1.11-1.84) for daytime frequency, 2.56 (1.81-3.63) for nocturia and 1.52 (0.86-2.69) for urgency (Figs. 19 & 20, Table 8).

In multivariable-adjusted time-dependent analyses, daytime frequency and nocturia remained significantly associated with an increased risk of death, while urgency showed only a suggestive association: the adjusted HR was 1.42 (1.11-1.83) for daytime frequency, 1.38 (1.07-1.79) for nocturia and 1.19 (0.94-1.50) for urgency (Table 8, Appendix 25). In multivariable-adjusted analyses with fixed baseline characteristics, only nocturia was suggestively associated with increased risk of death: the adjusted HR was 0.94 (0.52-1.68) for urgency, 1.09 (0.84-1.42) for daytime frequency and 1.41 (0.99-2.02) for nocturia (Table 8, Appendix 26).

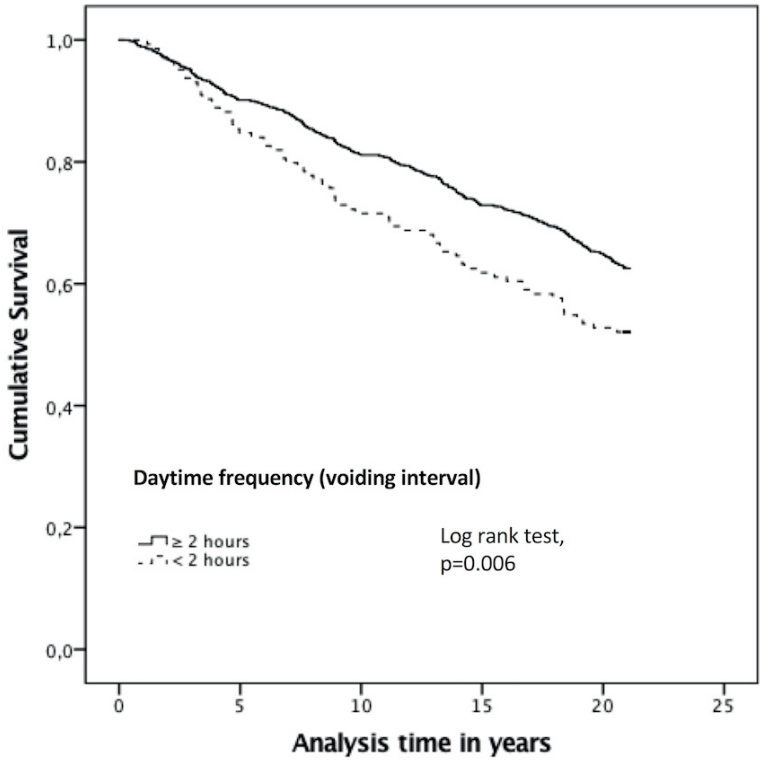
Table 8. Unadjusted and adjusted associations of urinary urgency, frequency and nocturia with all-cause mortality in Cox regression analyses using variable values updated every five years (time-dependent analysis) and values fixed to the baseline assessment of 1994 (fixed analysis) – Study IV.

		Urgency		Frequency		Nocturia	
		HR	95% CI	HR	95% CI	HR	95% CI
Time-dependent analysis	Unadjusted	1.71	1.36-2.14	1.95	1.52-2.49	2.31	1.79-2.98
	Adjusted [a]	1.19	0.94-1.50	1.42	1.11-1.83	1.38	1.07-1.79
Fixed analysis	Unadjusted	1.52	0.86-2.69	1.43	1.11-1.84	2.56	1.81-3.63
	Adjusted [b]	0.94	0.52-1.68	1.09	0.84-1.42	1.41	0.99-2.02

[a] A regression model including the year of birth and following categorical variables with time-varying values: LUTS, marital status, BMI, smoking, alcohol consumption, diabetes, hypertension, cardiac disease, pulmonary disease, cerebrovascular disease, neurological disease and cancer. "Last observation carried forward" method (Little & Rubin 2002) used for comorbidities with missing values in the follow-up rounds.

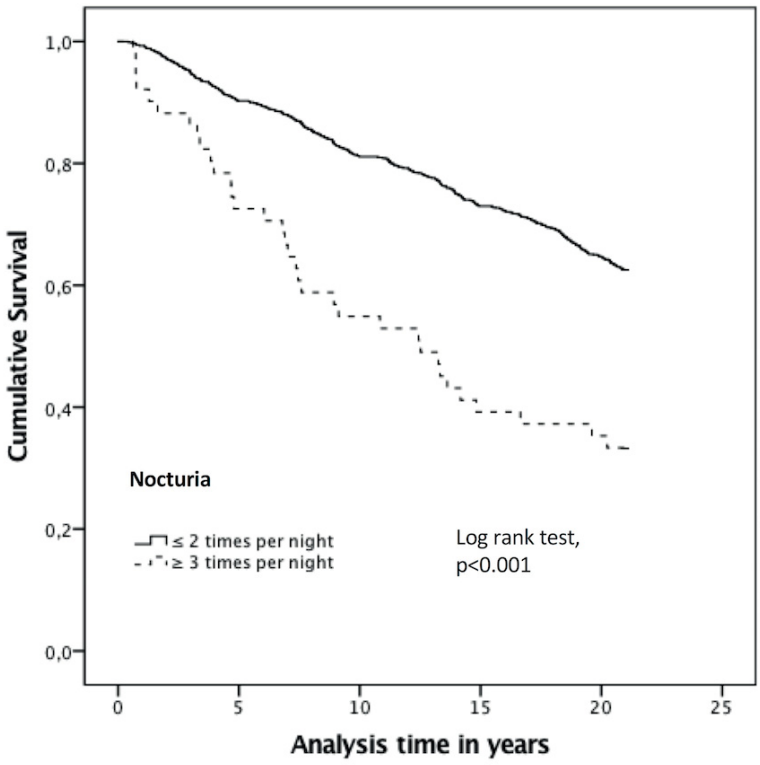
[b] All above-mentioned variables treated as fixed categorical variables in the regression model i.e. the variable values fixed to the baseline assessment of 1994.

Figure 19. Kaplan-Meier curves for men with and without daytime frequency at baseline (1994) – Study IV.



Number at risk			
≥ 2 hours	1 188	964	771
< 2 hours	144	103	76

Figure 20. Kaplan-Meier curves for men with and without nocturia at baseline (1994) – Study IV.



Number at risk			
≤2 times/night	1 281	1 039	829
≥3 times/night	51	37	18

In the regression analysis, a significant interaction was found between smoking and urgency (p=0.02), likewise between previously diagnosed cardiac disease and urgency (p=0.04). The effect of urgency was suggestively stronger among non-smokers than smokers (HR 1.46, 1.12–1.91 vs. 0.73, 0.45–1.20) and among those without a diagnosed cardiac disease compared to those with a diagnosis (HR 1.30, 0.95–1.79 vs. 1.04, 0.73–1.48) (Table 9). The effects of daytime frequency and nocturia showed no significant differences between any subgroups (Appendix 27).

Table 9. Unadjusted and adjusted association analyses for variables with significant interaction in the regression models: association of urinary urgency with mortality among smoking and non-smoking men and among men with and without previously diagnosed cardiac disease – Study IV.

	Unadjusted		Adjusted [a]	
	HR	**95% CI**	**HR**	**95% CI**
Current smoking				
Yes	0.95	0.60-1.51	0.73	0.45-1.20
No	2.09	1.61-2.71	1.46	1.12-1.91
Cardiac disease				
Yes	1.20	0.86-1.69	1.04	0.73-1.48
No	2.11	1.55-2.86	1.30	0.95-1.79

[a] A regression model including the year of birth and following categorical variables with time-varying values: LUTS, marital status, BMI, smoking, alcohol consumption, diabetes, hypertension, cardiac disease, pulmonary disease, cerebrovascular disease, neurological disease and cancer. "Last observation carried forward" method (Little & Rubin 2002) used for comorbidities with missing values in the follow-up rounds.

6 DISCUSSION

6.1 Summary

In this thesis, we summarised the incidence and remission of nocturia among community-dwelling people using data from five low and eight high risk of bias studies. Across all available studies, the pooled incidence of nocturia was 0.4% per year among adults aged <40 years, 2.8% among those aged 40–59 years and 11.5% among those aged 60 years or more, while the overall pooled remission rate was 12.1% per year. Estimates, however, varied considerably among studies. While incidence did not depend on nocturia case definition, remission was more common in cases of more frequent nocturia episodes: 6.7% per year for 1 void/night, 15.5% for 2 voids/night, and 22.3% for 3 voids/night. Estimates did not differ between genders, length of follow-up or study risk of bias.

We also summarised the relative death risk associated with nocturia among community-dwelling people using data from two low and nine high risk of bias studies and found a 27% increase in relative risk of death in adults with nocturia (defined as either ≥2 or ≥3 voids/night) compared to those without nocturia after adjusting for age, gender and various comorbidities. This corresponds to a nocturia-associated increase in the overall five-year absolute death risk of 1.6% among those aged 60 years and 4.0% among those aged 75 years. The magnitude of the association did not differ across a number of predictor variables.

We further summarised the relative risks of falls and fractures associated with nocturia among community-dwelling people using data from two low and three high risk of bias studies and found an excess relative risk of 20% for falling at least once, and an excess relative risk of 38% for falling recurrently during follow-up in people with nocturia compared to those without nocturia at baseline. The 20% relative risk increase corresponds to a nocturia-associated increase in the absolute annual risk of falling by 5.5% among people aged 65 years and by 7.5% among people aged 80 years. Similarly, from one low and four high risk of bias studies we found a possible increased relative risk of fracture of 32% in people with nocturia compared to people without nocturia after adjusting for age, gender and various comorbidities. The absolute risk of fractures was 0.9% higher in people with nocturia than in people

without nocturia among those aged 65 years, and 1.2% higher among those aged 80 years.

Finally, we examined the association of three common urinary storage symptoms – daytime frequency, nocturia and urgency – with mortality in a population-based cohort of middle-aged and elderly Finnish men. In the course of a follow-up of 21 years, we observed a 1.4-fold increased risk of death in men with daytime frequency and nocturia, even after adjustments for behavioural risk factors and comorbidities. However, the associations were established only in analyses where the symptoms and comorbidities were updated every five years, whereas the sensitivity analyses with fixed baseline characteristics did not show any significant association between the symptoms assessed and mortality.

6.2 Strengths

The strengths of this thesis include the utilisation of robust methods to provide the best available evidence on the natural course of nocturia and associated risks of falls, fractures and mortality. Besides that the data are of importance as the world population is rapidly ageing, the work provides innovative approaches for future systematic reviews and meta-analyses, as well as longitudinal association studies of LUTS.

To the best of our knowledge, the systematic reviews included in the thesis (Studies I-III) provide, to date, the most comprehensive estimates of the natural course of nocturia and of the associated risks of morbidity and mortality. To facilitate communication between patients and healthcare providers as well knowledge translation of the information, we provided absolute effects in addition to relative estimates of the associations of nocturia with falls, fractures and mortality. For this purpose, we also meta-analysed the prevalence of nocturia; this information is likely of interest itself to many researchers, clinicians, patients and other stakeholders, see Appendix 6. The reviews involved a contemporary and comprehensive search of both published and unpublished studies without language restrictions, the duplicate assessment of eligibility and data extraction, and the appraisal of risk of bias. We used appropriate statistical methods to generate pooled estimates, followed a pre-specified data analysis plan, and employed a limited number of important and plausible hypotheses to explore potential determinants of heterogeneity. We applied and further refined novel approaches to risk of bias assessment (Tikkinen et al. 2012), and successfully contacted many authors for clarifications and additional data.

Finally, we appraised the quality of evidence using the GRADE approach for inferences regarding nocturia both as a prognostic factor and as a causal factor for falls, fractures and mortality.

The original population-based study included in the thesis, TAMUS (Study IV), provides two important improvements on earlier longitudinal association studies exploring LUTS and mortality. Firstly, we are not aware of any former study utilising repeated assessments and thus taking into account the fluctuation and development of symptoms and comorbidities during follow-up. Secondly, our follow-up is longer than in any study so far on the topic and covers more than 500 deaths (including >70 deaths among men with each of the LUTS examined).

6.3 Limitations

Although the estimates presented in the thesis for the course and consequences nocturia are among the most accurate to date and well-applicable as a reference for clinical interpretation, the work inevitably involves several limitations. The weaknesses of the eligible studies account for the majority of the limitations of the three systematic reviews (Studies I-III). Although we excluded all studies examining the effect of any intervention, all reviews did include some people receiving interventions and therefore, are somewhat limited as not entirely representing the "natural" history. In all systematic reviews, none of the included studies was free of risk of bias and limitations related to non-representativeness of source populations, inaccuracy in assessments of nocturia, falls, fractures and mortality, missing data and inadequately adjusted analyses were common. Furthermore, our appraisals of risk of bias should be interpreted cautiously due to limited testing of the instruments.

In prospective studies of nocturia, it is challenging to determine the most appropriate follow-up time for measurements of patient-important incidence and remission of nocturia in order to differentiate between short-term fluctuating and longer-term patient-important symptoms. Although we chose to include studies with a follow-up of three months or more, we found no eligible study with follow-up of less than six months. The variation in follow-up times makes comparison of estimates challenging because of the fluctuating nature of nocturia (Vaughan et al. 2013, Yoshimura & Terai 2005). Accordingly, pooling the measures from studies with follow-up times varying from six months to 16 years inevitably involves some approximation, especially when trying to estimate average annual incidence and

remission (Study I) but also in cases of longitudinal association studies if repeated assessments in the course of follow-up are unavailable (Studies II and III).

The paucity of age- and gender-stratified measures limits the comparability of the estimates on the incidence and remission of nocturia (Study I). Similarly, the lack of age- and gender-specific estimates in the elderly age groups leads to approximation when estimating the risks of falls, fractures and mortality in elderly population (Studies II and III). To rule out the temporary effects of pregnancy on the lower urinary tract, diuresis and sleep, as well as frequent nightly awakenings in the post-partum period due to various reasons, such as baby care (Lose et al. 2001, Moline et al. 2003, Tikkinen et al. 2008), we excluded studies with baseline LUTS assessed either during pregnancy or in the first post-partum year.

Due to an uneven global distribution of studies, we were unable to explore the plausible regional differences between the estimates. Respectively, for the meta-analysis of incidence of nocturia (Study I), we included 12 studies of which seven were conducted in Europe, two in East Asia, and three in North America. Similarly, for the meta-analysis of remission of nocturia (Study I), we included 12 studies of which seven studies were conducted in Europe, three in East Asia and two in North America. While none of the European studies on nocturia incidence or remission included older women or younger men, and none of the North American studies provided age-stratified estimates for younger people, the reliability of comparing the estimates by study region was compromised. Similarly, while the majority of the studies included in the systematic reviews exploring the associations of nocturia were conducted in Western populations (8 out of 10 studies of mortality, 8 out of 9 studies of falls/fractures) the pooled estimates were considered valid for application to Western populations only, albeit with approximation (Figs. 10 & 14).

Another limitation is the lack of frequency volume charts (FVC) in most of the reports included. According to the guidelines, FVC (or bladder diary) is a mandatory tool in clinical practice when evaluating patients with nocturia in order to differentiate between the various causes of nocturia, such as nocturnal polyuria (Hashim et al. 2019). However, according to a recent meta-analysis, the association of nocturnal polyuria with nocturia appears to be less obvious than usually thought (Hofmeester et al. 2014).

Although questionnaires are susceptible to recall bias as they rely on the respondent's memory, in earlier studies, increasing accuracy of questionnaires (in relation to FVC or bladder diary) has been found among those with fewer nocturia episodes (Jaffe et al. 2002, Yoshimura & Terai 2005). Therefore, our pooled estimates with pre-defined case definitions ($\geq$1, $\geq$2, or $\geq$3 voids/night) are less likely

to suffer from recall bias. FVCs also have limitations. First, if used at population level, the studies using FVCs are likely to suffer from low response rates (as FVCs are burdensome to record). For instance, in the only study included (van Doorn et al. 2011), of the 3398 men invited, 1225 completed FVC and 1122 were included in the baseline population. After 2.1 years of follow-up, FVCs were available for 692 individuals. Secondly, questionnaires assess the typical frequency over a longer time period retrospectively, whereas voiding FVCs typically assess one, two, or three nights prospectively. Hence, the studies compare two different time periods. The nights during FVC may not have been typical. Finally, participating in a prospective FVC evaluation may alter voiding habits (bladder training effect) (Tikkinen 2010).

Although the analyses in the systematic reviews of the associations of nocturia (Studies II & III) showed no effect for nocturia case definition, only three studies of mortality and two studies of falls and fractures provided estimates for nocturia as a discrete variable with multiple values (number of voids), limiting our analyses to test for an exposure-response relationship between nocturia and the outcomes.

Regarding the specific limitations of the systematic review of the association between nocturia and mortality (Study II), none of the studies included addressed causes of death and none of the studies utilised more sophisticated analytical techniques, such as structural equation modelling, to identify potential causal pathways between nocturia and mortality (Bielby & Hauser 1977). However, the establishment of a relationship between a risk/causal factor and mortality does not necessarily require addressing all the specific causes of death as this is a different question. Nevertheless, when causation is an issue and one has only observational evidence, it is reasonable to attempt such inferences – and indeed investigators do so frequently at the risk of making extravagant claims of causal effects (e.g. World Health Organization claims about red meat and cancer) (Bouvard et al. 2015).

There was also a paucity of studies assessing sleep disorders as potential comorbid conditions with nocturia and thus, we were unable to differentiate between the roles of insomnia symptoms as potential confounders vs. mediators for mortality (nocturia caused by primary insomnia vs. insomnia secondary to nocturia) (Ancoli-Israel et al. 2011). Given that, especially among the older people, nocturia is one of the leading causes of sleep disruption, which has further been shown to prognosticate mortality, analyses to test effect modification by sleep disorders would be relevant (Cappuccio et al. 2010, Da Silva et al. 2016). Accordingly, in the two available studies exploring the role of sleep disruption as one of the potential mediators between nocturia and mortality, both conducted in Western male populations and one of them excluded from our review due to being an interventional study (a randomised trial of 5α-

reductase inhibitor, dutasteride, for prostate cancer chemoprevention), the association between nocturia and mortality turned non-significant after controlling the estimates for sleep disorders and other comorbidities (Endeshaw et al. 2016, Bliwise et al. 2019).

One specific limitation of the systematic review of the association between nocturia and falls/fractures (Study III) was the small numbers of events, resulting in somewhat wide confidence intervals around the estimates. Because the majority of studies were at high risk of bias, quality ratings were low for prognosis of fractures and very low for causation for both falls and fractures (indeed no data are available on whether successful treatment of nocturia prevents falls or fractures, evidence that would be required to be confident about a causal relationship).

Regarding the limitations of TAMUS (Study II), the nocturia question in DAN-PSS-1 does not distinguish between one void and two voids per night. Of the response options of DAN-PSS-1, one or two voids/night was considered unlikely to distinguish meaningful nocturia and thus, ≥3 voids/night was considered a more robust indicator of important nocturia. Furthermore, although the incidence of nocturia is independent of nocturia case definition (≥1, ≥2 or ≥3 voids/night) according to our meta-analysis (Study I), remission frequency increases with more stringent criteria and accordingly, due to a more stringent case definition in our analyses, remission over time is more likely and repeated assessments are therefore crucial.

Due to the relatively small number of deaths related to specific symptoms, our study did not have adequate statistical power to analyse the impact of multiple LUTS in combination. However, earlier findings suggest that storage symptoms frequently overlap and various LUTS often occur in combination (Tikkinen et al. 2007, Sexton et al. 2009). Furthermore, we were unable to assess the effect of treatments of LUTS on death. However, according to earlier studies, only a minority of men seek treatment for their LUTS (Sexton et al. 2009, Chong et al. 2012) and response to treatment may be unsatisfactory, particularly for storage symptoms (Taylor et al. 2007, Han et al. 2014, Michel & De La Rosette 2005). Finally, some residual confounding is likely present in spite of extensive adjustments of the estimates with various medical conditions and lifestyle factors

6.4 Nocturia as a cause vs. as a risk factor

Although randomised trials provide estimates of treatment effect with the lowest risk of bias, the populations enrolled are likely to differ from general populations in a variety of ways, making application to general populations limited (van Spall et al. 2007). Hence, in order to explore the natural course of nocturia and associated risks, we chose to provide estimates from observational studies of unselected patients; such studies are likely to be the best source of estimates of prognosis (Iorio et al. 2015).

While nocturia is arguably more of a symptom than a disease, its applicability to the GRADE framework on prognosis can be justified by the synonymous use of the terms "risk factor" and "prognostic factor". Some authors use prognosis as predicting outcome in individuals who already have a target condition (for instance, the prognosis in people with cancer), and distinguish this from risk as predicting outcome in those without a target condition (Guyatt et al. 2008a). Using the language in this way we are addressing risk and not prognosis. In this example, nocturia can be a marker of having other risk factors for falls, fractures and mortality. To state the distinction in terms of the topic of this thesis: if one has already had a fracture, one might talk about the prognosis regarding a second fracture. If one has not had a fracture, one would not talk about prognosis but rather risk of having a fracture. However, in this thesis, we have not made this distinction and use "risk factor" and "prognostic factor" synonymously.

The association between nocturia and mortality likely reflects chronic illness as a cause of both nocturia and mortality. For instance, it is not difficult to imagine how diabetes could cause both nocturia and premature death. It is less likely, but still possible, that nocturia is on the causal pathway leading to premature death. For instance, impaired sleep as a result of nocturia could impair physiological nighttime blood pressure dipping, increase sympathetic activity (Obayashi et al. 2015), and thus increase cardiovascular deaths. In addition, fractures and other injuries may result from falls or other accidents related to frequent nighttime toileting and daytime fatigue, and complications of these events could result in premature death. These causal pathways are, however, speculative as one should be very cautious about making causal inferences from observational studies.

The relationship between nocturia and all-cause mortality is somewhat comparable to the association between smoking and all-cause mortality where exposure is causal through multiple mechanisms (CVD, COPD, cancer etc.). However, whereas a robust causality between smoking and all-cause mortality has

been established from observational studies with an indication of large effect and a dose-response relationship (Reitsma et al. 2017), the magnitude of the association between nocturia and mortality is small, and there is no evidence of a dose-response relationship. Therefore, we can only speculate on mediating comorbidities such as falls, fractures and cardiovascular outcomes as a result of sleep disturbance.

An important message of the thesis is that one can address two different questions: is there a true association between nocturia and mortality, falls or fractures, and does nocturia cause increase in deaths, falls or fractures? Accordingly, while the evidence is moderate for the association between nocturia and mortality, moderate for the association between nocturia and falls, and low for the association between nocturia and fractures, the evidence is only very low for causation (Tables 4 & 6).

6.5 Implications of the findings

The pooled estimates of all available observational cohort studies highlight the burden of nocturia among older men and women compared with that in younger adults. Those aged over 60 years were nearly four times more likely to develop nocturia than were adults aged 40–59 years. Also, while one out of every eight persons with nocturia reported remission annually, for clinicians and patients, nocturia remains a challenging condition to treat (Marshall et al. 2015, Drake 2015).

Remission of nocturia was more common in people with more frequent nightly episodes, with more than one out of five persons with three or more nightly episodes experiencing resolution to two or less episodes at follow-up. The hypothetical mechanisms explaining spontaneous resolution of nocturia include fluctuations in the functional bladder capacity, diuresis and sleep, possibly reflecting variation in individuals' general health status and lifestyle factors. Therefore, in addition to plasticity in the function and morphology of the lower urinary tract with age, a higher tendency of spontaneous resolution suggests presence of various modifiable risk factors in people with more frequent nocturia episodes. Finally, a portion of the fluctuation noted in nocturia in these analyses may represent regression to the mean (Bland & Altman 1994).

Although nocturia is a very common symptom at a population-level, the majority of people with nocturia do not report moderate or major bother from it. 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, Tikkinen 2010) and can lead to medical over-use. Risks of overdiagnosis and disease mongering should be kept in mind when creating guidelines. Individual healthcare providers should focus on patients with bothersome nocturia.

The findings of the population-based TAMUS study suggest aiming for repeated assessments when designing long-term prospective studies of male LUTS-associated outcomes, including mortality. Due to the fluctuating nature of symptoms (Vaughan et al. 2014), repeated assessments are probably more reliable than fixed baseline assessments in the detection of patient-important and persistent symptoms, often associated with ill health. We found an indication of a 1.4-fold increased risk of death in Finnish men presenting with nocturia.

Due to challenges related to treatments, nocturia may warrant more attention as a separate clinical entity. According to all available observational cohort studies conducted predominantly in middle-aged and older people, we found a probable 1.3-fold increased risk of premature death associated with nocturia. Similarly, according to all available cohort studies conducted predominantly in older people, we found a probable 1.2-fold increased risk of falls, and a possible 1.3-fold increased risk of fractures associated with nocturia. Clinicians and patients should be aware that nocturia occurring at least twice per night may be a marker of ill health and lead, via a number of potential pathways, to premature death. Especially in the cases of elderly patients with early signs of frailty, the increased risks of falls and fractures may suggest considering occupational therapy assessment of their home environment if the patient also reports two or more episodes of nocturia.

Although urological treatments have the potential to improve the quality of life of patients with nocturia, clinicians should focus not only on treating the symptom, but also on exploring patients' general health taking into account the relevant risk factors for each individual (Oelke et al. 2016, Sakalis et al. 2017). Especially when managing older adults reporting nocturia, the treatment requires understanding of the multifactorial aetiology of nocturia. At its worst, medical treatment of nocturia by manipulating diuresis, sleep or lower urinary tract function, may cause more harm than good, especially in the case of frail elderly subjects (Vaughan et al. 2016, Chrischilles et al. 2001, Welk et al. 2015). Along with the ageing of populations worldwide and the well-recognised negative health impact of frequent nocturia (Tikkinen et al. 2010, Zhang et al. 2015, Han et al. 2017) development of well-tolerated novel treatment strategies remains a research priority.

Randomised trials on the impact of nocturia treatment have mostly examined only a few nocturia-related short-term outcomes such as QoL and sleep, while long-term data on nocturia-related morbidity is lacking (Cornu et al. 2012, Shigehara et al. 2017). As evidence of nocturia as a causal factor for mortality seems to be lacking, the potential mediators of mortality, such as falls and cardiovascular events, could be included as outcomes in randomised trials of nocturia management, with sufficiently long follow-up to detect these outcomes and even the mortality related to them.

7 CONCLUSIONS

The evidence available suggests that nocturia onset is strongly associated with age, with much higher rates in those over 60 years while remission occurs in approximately 12% each year. Moderate-quality evidence suggests that nocturia is associated with a 1.2-fold risk for falls and low-quality evidence suggests that nocturia is associated with a 1.3-fold risk for fractures. Furthermore, moderate quality evidence suggests that nocturia is associated with a 1.3-fold risk of death.

The estimates, presented in the thesis, can aid with management decisions and counselling related to nocturia and associated comorbidities. This work provides two core messages for clinical practice and future research: first, in patients with nocturia the underlying health conditions warrant increased attention. Second, future investigations should address the impact of treatment for nocturia on falls and fractures with an adequately long follow-up to detect further morbidity and mortality.

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10 APPENDICES

Appendix 1. Search strategies – Studies I-III.

Database: PubMed
Search strategy:

nocturia OR nycturia OR ((noctur* OR night*) AND (pollakiuria OR void* OR urination OR micturition OR polyuria OR "LUTS" OR "lower urinary tract symptoms" OR "BPH" OR "benign prostatic hyperplasia")) OR "night* frequency" OR "nocturnal frequency" AND (longitudinal OR "natural history" OR cohort OR incidence OR remission OR progression OR prospective OR "community-based" OR "population-based" OR epidemiol* OR "follow-up")

Database: Scopus
Search strategy:

TITLE-ABS-KEY (nocturia OR nycturia OR ((noctur* OR night*) AND (pollakiuria OR void* OR urination OR micturition OR polyuria OR "LUTS" OR "lower urinary tract symptoms" OR "BPH" OR "benign prostatic hyperplasia")) OR "night* frequency" OR "nocturnal frequency" AND (longitudinal OR "natural history" OR cohort OR incidence OR remission OR progression OR prospective OR "community-based" OR "population-based" OR epidemiol* OR "follow-up"))

Database: Cumulative Index to Nursing and Allied Health Literature (CINAHL)
Search strategy:

S8 S6 and S7
S7 S1 or S3 or S5
S6 ((MH "Prospective Studies+") OR prospective OR longitudinal OR (MH "Incidence") OR incidence OR (MH "Disease Remission") OR remission OR (MH "Disease Progression") OR progression OR (MH "Epidemiology+") OR epidemiol* OR "natural history" OR "community-based" OR "population-based" OR cohort OR "follow-up")
S5 S2 and S4
S4 (pollakiuria OR void* OR urination OR micturition OR polyuria OR "LUTS" OR "lower urinary tract symptoms" OR (MH "Prostatic Hypertrophy") OR "benign prostatic hyperplasia" OR "BPH")
S3 ("night* frequency" OR "nocturnal frequency")
S2 noctur* OR night*
S1 nocturia OR nycturia

Database: Abstracts published in the annual meetings of the American Urological Association (AUA), European Association of Urology (EAU), International Continence Society (ICS) and International Urogynecological Association (IUGA) from years 2005-2017
Search Strategy:

night* OR noctur* OR nycturia

Appendix 2. Tool to assess risk of bias in longitudinal symptom research studies aimed at the general population – Study I.

1. Is the source population (sampling frame) representative of the general population?

Definitely yes	Probably yes	Probably no	Definitely no
(low risk of bias)			(high risk of bias)

Examples of **low risk of bias**: Selection of target population from a representative population roster such as national population registry with a response proportion more than 50% at baseline and missing data in the key characteristics within questionnaires less than 20%. Provincial or single community-based study with a response proportion more than 75% at baseline and missing data within questionnaires less than 10%.

Examples of **high risk of bias**: Selection of target population from a representative population roster such as national or provincial population registry with a response proportion less than 50% at baseline or missing data in the key characteristics within questionnaires more than 20%. All hospital-based patient records; studies where the source population cannot be defined (or enumerated), i.e. any volunteer studies using self-recruitment (including health screening studies).

2. Is the assessment of the outcome accurate both at baseline and at follow-up?

Definitely yes	Probably yes	Probably no	Definitely no
(low risk of bias)			(high risk of bias)

Examples of **low risk of bias**: Repeated interview or other ascertainment asking about current state with validated instrument or method (with demonstrated validity) with a clearly specified time window for the assessment (for time-dependent conditions).

Examples of **high risk of bias**: Unvalidated instrument or method with concern of accuracy of responses; Uncertain how information was obtained; Studies with non-standardised clinical interviews (including physicians' unstructured assessment of symptoms); Studies, which assessed primary outcome as "physician-diagnosed condition"; Simple assessment of the presence (or absence) of the symptom(s) without making an effort to quantify the severity/extent; Use of different instruments at different time points with concern of accuracy of responses; Not clearly specified time window for the assessment (for time-dependent conditions).

3. Is there little missing data in the follow-up?

Definitely yes	Probably yes	Probably no	Definitely no
(low risk of bias)			(high risk of bias)

Examples of **low risk of bias**: High response proportion (rate) at follow-up with little missing data (in the key characteristics): response proportion was more than 75% and missing data in the key characteristics within questionnaires less than 10%.

Examples of **high risk of bias**: Low response proportion at follow-up with high level of missing data: response proportion was <50% and missing data in the key characteristics within questionnaires more than 20%.

Appendix 3. Tool to assess risk of bias in longitudinal research studies with a nocturia population aimed at measuring mortality – Study II.

1. Is the source population (sampling frame) representative of the general population?

Definitely yes (low risk of bias)	Probably yes	Probably no	Definitely no (high risk of bias)

Examples of **low risk of bias**: Selection of target population from a representative population roster such as a hospital or healthcare registry with a response proportion more than 50% at baseline and missing data in the key characteristics within questionnaires less than 20%.

Examples of **high risk of bias**: Selection of target population from a representative population roster such as a hospital registry with a response proportion less than 50% at baseline or missing data in the key characteristics within questionnaires more than 20%.

2. Is the assessment of nocturia at baseline accurate?

Definitely yes (low risk of bias)	Probably yes	Probably no	Definitely no (high risk of bias)

Examples of **low risk of bias**: Validated instrument or methods with an assessment of nocturia at baseline with a clear quantification and definition of nocturia.

Examples of **high risk of bias**: Invalidated instrument or method with concern of accuracy of responses; Uncertain how information was obtained; Simple assessment of the presence (or absence) of the symptom(s) without making an effort to quantify the severity/extent.

3. Is the assessment of mortality accurate during follow-up?

Definitely yes (low risk of bias)	Probably yes	Probably no	Definitely no (high risk of bias)

Examples of **low risk of bias**: Data collection has been conducted by a registry or hospital records; Data collection relies on a passive method (e.g. not by patient´s peers) and depends on a registry.

Examples of **high risk of bias**: Data collection depended on the reporting of patient´s relatives or peers.

4. Is there little missing data in the follow-up?

Definitely yes (low risk of bias)	Probably yes	Probably no	Definitely no (high risk of bias)

Examples of **low risk of bias**: High response proportion (rate) at follow-up with little missing data (in the key characteristics): response proportion was more than 95% and missing data in the key characteristics within questionnaires less than 10%.

Examples of **high risk of bias**: Low response proportion at follow-up with high level of missing data: response proportion was less than 90% and missing data in the key characteristics within questionnaires more than 10%.

5. Did the statistical analysis adjust for all important prognostic variables?

Definitely yes (low risk of bias)	Mostly yes	Mostly no	Definitely no (high risk of bias)

Examples of **low risk of bias**: adjustment for at least age, gender, smoking and comorbidity.

Examples of **high risk of bias**: failure of adjustment for one or more of age, gender, smoking and comorbidity.

Appendix 4. Tool to assess risk of bias in longitudinal research studies with a nocturia population aimed at measuring falls/fractures – Study III.

1. Is the source population (sampling frame) representative of the general population?

Definitely yes	Probably yes	Probably no	Definitely no
(low risk of bias)			(high risk of bias)

Examples of **low risk of bias**: Selection of target population from a representative population roster such as a hospital or healthcare registry with a response proportion more than 50% at baseline and missing data in the key characteristics within questionnaires less than 20%.

Examples of **high risk of bias**: Selection of target population from a representative population roster such as a hospital registry with a response proportion less than 50% at baseline or missing data in the key characteristics within questionnaires more than 20%.

2. Is the assessment of nocturia at baseline accurate?

Definitely yes	Probably yes	Probably no	Definitely no
(low risk of bias)			(high risk of bias)

Examples of **low risk of bias**: Validated instrument or methods with an assessment of nocturia at baseline with a clear quantification and definition of nocturia.

Examples of **high risk of bias**: Invalidated instrument or method with concern of accuracy of responses; Uncertain how information was obtained; Simple assessment of the presence (or absence) of the symptom(s) without making an effort to quantify the severity/extent.

3.a) Is the assessment of falls accurate during follow-up?

Definitely yes	Probably yes	Probably no	Definitely no
(low risk of bias)			(high risk of bias)

Examples of **low risk of bias**: prospective falls diary for falls that has been filled in by the patient.

Examples of **high risk of bias**: depending on the memory of patients (or peers) for retrospective evaluation of their falls.

3.b) Is the assessment of fractures accurate during follow-up?

Definitely yes	Probably yes	Probably no	Definitely no
(low risk of bias)			(high risk of bias)

Examples of **low risk of bias**: medical records or national / hospital registries for fractures.

Examples of **high risk of bias**: depending on the memory of patients (or peers) for retrospective evaluation of their fractures.

4. Is there little missing data in the follow-up?

Definitely yes	Probably yes	Probably no	Definitely no

(low risk of bias) (high risk of bias)
Examples of **low risk of bias**: High response proportion (rate) at follow-up with little missing data (in the key characteristics): response proportion was more than 95% and missing data in the key characteristics within questionnaires less than 10%.

Examples of **high risk of bias**: Low response proportion at follow-up with high level of missing data: response proportion was less than 90% and missing data in the key characteristics within questionnaires more than 10%.

5.a) Did the statistical analysis adjust for all important prognostic variables for falls?
Definitely yes Mostly yes Mostly no Definitely no
(low risk of bias) (high risk of bias)

Examples of **low risk of bias**: adjustment for at least age, gender, history of recent falls and comorbidity.

Examples of **high risk of bias**: failure of adjustment for one or more of age, gender, history of recent falls and comorbidity.

5.b) Did the statistical analysis adjust for all important prognostic variables for fractures?
Definitely yes Mostly yes Mostly no Definitely no
(low risk of bias) (high risk of bias)

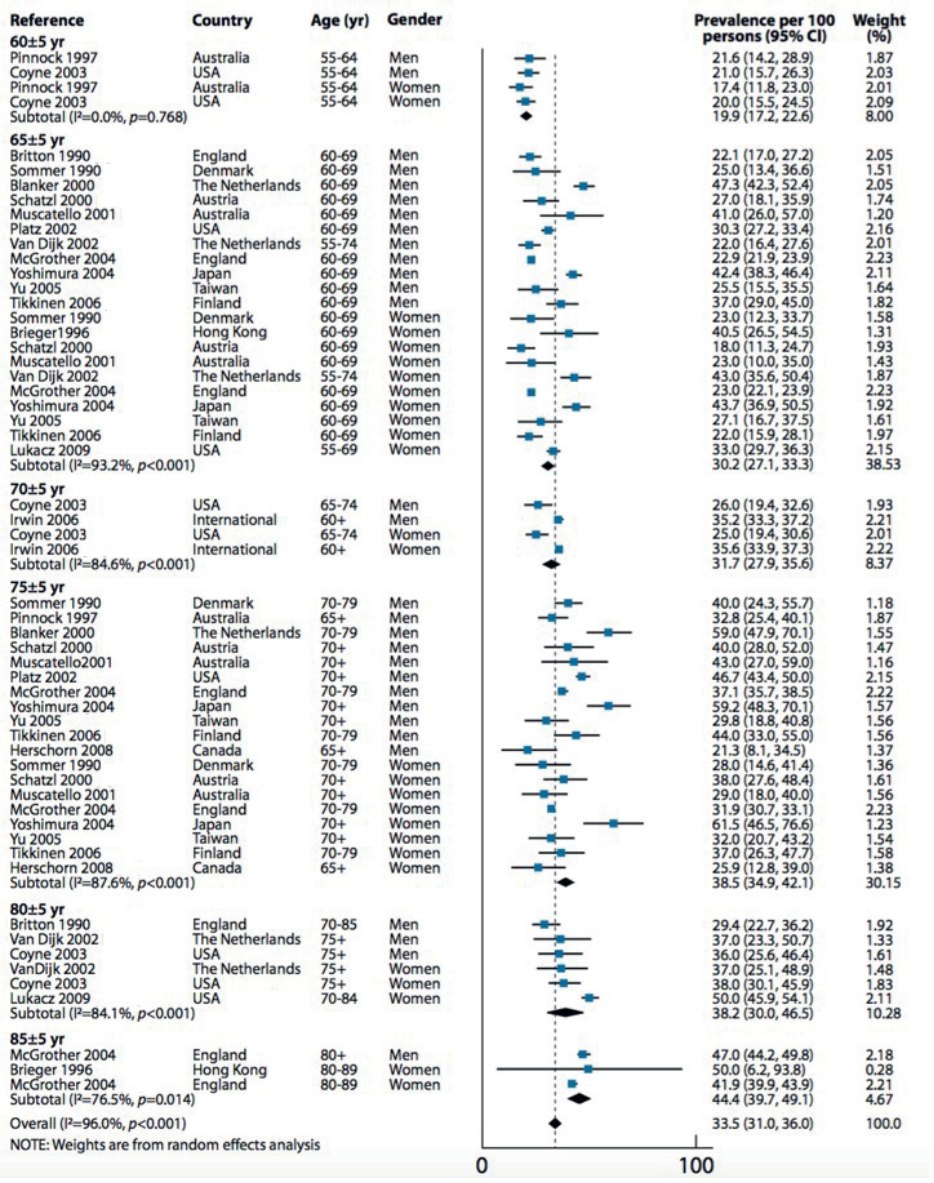
Examples of **low risk of bias**: adjustment for at least age, gender, history of recent falls and any factor indicating osteoporosis based on either diagnostic testing, history of recent fractures or comorbidity with a strong association.

Examples of **high risk of bias**: adjustment for at least age, gender, history of recent falls and any factor indicating osteoporosis.

Appendix 5. Further information on simple versus actuarial cumulative incidence/remission methodology – Study I.

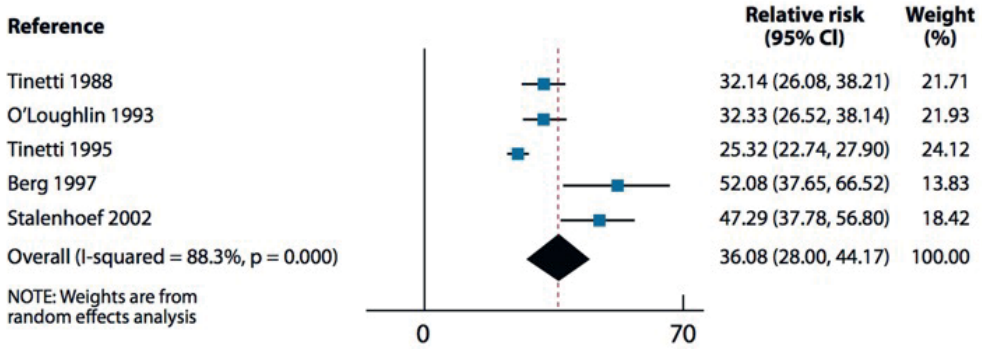
In calculating the person-years for incidence and remission rates the simple cumulative method was considered to be equally appropriate with the actuarial cumulative method. In the latter, the assumption is that the symptom was developed at a half-way point between follow-ups when it is not known exactly when a person develops the symptom in question. However, in the case of fluctuating symptom such as nocturia where short-term incidence and remission is remarkably high, the cumulative incidence and remission at the end of each follow-up is actually the net effect resulting from a symptom becoming incident and remittent in turns. There were only slight differences in the pooled estimates calculated with both methods: simple vs. actuarial cumulative incidence 49.4 (41.3-57.5) vs. 55.8 (46.6-65.0) per 1000 person-years, simple vs. actuarial cumulative remission 121.3 (95.2-147.4) vs. 154.5 (122.8-186.3.0) per 1000 person-years.

Appendix 6. Forest plot of prevalence of nocturia in population-based samples including people aged ≥60 yr and using a nocturia case definition of ≥2 voids/night – Studies II &III.



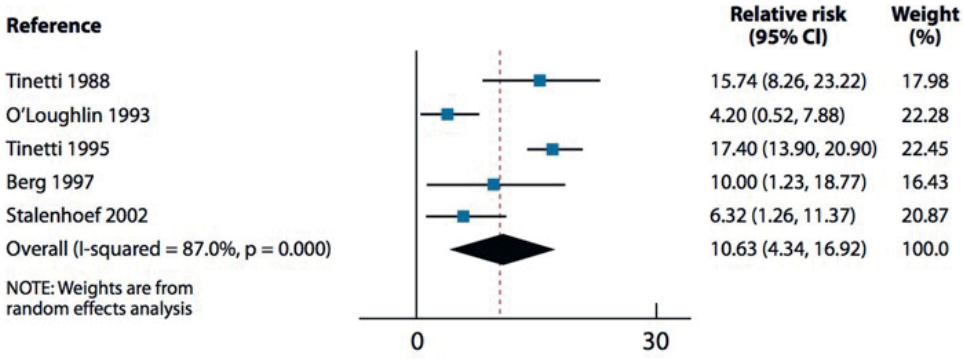
Note: mean age ranges are overlapping due to unavailability of reported mean ages in cases of several studies. Therefore, by relying on an assumption of samples complying with normal age distribution, subgroups of studies were placed under age categories by selecting the mean age range with a midpoint closest to the estimated mean age of each sample.

Appendix 7. Forest plot of incidence rates of fallers per 100 person-years of follow-up in prospective Western population-based studies – Study III.



Note: The studies presented in the figure, providing data on the annual number of fallers (persons with ≥1 falls/year) and resulting fractures were extracted from a previous systematic review (Figure 5 of Morrison et al. 2013). To avoid potential selection bias, a study including only previous fallers was excluded from the analyses (Nevitt et al. 1989).

Appendix 8. Forest plot of proportion of individuals with a fall-related fracture per 100 fallers in prospective Western population-based studies – Study III.



Note: The studies presented in the figure, providing data on the annual number of fallers (persons with ≥1 falls/year) and resulting fractures were extracted from a previous systematic review (Figure 5 of Morrison et al. 2013). To avoid potential selection bias, a study including only previous fallers was excluded from the analyses (Nevitt et al. 1989).

Appendix 9. Questionnaire of the Tampere Ageing Male Urologic Study (TAMUS) in 2009 – Study IV.

MIESTEN UROLOGISET OIREET
KYSELYLOMAKE OSA I Päivämäärä vastaushetkellä: / **2009**

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

1 **HENKILÖTIEDOT**

SYNTYMÄAIKA / / 19
päivä kuukausi vuosi

2 **AMMATTI**

0 Olen työelämässä ja ammattini on (kirjoittakaa ruutuun)

1 Olen eläkkeellä, ammattini oli

2 Olen työttömänä, ammattini on

3 **KOULUTUS**

0 Kansakoulu

1 Ammattikoulu tai vastaava

2 Opistotutkinto

3 Yliopisto- tai korkeakoulututkinto

4 **SIVIILISÄÄTY**

0 Naimisissa tai avoliitossa
1 Eronnut Vuonna _____
2 Leski Vuodesta _____
3 Naimaton

5 **TERVEYS**

Viimeisen viiden vuoden aikana terveyteni on

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

6 **PITUUS JA PAINO**

Pituuteni on [cm] Painoni on [kg]

7 **TUPAKOINTI**

Tupakoitteko nykyään tai oletteko koskaan tupakoinut säännöllisesti?
Tupakoinnilla tarkoitetaan savukkeiden, sikarien tai piipun polttoa.

[0] **En**
[1] **Kyllä**
[2] **Olen lopettanut tupakoinnin**

Jos tupakoitte tai olette tupakoineet, vastatkaa vielä seuraaviin kysymyksiin:

Minä vuonna aloititte **säännöllisen** tupakoinnin? Vuonna [ ]
Jos olette lopettanut tupakoinnin, minä vuonna? Vuonna [ ]

Kuinka paljon poltatte **päivittäin** nykyään?
Tai, kuinka paljon poltitte päivittäin ennen lopettamista?

Savukkeita tai pikkusikareja [ ] kpl
Piippua [ ] pesällistä
Sikareja [ ] kpl

8 **MUUT NAUTINTOAINEET**

Juotteko kahvia tai teetä päivittäin?

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

Juotteko alkoholipitoisia juomia?

[3] **En lainkaan.** Voitte siirtyä kysymysryhmään 9.
[4] **Kyllä, satunnaisesti, mutta en joka viikko.**
[5] **Kyllä, viikoittain**
Jos käytätte alkoholia viikoittain, arvioikaa keskimääräinen **viikoittainen** kulutuksenne tässä.

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

9 **SAIRAUDET JA VAMMAT**

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

0 En sairasta, enkä ole sairastanut mitään näistä sairauksista.

1 Sokeritauti
2 Kohonnut verenpaine
3 Sepelvaltimotauti
4 Muu sydänsairaus
5 Nivelkulumia
6 Ummetus
7 Ulosteen pidätyskyvyttömyyttä
8 Keuhkosairaus
9 Neurologinen sairaus, mikä _____
10 Aivoverenkierron häiriö tai halvaus
11 Pikäaikainen selkäkipu
12 Selkäytimen vamma
13 Selkärankareuma
14 Masennus
15 Nivelreuma
16 Maha- tai pohjukkaissuolen haava
17 Korkea veren kolesteroli
18 Uniapnea
19 Syöpä, mikä _____

10 **TUTKIMUKSET JA LEIKKAUKSET**

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

0 Ei mitään tässä luetelluista.

1 Peräsuolen poistoleikkaus
2 Lonkka- tai polviproteesileikkaus
3 Selkäleikkaus
4 Verisuonileikkaus, (koronaariohitus, valtimon pullistuma tai ahtauma tms.)
5 Eturauhasen höyläysleikkaus (TURP)
6 Eturauhasen liikakasvun avoleikkaus
7 Eturauhasen poistoleikkaus syövän vuoksi
8 Virtsarakkoon kohdistunut leikkaus (avoin tai tähystysleikkaus)
9 PSA-verikoe (eturauhassyöpätesti)

11 **MUU HOITO**

Oletteko viimeisen viiden vuoden aikana saanut hoitoa erektiohäiriön vuoksi?

0 **En**
1 **Kyllä**

Jos olette saanut hoitoa, valitkaa tästä saamanne hoito:

2 Tablettihoito Mikä lääke _____
3 Pistoshoito
4 Muu hoito Mikä _____

Oletteko viimeisen viiden vuoden aikana saanut hoitoa miehen vaihdevuosivaivojen (andropaussi) vuoksi?

5 **En**
6 **Kyllä** Mitä hoitoa _____

OSA II

VIRTSAAMINEN JA SUKUPUOLITOIMINNAT:

Tämä kysely koostuu kahdenlaisista kysymyksistä:

A-kysymyksissä kysytään virtsaamioireen esiintymistä tai voimakkuutta.

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

Vastatkaa jokaiseen kysymykseen merkitsemällä rasti sopivan vastausvaihtoehdon kohdalle.

1 A	**Täytyykö virtsaamisen alkamista odottaa?** ☐ Ei koskaan ☐ Harvoin ☐ Usein ☐ Aina	1 B	**Mikäli joudutte odottamaan virtsaamisen alkamista, kuinka paljon siitä on Teille haittaa?** ☐ Ei lainkaan ☐ Vähän ☐ Kohtalaisesti ☐ Hyvin paljon
2 A	**Tuleeko virtsa omasta mielestänne:** ☐ Normaalisti ☐ Heikosti ☐ Hyvin heikosti ☐ Tipoittain	2 B	**Mikäli virtsa tulee heikosti, kuinka paljon siitä on Teille haittaa?** ☐ Ei lainkaan ☐ Vähän ☐ Kohtalaisesti ☐ Hyvin paljon
3 A	**Tuntuuko, että virtsatessanne rakko tyhjenee täysin?** ☐ Kyllä, aina ☐ Usein ☐ Harvoin ☐ Ei koskaan	3 B	**Mikäli tunnette, ettei rakko tyhjene, täysin kuinka paljon siitä on Teille haittaa?** ☐ Ei lainkaan ☐ Vähän ☐ Kohtalaisesti ☐ Hyvin paljon
4 A	**Joudutteko ponnistamaan virtsaamisen aloittamiseksi tai virtsaamisen jatkamiseksi?** ☐ En koskaan ☐ Harvoin ☐ Usein ☐ Aina	4 B	**Mikäli joudutte ponnistelemaan, kuinka paljon siitä on Teille haittaa?** ☐ Ei lainkaan ☐ Vähän ☐ Kohtalaisesti ☐ Hyvin paljon
5 A	**Tippuuko virtsa vielä, vaikka luulitte virtsaamisen loppuneen (jälkitippuminen)?** ☐ Ei koskaan ☐ Kyllä, WC:ssä ☐ Hieman alushousuihin ☐ Runsaasti alushousuihin	5 B	**Mikäli jälkitippumista esiintyy kuinka paljon siitä on Teille haittaa?** ☐ Ei lainkaan ☐ Vähän ☐ Kohtalaisesti ☐ Hyvin paljon
6 A	**Kuinka pitkä on pisin kahden virtsaamisen välinen aika päivällä?** ☐ Yli 3 tuntia ☐ 2-3 tuntia ☐ 1-2 tuntia ☐ Alle tunti	6 B	**Mikäli joudutte virtsaamaan usein, kuinka paljon siitä on Teille haittaa?** ☐ Ei lainkaan ☐ Vähän ☐ Kohtalaisesti ☐ Hyvin paljon
7 A	**Kuinka monta kertaa joudutte virtsaamaan yön aikana?** ☐ 0 kertaa ☐ 1-2 kertaa ☐ 3-4 kertaa ☐ 5 kertaa tai useammin	7 B	**Mikäli joudutte virtsaamaan yöllä, kuinka paljon siitä on Teille haittaa?** ☐ Ei lainkaan ☐ Vähän ☐ Kohtalaisesti ☐ Hyvin paljon
8 A	**Tuleeko Teille äkillinen virtsaamistarve?** ☐ Ei koskaan ☐ Harvoin ☐ Usein ☐ Aina	8 B	**Mikäli Teille tulee äkillinen virtsaamis-tarve, kuinka paljon siitä on Teille haittaa?** ☐ Ei lainkaan ☐ Vähän ☐ Kohtalaisesti ☐ Hyvin paljon

9 A	**Tuleeko virtsaamisen tarve niin voimakkaana että virtsa karkaa ennen kuin ehditte WC:hen?** ☐ Ei koskaan ☐ Harvoin ☐ Usein ☐ Aina	9 B	**Mikäli virtsa karkaa ennen kuin ehditte WC:hen, kuinka paljon siitä on Teille haittaa?** ☐ Ei lainkaan ☐ Vähän ☐ Kohtalaisesti ☐ Hyvin paljon
10 A	**Tunnetteko virtsatessanne kipua tai poltetta?** ☐ En koskaan ☐ Harvoin ☐ Usein ☐ Aina	10 B	**Mikäli virtsatessanne tuntuu kipua tai poltetta, kuinka paljon siitä on Teille haittaa?** ☐ Ei lainkaan ☐ Vähän ☐ Kohtalaisesti ☐ Hyvin paljon
11 A	**Karkaako virtsaa fyysisen ponnistuksen aikana (esim. yskiessänne, aivastaessanne tai nostaessanne)?** ☐ Ei koskaan ☐ Harvoin ☐ Usein ☐ Aina	11 B	**Mikäli virtsaa karkaa fyysisen ponnistuksen aikana, kuinka paljon siitä on Teille haittaa?** ☐ Ei lainkaan ☐ Vähän ☐ Kohtalaisesti ☐ Hyvin paljon
12 A	**Karkaako virtsaa ilman fyysistä ponnistusta ja ilman virtsaustarvetta?** ☐ Ei koskaan ☐ Harvoin ☐ Usein ☐ Aina	12 B	**Mikäli virtsaa karkaa ilman fyysistä ponnistusta ja virtsaustarvetta, kuinka paljon siitä on Teille haittaa?** ☐ Ei lainkaan ☐ Vähän ☐ Kohtalaisesti ☐ Hyvin paljon
13.	**Kuinka usein *viimeksi kuluneen kuukauden aikana olette tavallisimmin joutunut nousemaan virtsalle* mentyänne illalla nukkumaan ja ennen kuin nousitte aamulla ylös?**		☐ En kertaakaan ☐ Kerran yössä ☐ Kaksi kertaa yössä ☐ Kolme kertaa yössä ☐ Neljä kertaa yössä ☐ Viisi kertaa tai useammin yössä
14.	**Onko virtsaamistoiminnoissanne tapahtunut muutos (paraneminen tai huononeminen) viimeksi kuluneen viiden vuoden aikana?** ☐ Ei muutosta ☐ Kyllä, virtsaamiseni on huonontunut Milloin? _____ ☐ Kyllä, virtsaamiseni on parantunut Milloin? _____		
15.	**Kuinka tyytyväinen olette seksielämäänne?**		☐ Erittäin tyytyväinen ☐ Melko tyytyväinen ☐ En tyytyväinen enkä tyytymätön ☐ Melko tyytymätön ☐ Erittäin tyytymätön
16.	**Kuinka monta kertaa keskimäärin olette yhdynnässä kuukauden aikana?**		____ kertaa
17.	**Onko Teillä ollut vaikeuksia saada siitin jäykistymään ennen yhdyntää?**		☐ Ei koskaan ☐ Joskus ☐ Melko usein ☐ Aina, yhdyntä ei onnistu lainkaan
18.	**Onko Teillä ollut vaikeuksia saada siitin pysymään jäykkänä yhdynnän aikana?**		☐ Ei koskaan ☐ Joskus ☐ Melko usein ☐ Aina, yhdyntä ei onnistu lainkaan
19.	**Kuinka usein herätessänne siittimenne on ollut täysin jäykkä?**		☐ Päivittäin ☐ 2-3 kertaa viikossa ☐ Kerran viikossa ☐ Harvemmin kuin kerran viikossa
20.	**Onko erektiokyvyssänne tapahtunut muutos (paraneminen tai huonontuminen) viimeksi kuluneen viiden vuoden aikana?** ☐ Ei muutosta ☐ Kyllä, erektiokykyni on huonontunut Milloin? _____ ☐ Kyllä, erektiokykyni on parantunut Milloin? _____		

1. **Jos Teillä on virtsankarkailua päiväsaikaan, tarvitseeko Teidän vaihtaa vaatteita tai käyttää vaippaa?**

- ☐ Ei, virtsa ei karkaa
- ☐ Kyllä, vaihtaa alushousuja
- ☐ Kyllä, vaihtaa vaatteita
- ☐ Käytän vaippaa (tai tippasuojaa)

2. **Vähennättekö juomistanne virtsaoireiden helpottamiseksi ja voidaksenne tehdä haluamianne asioita?**

- ☐ En koskaan
- ☐ Silloin tällöin
- ☐ Joskus
- ☐ Useimmiten
- ☐ Jatkuvasti

3. **Kuinka paljon kaiken kaikkiaan virtsaoireet vaikuttavat elämäänne?**

- ☐ Ei lainkaan
- ☐ Hieman
- ☐ Jonkin verran
- ☐ Paljon

4. **Kuinka kauan Teillä on ollut haittaavia virtsaoireita?**

- ☐ Alle vuoden, ____ kk
- ☐ Vuodesta kahteen
- ☐ Kahdesta kolmeen vuotta
- ☐ Yli kolme vuotta

5. **Aiheuttavatko virtsavaivat Teille huolia?**

Pyydämme listaamaan mahdolliset huolenne alle

_____
_____
_____
_____
_____
_____
_____

6. **Jos virtsaoireenne jatkuisivat nykyisellään koko loppuelämänne, miltä se Teistä tuntuisi?**

- ☐ Täysin onnelliselta
- ☐ Hyvältä
- ☐ Enimmäkseen tyytyväiseltä
- ☐ Ei hyvältä eikä pahalta
- ☐ Enimmäkseen tyytymättömältä
- ☐ Hyvin onnettomalta
- ☐ Epätoivoiselta

OSA III

YLEISET ELÄMÄNLAATUKYSYMYKSET:

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

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

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

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

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

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

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

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

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

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

OSA IV

A. SUKUPUOLIELÄMÄN HÄIRIÖT:

Seuraavaa kysymyssarjaa arvioimme kahdesta eri näkökulmasta, riippuen mahdollisesta erektiolääkityksestänne. Pyydämme Teitä vastaamaan kahdesti, mikäli käytätte tai olette joskus käyttäneet erektiolääkettä. Jos käytössänne ei ole lainkaan erektiolääkitystä, riittää että vastaatte ainoastaan kohtaan A.

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

A. Siinä tapauksessa, että ette käytä tai ette ole ottaneet lääkettä,

1.	**Millaiseksi arvioitte luottamuksenne siihen, että voitte saavuttaa erektion ja säilyttää sen yhdynnän ajan?**	1 Hyvin vähäiseksi 2 Vähäiseksi 3 Kohtalaiseksi 4 Suureksi 5 Hyvin suureksi
2.	**Kun Teillä oli seksuaalisen kiihottumisen aikana erektioita, kuinka usein ne olivat tarpeeksi kovia yhdyntään?**	0 Ei seksuaalista toimintaa. 1 Ei koskaan tai ei juuri koskaan. 2 Muutaman kerran (harvemmin kuin joka toisella kerralla). 3 Joskus (noin joka toisella kerralla). 4 Useimmiten (useammin kuin joka toisella kerralla). 5 Melkein aina tai aina.
3.	**Kuinka usein pystyitte yhdynnässä ylläpitämään erektion sisään työntymisen jälkeen?**	0 Ei seksuaalista toimintaa. 1 Ei koskaan tai ei juuri koskaan. 2 Muutaman kerran (harvemmin kuin joka toisella kerralla). 3 Joskus (noin joka toisella kerralla). 4 Useimmiten (useammin kuin joka toisella kerralla). 5 Melkein aina tai aina.
4.	**Kuinka vaikeaa Teidän oli säilyttää erektionne yhdynnän loppuun saakka?**	0 En yrittänyt yhdyntää. 1 Äärimmäisen vaikeaa. 2 Hyvin vaikeaa. 3 Vaikeaa 4 Hieman vaikeaa. 5 Ei lainkaan vaikeaa.
5.	**Kun yrititte sukupuoliyhdyntää, kuinka usein saitte siitä tyydytystä?**	0 En yrittänyt yhdyntää. 1 En koskaan tai en juuri koskaan. 2 Muutaman kerran (harvemmin kuin joka toisella kerralla). 3 Joskus (noin joka toisella kerralla). 4 Useimmiten (useammin kuin joka toisella kerralla). 5 Melkein aina tai aina.

B. Siinä tapauksessa, että olette ottaneet lääkkeen,

1.	**Millaiseksi arvioitte luottamuksenne siihen, että voitte saavuttaa erektion ja säilyttää sen yhdynnän ajan?**	1 Hyvin vähäiseksi 2 Vähäiseksi 3 Kohtalaiseksi 4 Suureksi 5 Hyvin suureksi
2.	**Kun Teillä oli seksuaalisen kiihottumisen aikana erektioita, kuinka usein ne olivat tarpeeksi kovia yhdyntään?**	0 Ei seksuaalista toimintaa. 1 Ei koskaan tai ei juuri koskaan. 2 Muutaman kerran (harvemmin kuin joka toisella kerralla). 3 Joskus (noin joka toisella kerralla). 4 Useimmiten (useammin kuin joka toisella kerralla). 5 Melkein aina tai aina.
3.	**Kuinka usein pystyitte yhdynnässä ylläpitämään erektion sisään työntymisen jälkeen?**	0 Ei seksuaalista toimintaa. 1 Ei koskaan tai ei juuri koskaan. 2 Muutaman kerran (harvemmin kuin joka toisella kerralla). 3 Joskus (noin joka toisella kerralla). 4 Useimmiten (useammin kuin joka toisella kerralla). 5 Melkein aina tai aina.
4.	**Kuinka vaikeaa Teidän oli säilyttää erektionne yhdynnän loppuun saakka?**	0 En yrittänyt yhdyntää. 1 Äärimmäisen vaikeaa. 2 Hyvin vaikeaa. 3 Vaikeaa 4 Hieman vaikeaa. 5 Ei lainkaan vaikeaa.
5.	**Kun yrititte sukupuoliyhdyntää, kuinka usein saitte siitä tyydytystä?**	0 En yrittänyt yhdyntää. 1 En koskaan tai en juuri koskaan. 2 Muutaman kerran (harvemmin kuin joka toisella kerralla). 3 Joskus (noin joka toisella kerralla). 4 Useimmiten (useammin kuin joka toisella kerralla). 5 Melkein aina tai aina.

B. ELÄMÄNLAATUKYSELY MIESTEN SEKSUAALISUUDESTA:

Tämä kysely koostuu väittämistä, joissa kysytään ajatuksistasi ja tuntemuksistasi, joita sinulla saattaa olla sukupuolielämästäsi. Väittämä voi olla myönteinen tai kielteinen. Pyydämme sinua arvioimaan jokaista väittämää ja kertomaan, kuinka vahvasti olet samaa tai eri mieltä. Rastita yksi vastausvaihtoehto kuudesta.

Väittämiin vastattaessa käytetään seuraavia määritelmiä:
Sukupuolielämä: Tarkoittaa sekä fyysistä seksuaalista toimintaa että sinun ja kumppanisi välisen sukupuolisuhteen tunnepuolta.
Seksuaalinen toiminta/seksi: Kattaa kaiken toiminnan, mikä saattaa johtaa seksuaaliseen kiihottumiseen tai seksuaaliseen nautintoon, esim. yhdyntä, hyväily, esileikki, masturbaatio (itsetyydytys tai kumppanin suorittama) ja suuseksi (ts. kumppanin sinulle suorittama suuseksi).

	Täysin samaa mieltä	**Osittain samaa mieltä**	**Hieman samaa mieltä**	**Hieman eri mieltä**	**Osittain eri mieltä**	**Täysin eri mieltä**
1. Kun ajattelen sukupuoli-elämääni, tunnen itseni turhautuneeksi.						
2. Kun ajattelen sukupuoli-elämääni, tunnen oloni masentuneeksi.						
3. Kun ajattelen sukupuoli-elämääni, tunnen miehuuteni vajavaiseksi.						
4. Olen menettänyt luotta-muksen itseeni seksi-kumppanina.						
5. Kun ajattelen sukupuoli-elämääni, tunnen ahdistusta.						
6. Kun ajattelen sukupuoli-elämääni, tunnen suuttumusta.						
7. Olen huolissani sukupuoli-elämäni tulevaisuudesta.						
8. Kun ajattelen sukupuoli-elämääni, tunnen itseni vaivautuneeksi.						
9. Kun ajattelen sukupuoli-elämääni, tunnen syyllisyyttä.						
10. Kun ajattelen sukupuoli-elämääni, olen huolissani siitä, että kumppanini tuntee itsensä loukatuksi tai torjutuksi.						
11. Kun ajattelen sukupuoli-elämääni, minusta tuntuu ikään kuin olisin menettänyt jotain.						

OSA V

TOIMINTAKYKY JA AKTIIVISUUS:

A. YLEINEN TOIMINTAKYKY

Valitkaa kunkin kysymyksen jäljestä teille sopiva vastausvaihtoehto.

1.	**Oletteko viime aikoina pystynyt keskittymään töihinne?**	
		Paremmin kuin tavallisesti
		Yhtä hyvin kuin tavallisesti
		Huonommin kuin tavallisesti
		Paljon huonommin kuin tavallisesti

2.	**Oletteko viime aikoina valvonut paljon huolien vuoksi?**	
		En ollenkaan
		En enempää kuin tavallisesti
		Jonkin verran enemmän kuin tavallisesti
		Paljon enemmän kuin tavallisesti

3.	**Onko Teistä viime aikoina tuntunut siltä, että mukana olonne asioiden hoidossa on…**	
		Tavallista hyödyllisempää
		Yhtä hyödyllistä kuin tavallisesti
		Vähemmän hyödyllistä kuin tavallisesti
		Paljon vähemmän hyödyllistä kuin tavallisesti

4.	**Oletteko viime aikoina tuntenut kykenevänne päättämään asioista?**	
		Paremmin kuin tavallisesti
		Yhtä hyvin kuin tavallisesti
		Huonommin kuin tavallisesti
		Paljon huonommin kuin tavallisesti

5.	**Oletteko viime aikoina tuntenut olevanne jatkuvasti rasituksen alaisena?**	
		En ollenkaan
		En enempää kuin tavallisesti
		Jonkin verran enemmän kuin tavallisesti
		Paljon enemmän kuin tavallisesti

6.	**Onko Teistä viime aikoina tuntunut siltä, ettette voisi selviytyä vaikeuksistanne?**	
		Ei ollenkaan
		Ei enempää kuin tavallisesti
		Jonkin verran enemmän kuin tavallisesti
		Paljon enemmän kuin tavallisesti

7.	**Oletteko viime aikoina kyennyt nauttimaan tavallisista päivittäisistä toimistanne?**	
		Enemmän kuin tavallisesti
		Yhtä paljon kuin tavallisesti
		Vähemmän kuin tavallisesti
		Paljon vähemmän kuin tavallisesti

8. **Oletteko viime aikoina kyennyt kohtaamaan vaikeutenne?**

	Paremmin kuin tavallisesti
	Yhtä hyvin kuin tavallisesti
	Huonommin kuin tavallisesti
	Paljon huonommin kuin tavallisesti

9. **Oletteko viime aikoina tuntenut itsenne onnettomaksi ja masentuneeksi?**

	En ollenkaan
	En enempää kuin tavallisesti
	Jonkin verran enemmän kuin tavallisesti
	Paljon enemmän kuin tavallisesti

10. **Oletteko viime aikoina kadottanut itseluottamuksenne?**

	En ollenkaan
	En enempää kuin tavallisesti
	Jonkin verran enemmän kuin tavallisesti
	Paljon enemmän kuin tavallisesti

11. **Oletteko viime aikoina tuntenut itsenne ihmisenä arvottomaksi?**

	En ollenkaan
	En enempää kuin tavallisesti
	Jonkin verran enemmän kuin tavallisesti
	Paljon enemmän kuin tavallisesti

12. **Oletteko viime aikoina tuntenut itsenne kaiken kaikkiaan kohtalaisen onnelliseksi?**

	Enemmän kuin tavallisesti
	Yhtä paljon kuin tavallisesti
	Vähemmän kuin tavallisesti
	Paljon vähemmän kuin tavallisesti

B. LIIKUNTA-AKTIIVISUUS

Seuraavissa kysymyksissä kysytään aikaa, jonka käytätte fyysiseen aktiivisuuteen tavallisen viikon aikana. Niissä tiedustellaan toiminnoista, joita teette työpaikallanne, siirtyessänne paikasta toiseen, osana koti- ja pihatöitä sekä vapaa-aikananne virkistyksen, kuntoilun tai urheilun vuoksi.

1.A Kuinka monena päivänä tavallisen viikon aikana fyysinen aktiivisuutenne on ruumiillisesti **rasittavaa** (vaatii kovaa ponnistelua ja saa selvästi hengästymään), esimerkiksi painavien taakkojen nostamista, aerobicia tai reipasta pyöräilyä?

Vastaus:_____ päivänä.

1.B Kuinka paljon aikaa tavallisesti käytätte kaikkiaan tuollaisena päivänä **rasittavaan** fyysiseen aktiivisuuteen?

Vastaus:_____ tuntia _____ minuuttia.

2.A Kuinka monena päivänä tavallisen viikon aikana fyysinen aktiivisuutenne on ruumiillisesti **kohtuukuormitteista** (vaatii kohtuullista ponnistelua ja saa hengästymään lievästi), esimerkiksi kevyiden taakkojen kantamista tai pyöräilyä tasaista vauhtia. Älkää laskeko mukaan kävelyä.

Vastaus:_____ päivänä.

2.B Kuinka paljon aikaa tavallisesti käytätte kaikkiaan tuollaisena päivänä **kohtuukuormitteiseen** fyysiseen aktiivisuuteen?

Vastaus:_____ tuntia _____ minuuttia.

3.A Kuinka monena päivänä tavallisen viikon aikana **kävelette** vähintään 10 minuuttia kerrallaan? Tähän sisältyy kävely töissä ja kotona, kävely paikasta toiseen siirtyessänne ja kaikki muu kävely, jota ehkä harrastatte virkistyksen, urheilun ja kuntoilun vuoksi tai vapaa-aikananne.

Vastaus:_____ päivänä viikossa.

3.B Kuinka kauan aikaa tavallisesti käytätte kaiken kaikkiaan kävelyyn tuollaisena päivänä?

Vastaus:_____ tuntia _____ minuuttia.

3.C Millaista vauhtia **yleensä** kävelette?
Kävelettekö

1	ripeästi, niin että hengästytte selvästi?
2	kohtalaisen nopeasti, niin että hengästytte lievästi?
3	rauhallisesti, niin että ette hengästy?

Viimeiset kysymykset koskevat aikaa, jonka käytätte päivittäin istumiseen työssä, kotona, tehdessänne opiskelutehtäviä tai vapaa-aikananne. Tähän sisältyy aika, jonka käytätte pöydän ääressä istumiseen, ystävien luona olemiseen, lukemiseen tai television katselemiseen tai loikoiluun.

4.A Kuinka paljon aikaa käytätte yleensä istumiseen **arkipäivänä**?

Vastaus:_____ tuntia _____ minuuttia päivässä.

Kuinka paljon aikaa käytätte yleensä istumiseen **lauantaina ja sunnuntaina**?

4.B Vastaus:_____ tuntia _____ minuuttia päivässä.

OSA VI

TERVEYDEN LISÄKYSYMYKSET:

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

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

5. Virtsavaivojen vaikutus aktiviteettiin?

Kuinka usein mahdolliset virtsavaivanne vaikuttavat seuraaviin asioihin?

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

Pyydämme Teitä vielä ystävällisesti tarkastamaan että olette vastannut kaikkiin kysymyksiin.
Palauttakaa kysely oheisessa vastauskuoressa, postimaksu on maksettu puolestanne.
KIITÄMME TEITÄ SYDÄMELLISESTI OSALLISTUMISESTANNE!

Appendix 10. Incidence and remission of nocturia: subgroup analyses by nocturia case definition, age and gender – Study I.

Age group	Nocturia case definition	Gender	Incidence rate/ 1000 person-years			Remission rate/ 1000 person-years		
			No. of subgroups	Rate	95% CI	No. of subgroups	Rate	95% CI
18-39 years	≥ 1 voids/ night	Male	1	3.8	0.0-9.0	1	166.7	0.0-397.7
		Female	1	2.0	0.0-4.6	1	125.0	0.0-266.5
		Both	2	2.3	0.0-4.7	2	136.4	15.7-257.0
	≥ 2 voids/ night	Male	1	0.9	0.0-3.5			
		Female	2	4.2	0.0-11.9	1	95.2	1.9-188.6
		Both	3	2.6	0.0-6.1	1	95.2	1.9-188.6
40-59 years	≥ 1 voids/ night	Male	2	34.4	0.0-69.5	2	117.6	0.0-291.3
		Female	2	34.5	0.0-86.1	2	80.4	0.0-211.2
		Both	5	33.7	16.4-51.1	5	70.5	34.8-106.3
	≥ 2 voids/ night	Male	2	48.7	0.0-134.2	2	235.5	168.6-302.4
		Female	3	14.4	0.0-30.2	3	56.2	15.2-97.1
		Both	6	24.9	10.6-39.1	5	115.2	57.0-173.5
	≥ 3 voids/ night	Male	2	8.8	0.0-22.3	1	100.0	12.4-187.7
		Female	1	17.0	11.5-22.5	1	367.0	209.9-524.1
		Both	3	11.7	0.3-23.0	2	225.2	0.0-486.4
60+ years	≥ 1 voids/ night	Male	3	120.6	63.9-177.4	3	54.9	13.5-96.3
		Female	3	298.5	1.9-595.1	4	68.9	14.1-123.7
		Both	6	87.6	64.9-110.3	7	62.0	31.1-93.0
	≥ 2 voids/ night	Male	3	135.9	0.0-282.4	3	120.4	102.8-138.0
		Female	3	91.0	0.0-210.3	3	189.3	121.1-257.6
		Both	7	114.2	92.2-136.1	7	180.4	130.6-230.1
	≥ 3 voids/ night	Male	3	54.8	0.1-109.4	2	170.9	35.7-306.0
		Female	2	65.9	53.7-78.1	2	318.7	236.7-400.7
		Both	5	61.2	21.7-100.6	4	228.3	116.6-340.1
All	≥ 1 voids/ night	Male	6	48.9	29.0-68.8	6	65.7	35.4-96.0
		Female	6	34.9	20.7-49.0	7	74.6	35.0-114.2
		Both	13	40.8	30.1-51.5	14	66.9	45.4-88.5
	≥ 2 voids/ night	Male	6	63.3	46.2-80.3	5	141.6	109.9-173.3
		Female	7	20.5	12.6-28.3	7	122.6	54.9-190.3
		Both	16	43.5	35.5-51.5	13	154.8	103.7-205.8
	≥ 3 voids/ night	Male	5	34.0	18.5-49.5	3	149.9	49.3-250.5
		Female	3	49.4	6.3-92.5	3	329.0	256.3-401.7
		Both	8	37.3	23.7-51.0	6	222.9	132.4-313.4

Appendix 11. Multivariable meta-regression for incidence of nocturia per 1000 person-years of follow-up by three different nocturia case definitions – Study I.

Nocturia case definition	Study-level variable	Effect on incidence rate	*p*-value	95% CI
≥1 voids/night	**Age**	4.7	0.12	-1.4 to 10.8
	Follow-up time	-49.7	0.06	-100.9 to 1.5
	Gender distribution	-25.3	0.75	-203.8 to 153.3
	Risk of bias	-55.9	0.62	-304.7 to 192.9
≥2 voids/night	**Age**	2.5	0.04	0.1 to 4.9
	Follow-up time	-11.2	0.06	-22.8 to 0.4
	Gender distribution	30.8	0.38	-42.8 to 104.3
	Risk of bias	-89.2	0.07	-186.2 to 7.7
≥3 voids/night	**Age**	2.6	0.06	-0.2 to 5.4
	Follow-up time	-16.6	0.14	-43.2 to 10.0
	Gender distribution	28.0	0.33	-48.1 to 104.0
	Risk of bias	-18.7	0.54	-105.8 to 68.4

Appendix 12. Multivariable meta-regression for remission of nocturia per 1000 person-years of follow-up by three different nocturia case definitions – Study I.

Nocturia case definition	Study-level variable	Effect on remission rate	*p*-value	95% CI
≥1 voids/night	**Age**	-0.2	0.92	-4.1 to 3.8
	Follow-up time	11.7	0.35	-15.0 to 38.4
	Gender distribution	-11.5	0.80	-108.6 to 85.7
	Risk of bias	85.7	0.19	-51.6 to 223.1
≥2 voids/night	**Age**	0.7	0.69	-3.4 to 4.9
	Follow-up time	-20.0	0.006	-32.6 to -7.5
	Gender distribution	10.9	0.79	-80.3 to 102.1
	Risk of bias	-121.3	0.04	-235.1 to -7.5
≥3 voids/night	**Age**	-0.1	0.99	-42.9 to 42.8
	Follow-up time	-46.6	0.33	-389.5 to 296.3
	Gender distribution	76.5	0.36	-547.3 to 700.3
	Risk of bias	-47.6	0.76	-1586.0 to 1490.8

Appendix 13. Relative measures of association of nocturia with mortality – Study II.

Study	Gender	Age strata	Nocturia case definition [a]	No. of people in follow-up	Prevalence of nocturia at baseline	Mortality rate for people without nocturia at baseline (baseline risk)	Relative measure of association, 95% confidence interval	Adjusted variables (besides age)
Asplund 1999	Both sex	53-92 yr, mean 73 yr	3+	6143	8%	13% in 4.5 yr	1.28, 1.01-1.62 (RR) [b]	Gender, diabetes, health status, spasmodic chest pain, history of stroke
Bursztyn 2006	Both sex	All aged 70 yr	2+	456	35%	10% in 5 yr	0.89, 0.55-1.43 (HR)	E.g. gender, CHD, diabetes, diuretic medication, health status
Fitzgerald 2009	Men	60-69 yr, mean 64 yr	3+	734	35%	6% in 2 yr	1.21, 0.70-2.04 (RR) [b]	Diabetes, history of heart attack [c]
		70-99 yr, mean 78 yr	3+	746	46%	20% in 2 yr	1.02, 0.74-1.35 (RR) [b]	
Nakagawa 2010	Both sex	70-97 yr, mean 76 yr	2+	784	46%	4% in 5 yr	1.98, 1.09-3.59 (HR)	E.g. gender, BMI, CHD, diabetes, diuretic medication
Kupelian 2011	Men	20-49 yr, mean 33 yr	2+	4031	8%	1% in 5 yr	2.56, 1.32-4.94 (HR)	E.g. BMI, CVD, diabetes, diuretic medication, smoking
		50-64 yr, mean 58 yr	2+	1378	24%	5% in 5 yr	1.60, 1.06-2.41 (HR)	
		65-90 yr, mean 75 yr	2+	2056	43%	19% in 5 yr	1.35, 1.11-1.63 (HR)	
	Women	20-49 yr, mean 33 yr	2+	4800	13%	1% in 5 yr	1.10, 0.66-1.86 (HR)	
		50-64 yr, mean 57 yr	2+	1513	25%	2% in 5 yr	1.94, 1.27-2.96 (HR)	
		65-90 yr, mean 76 yr	2+	2220	42%	14% in 5 yr	1.19, 1.04-1.37 (HR)	

Galizia 2012	Both sex	65+ yr, mean 74 yr	2+	1288	46%	17% in 5 yr	1.02, 1.01-1.27 (HR)	E.g. gender, CCI, MMSE score, fractures, falls
Lightner 2012	Men	40-59 yr, mean 48 yr	2+	1705	Unclear [d]	Unclear	1.31, 0.73-2.35 (HR)	BMI, CHD, LUTS medication
		60-79 yr, mean 68 yr	2+	742	Unclear [d]	Unclear	1.48, 1.15-1.91 (HR)	
Van Doorn 2012	Men	50-78 yr, mean 61 yr	2+	1114	34%	4% in 5 yr	1.03, 0.75-1.42 (HR)	Hypertension, COPD, smoking
Chung 2014 [e]	Both sex	32-94 yr, mean 63 yr	3+	1301	25%	10% in 2.5 yr	1.89, 1.01-3.45 (RR) [b]	Duration of diabetes
Endeshaw 2016	Men	70-79 yr, mean 74 yr	3+ [f]	1478	23%	13% in 5 yr	1.18, 0.97-1.44 (HR)	E.g. BMI, CVD, diabetes, diuretic medication, smoking
Åkerla 2019	Men	50-60 yr, mean 55 yr	3+	1021	2.50%	5% in 5 yr	1.20, 0.81-1.80 (HR)	E.g. BMI, CHD, diabetes, pulmonary disease, smoking

A case definition of " 2+" refers to nocturia ≥ 2 vs. 0-1 voids/night, " 3+" refers to ≥ 3 vs. 0-2 voids/night.
[b] Relative risk (RR) converted from odds ratio (OR) using formula: RR = OR / (1 – p + (p x OR)), where p represents the baseline risk.
[c] Multivariable regression model built by stepwise regression using potential confounders and mediators for nocturia-related death risk (previously unpublished data).
[d] Prevalence of nocturia reported for all included men aged 40-79 yr with no age-stratification (18% of men having ≥ 2 voids/night).
[e] Patiens of hospital diabetic clinic with type 2 diabetes.
[f] Nocturia case definition of ≥ 3 vs. 0-1 voids/night. No statistical difference between HR' s when nocturia defined as ≥ 2 and 0-1 voids/night.
BMI = body mass index, CCI = Charlson Comorbidity Index, CHD = coronary heart disease, CVD = cardiovascular disease, COPD = chronic obstructive pulmonary disease, HR = hazard ratio, LUTS = lower urinary tract symptoms, MMSE = Mini Mental State Examination

Appendix 14. Relative measures of association of nocturia with mortality – additional estimates included in the subgroup meta-analyses of Study II.

Study	Gender	Age strata	Nocturia case definition (voids/night) [a]	Hazard ratio, 95% confidence interval	Adjusted variables (besides age)
Nakagawa 2010 [b]	Both sex	70-97 yr, mean 76 yr	2 vs. 0-1	1.59, 0.80-3.17	E.g. gender, BMI, CHD, diabetes, diuretic medication
			3 vs. 0-1	2.34, 1.09-5.00	
			≥4 vs. 0-1	3.60, 1.38-9.35	
Kupelian 2011	Men	20-49 yr, mean 33 yr	2 vs. 0	2.55, 1.12-5.83	E.g. BMI, CVD, diabetes, diuretic medication, smoking
			≥3 vs. 0	3.94, 1.80-8.64	
		50-64 yr, mean 58 yr	2 vs. 0	1.16, 0.66-2.05	
			≥3 vs. 0	1.85, 0.97-3.53	
		65-90 yr, mean 75 yr	2 vs. 0	1.38, 1.04-1.84	
			≥3 vs. 0	1.45, 1.06-1.98	
	Women	20-49 yr, mean 33 yr	2 vs. 0	1.19, 0.53-2.69	
			≥3 vs. 0	1.38, 0.66-2.89	
		50-64 yr, mean 57 yr	2 vs. 0	2.25, 1.46-3.46	
			≥3 vs. 0	1.87, 0.89-3.90	
		65-90 yr, mean 76 yr	2 vs. 0	1.04, 0.85-1.28	
			≥3 vs. 0	1.12, 0.85-1.48	
Endeshaw 2016	Men	70-79 yr, mean 74 yr	2 vs. 0-1	1.04, 0.87-1.26	E.g. BMI, CVD, diabetes, diuretic medication, smoking
			≥3 vs. 0-1	1.18, 0.97-1.44	

[a] Nocturia treated as a three-value categorical (discrete) variable.
[b] Supplementary data extracted from a conference abstract (*Nakagawa H, Niu K, Kaiho Y, Ikeda Y, Arai Y. Mortality in the elderly correlates with frequency of nighttime voiding: results of a 5-year prospective cohort study in Japan. AUA annual meeting 2010, abstract 3*).
BMI = body mass index, CHD = coronary heart disease, CVD = cardiovascular disease, HR = hazard ratio

Appendix 15. Relative measures of association of nocturia with mortality – subgroup meta-analyses stratified by age, gender, follow-up time, nocturia case definition, risk of bias and study region (Study II).

Variable		No. of studies	No. of subgroups [a]	Relative risk [b]	95% CI	I^2 (%) [c]
Mean age	18-49 yr	2	3	1.49	0.92-2.42	50.7
	50-69 yr	6	7	1.40	1.18-1.67	26.8
	≥70 yr	8	9	1.19	1.07-1.33	49.8
Gender	Male	6	11	1.30	1.16-1.45	23.0
	Female	1	3	1.34	0.98-1.83	58.7
	Mixed	5	5	1.23	0.97-1.56	62.6
Follow-up time	<10 yr	6	13	1.30	1.16-1.45	36.6
	≥10 yr	5	6	1.22	1.00-1.48	58.6
Nocturia case definition (voids/night)	≥2 vs. 0-1 [d]	6	12	1.30	1.13-1.49	62.0
	≥3 vs. 0-2 [d]	5	7	1.24	1.10-1.39	0.0
	2 vs. 0-1 [e]	3	8	1.32	1.07-1.64	59.0
	≥3 vs. 0-1 [e]	3	8	1.50	1.19-1.88	51.7
	≥4 vs. 0-1 [e]	1	1	3.60	1.38-9.35	
Risk of bias	Low	4	11	1.34	1.17-1.54	61.7
	High	7	8	1.18	1.04-1.35	18.2
Region	West Asia	1	1	0.89	0.55-1.43	
	East Asia	2	2	1.94	1.26-2.97	0.0
	Europe	4	5	1.16	0.99-1.36	47.3
	North America	4	11	1.31	1.17-1.46	33.0

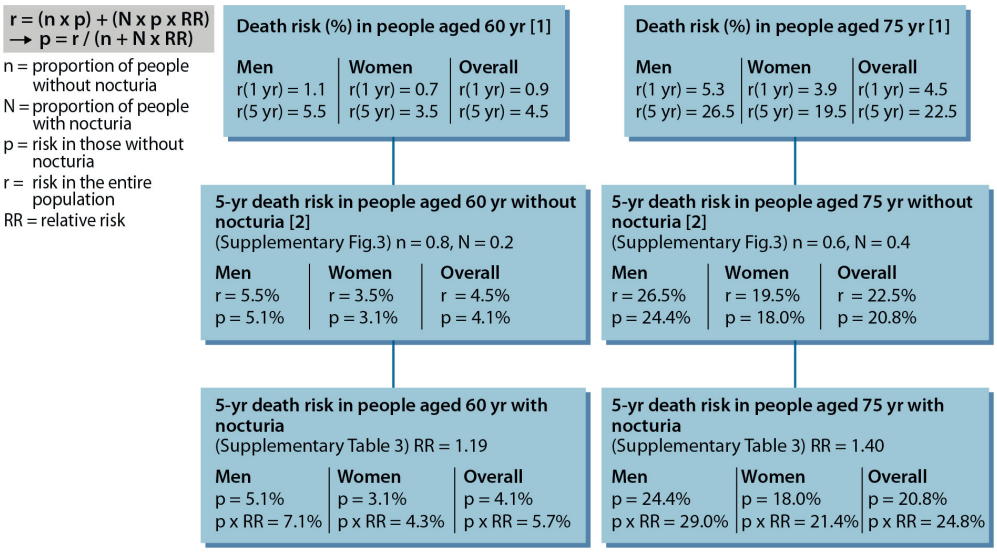
[a] Stratified by mean age (18-49 yr, 50-69 yr, ≥70 yr) and gender when data available.
[b] Pooled estimate for subgroups of studies.
[c] Variation due to heterogeneity (random-effects meta-analyses).
[d] Estimates from studies treating nocturia as a two-value categorical variable.
[e] Estimates from studies treating nocturia as a three-value categorical (discrete) variable to test exposure-response relationship.

Appendix 16. Unadjusted and adjusted meta-regression analyses for relative measures of association of nocturia with mortality – Study II.

Study-level variable	Univariable model			Multivariable model		
	Unadjusted coefficient [a]	95% CI	*p*-value	Adjusted coefficient [b]	95% CI	*p*-value
Mean age <70 yr	1.17	0.96-1.43	0.12	1.23	0.98-1.54	0.07
Male gender	1.04	0.85-1.29	0.67	1.01	0.83-1.25	0.85
Follow-up time <10 yr	1.11	0.89-1.38	0.34	1.19	0.96-1.46	0.10
Nocturia 3+	0.97	0.78-1.21	0.99	1.09	0.84-1.43	0.48
High risk of bias	0.89	0.72-1.09	0.25	0.84	0.65-1.08	0.15

[a] Meta-regression coefficient, representing interaction between nocturia-associated death risk (relative risk) and each categorical variable: mean age <70 vs. ≥70 yr, male vs. female or mixed gender, follow-up time <10 vs. ≥10 yr, nocturia ≥3 vs. ≥2 voids/night, high vs. low risk of bias.
[b] Adjusted for all covariables. Proportion of between-study variance explained (adjusted R^2) = 66.4%, residual variation due to heterogeneity (I^2 res.) = 24.7%.

Appendix 17. Flow chart of data used in calculations of baseline risks. – Study II.



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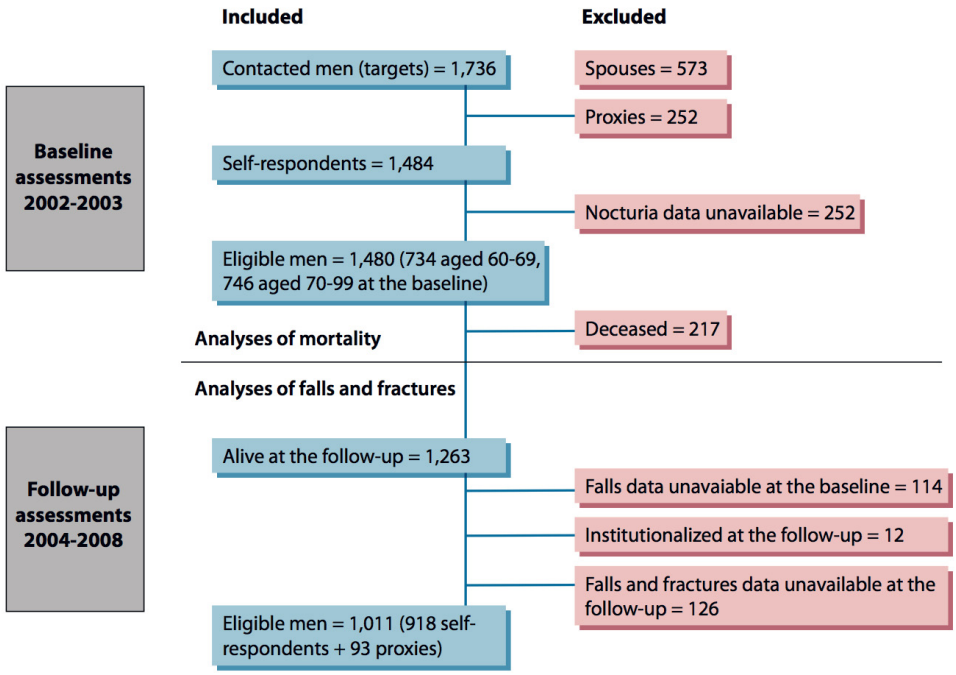
1. Centers for Disease Control and Prevention. Available from: https://www.cdc.gov/nchs/data_access/vitalstatsonline.htm
2. Bosch JL, Weiss JP. Prevalence and causes of nocturia. J Urol 2010;184:440-6.

Appendix 18. Flow chart of the assessments of nocturia, mortality, falls and fractures in the PREHCO study – Studies II and III.



Appendix 19. Relative measures of association of nocturia with falls and fractures – Study III.

Study	Gender	Age	No. of people in follow-up	Nocturia case definition (voids/night)	Prevalence of nocturia at baseline	Endpoint	Fall/fracture rate for people without nocturia at baseline (baseline risk)	Relative risk, 95% confidence interval	Adjusted variables (besides age)
Fitzgerald 2009	Men	60-99 yr, mean 70 yr	1011	≥ 3 vs. 0-2	39%	≥ 1 falls	26.1% / yr	1.25, 1.02-1.50 [a]	Sleep medication, diabetes, history of falls [b]
						≥ 2 falls	14.7% / yr	1.38, 1.11-1.71 [a]	
						Any fracture	1.6% / yr	1.38, 0.57-3.32 [a]	History of falls, history of fractures [b]
Parsons 2009	Men	65-100 yr, mean 74 yr	5872	2-3 vs. 0-1	56%	≥ 1 falls	22.6% / yr	1.05, 0.96-1.16	History of falls, history of dizziness, mobility limitation, number of narrow-walk trials completed
						≥ 2 falls	9.7% /yr	1.23, 1.08-1.41	
				≥ 4 vs. 0-1	9%	≥ 1 falls	22.6% / yr	1.11, 0.95-1.28	
						≥ 2 falls	9.7% /yr	1.42, 1.16-1.74	
Temml 2009	Men	41-80 yr, mean 52 yr	1820	≥ 2 vs. 0-1	21%	Hip fracture	1.0% / 5 yr	1.36,1.03-1.79 [a]	None
Frost 2010	Men	60-75 yr, mean 65 yr	4696	≥ 1 vs. 0	1% [c]	Any fracture	4.3% / 5 yr	2.25, 0.83-6.07 (HR)	BMI
						Osteoporotic fracture	1.8% / 5 yr	1.37, 0.19-9.86 (HR)	

Nakagawa 2010	Both sex	70-97 yr, mean 76 yr	784	≥ 2 vs. 0-1	Men: Unclear	Any fracture	2.3% / 5 yr	2.61, 0.76-8.95 (HR)	Gender, BMI, tranquilizers, hypnotics, diuretics, functional reach
					Women: Unclear	Any fracture	4.6% / 5 yr	2.07, 0.95-4.51 (HR)	
					Mixed: 46%	Any fracture	3.5% / 5 yr	2.01, 1.04-3.87 (HR)	
						Fall-related fr.	2.6% / 5 yr	2.20, 1.04-4.68 (HR)	
Vaughan 2010	Both sex	65-93 yr, mean 75 yr	692	≥ 3 vs. 0-2	28%	≥ 1 falls	15% / yr	1.28, 1.02-1.59	Gender, diabetes, gait speed, length of follow-up, race
Stenhagen 2013	Both sex	60-93 yr, mean 71 yr	1720	≥ 3 vs. 0-2	6%	≥ 1 falls	16% / 6 mo	1.57, 1.10-2.16 [a]	Gender
Marshall 2016	Men	Range 65-100 yr, mean 73 yr	5989	2-3 vs. 0-1	56%	Non-spine fr.	Unclear	1.0, 0.9-1.2 (HR)	History of falls, history of fractures, enrollment site, baseline hip BMD
				≥ 4 vs. 0-1	9%	Non-spine fr.	Unclear	1.0, 0.8-1.3 (HR)	
Noguchi 2016	Men	70-97 yr, mean 76 yr	1366	2-3 vs. 0-1	45%	≥ 1 falls	Unclear	1.17, 0.87-1.58	Birth country, dizziness, visual impairment, arthritis, psychotropic medication, anthihypertensive medication, walking aid use
						≥ 2 falls	Unclear	1.30, 0.81-2.10	
				≥ 4 vs. 0-1	10%	≥ 1 falls	Unclear	1.11, 0.69-1.78	
						≥ 2 falls	Unclear	1.38, 0.68-2.81	

[a] Relative risk (RR) converted from odds ratio (OR) using formula: RR = OR / (1 – p + (p x OR)), where p represents the baseline risk.
[b] Multivariable regression model built by stepwise regression using potential confounders and mediators for nocturia-related fall and fracture risk (previously unpublished data).
[c] Nocturia recorded only for persons who volunteered the symptom.
BMD = bone mineral density, BMI = body mass index, CCI = Charlson Comorbidity Index, CHD = coronary heart disease, CVD = cardiovascular disease, HR = hazard ratio,
MMSE = Mini Mental State Examination

Appendix 20. Relative risk of falling at least least once in the follow-up in people with nocturia – subgroup meta-analyses stratified by age, gender, follow-up time, nocturia case definition and risk of bias (Study III).

Variable		No. of studies	Relative risk	95% CI	I^2 (%) [a]
Mean age [b]	≤74 yr	3	1.21	0.99-1.49	70.8
	>74 yr	2	1.24	1.04-1.48	0.0
Gender	Male	3	1.11	0.99-1.25	27.3
	Mixed	2	1.36	1.13-1.64	0.0
Follow-up time [b]	<3 yr	2	1.06	0.97-1.16	0.0
	≥3 yr	3	1.31	1.14-1.49	0.0
Nocturia case definition (voids/night)	≥3 vs. 0-2 [c]	3	1.31	1.14-1.49	0.0
	2-3 vs. 0-1 [d]	2	1.06	0.97-1.16	0.0
	≥4 vs. 0-1 [d]	2	1.24	1.09-1.40	0.0
Risk of bias	Low	2	1.13	0.94-1.36	61.4
	High	3	1.28	1.11-1.49	0.0

[a] Variation due to heterogeneity (random-effects meta-analyses).
[b] Median split.
[c] Estimates from studies treating nocturia as a two-value categorical variable.
[d] Estimates from studies treating nocturia as a three-value categorical (discrete) variable to test exposure-response relationship.

Appendix 21. Relative risk of recurrent falls in the follow-up in people with nocturia – subgroup meta-analyses stratified by age, gender, follow-up time, nocturia case definition and risk of bias (Study III).

Variable		No. of studies	Relative risk	95% CI	I^2 (%) [a]
Mean age [b]	<74 yr	1	1.66	1.29-2.11	
	≥74 yr	2	1.23	1.09-1.40	0.0
Gender	Male	3	1.38	1.11-1.71	54.7
	Female	0			
Follow-up time [b]	1 yr	2	1.23	1.09-1.40	0.0
	>1 yr	1	1.66	1.29-2.11	
Nocturia case definition (voids/night)	≥3 vs. 0-2 [c]	1	1.66	1.29-2.11	
	2-3 vs. 0-1 [d]	2	1.23	1.09-1.40	0.0
	≥4 vs. 0-1 [d]	2	1.42	1.17-1.72	0.0
Risk of bias	Low	1	1.23	1.08-1.41	
	High	2	1.58	1.27-1.96	0.0

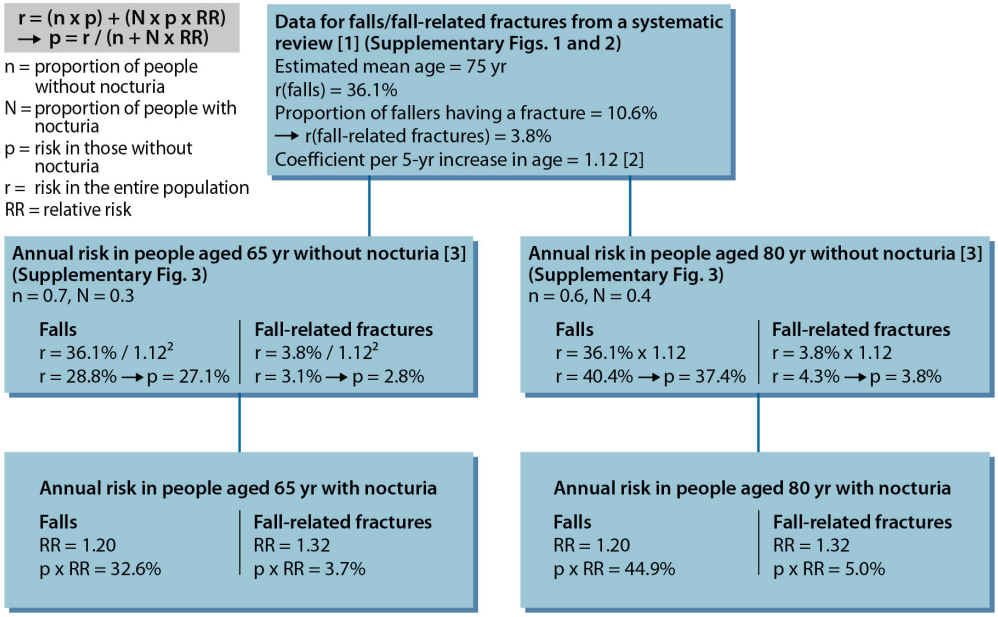
[a] Variation due to heterogeneity (random-effects meta-analyses).
[b] Median split.
[c] Estimates from a study treating nocturia as a two-value categorical variable.
[d] Estimates from studies treating nocturia as a three-value categorical (discrete) variable to test exposure-response relationship.

Appendix 22. Relative risk of fractures in people with nocturia – subgroup meta-analyses stratified by age, gender, follow-up time, nocturia case definition and risk of bias (Study III).

Variable		No. of studies	Relative risk	95% CI	I^2 (%) [a]
Mean age [b]	≤70 yr	3	1.41	1.09-1.82	0.0
	>70 yr	2	1.31	0.67-2.56	75.8
Gender	Male	5	1.27	0.95-1.69	50.5
	Female	1	2.07	0.95-4.51	
Follow-up time [b]	≤5 yr	4	1.47	1.16-1.87	0.0
	>5 yr	1	1.00	0.90-1.20	
Nocturia case definition (voids/night)	≥1 vs. 0 or ≥2 vs. 0-1	4	1.33	0.96-1.85	67.3
	≥3 vs. 0-2	1	1.38	0.57-3.32	
Risk of bias	Low	1	1.00	0.90-1.20	
	High	4	1.47	1.16-1.87	0.0

[a] Variation due to heterogeneity (random-effects meta-analyses).
[b] Median split.

Appendix 23. Flow chart of data used in calculations of baseline risks of falls and fall-related fractures – Study III.



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2. Deandrea S, Lucenteforte E, Bravi F et al. Risk factors for falls in community-dwelling older people: a systematic review and meta-analysis. Epidemiology 2010;21:658-68.
3. Bosch JL, Weiss JP. Prevalence and causes of nocturia. J Urol 2010;184:440-6.

Appendix 24. Characteristics of men at various stages of follow-up – Study IV.

	1994		1999		2004		2009	
	n	%	n	%	n	%	n	%
Number of men	1 332		1 193		1 067		955	
Urgency [a]	24	1.8	173	14.5	190	17.8	182	19.1
Daytime frequency	144	10.8	87	7.3	82	7.7	70	7.3
Nocturia	51	3.8	69	5.8	100	9.4	85	8.9
Year of birth								
1944	544	40.8	513	43.0	498	46.7	476	49.8
1934	477	35.8	452	37.9	412	38.6	367	38.4
1924	311	23.3	228	19.1	157	14.7	112	11.7
Marital status								
Married/cohabiting	1 086	81.5	981	82.2	865	81.1	754	79.0
Single/divorced	198	14.9	158	13.2	144	13.5	119	12.5
Widowed	48	3.6	54	4.5	58	5.4	82	8.6
BMI								
≤25	465	34.9	374	31.3	349	32.7	329	34.5
25-30	654	49.1	625	52.4	520	48.7	459	48.1
>30	213	16.0	194	16.3	198	18.6	167	17.5
Current smoking	258	19.4	193	16.2	149	14.0	116	12.1
Alcohol intake >150 g/week	270	20.3	195	16.3	172	16.1	67	7.0
Medical conditions								
Diabetes	98	7.4	100	8.4	128	12.0	157	16.4
Hypertension	398	29.9	325	34.0	492	46.1	470	49.2
Cardiac disease	238	17.9	227	19.0	248	23.2	268	28.1
Pulmonary disease	127	9.5	152	12.7	126	11.8	103	10.8
Cerebrovascular disease	60	4.5	50	4.2	64	6.0	59	6.2
Cancer	43	3.2	70	5.9	101	9.5	146	15.3
Neurological disease	29	2.2	44	3.7	40	3.7	59	6.2

[a] Assessed with a modified question in 1994.

Appendix 25. Unadjusted and adjusted associations of LUTS and covariables with all-cause mortality in the follow-up of 21 years - Cox regression analyses with variable values updated every five years (time-dependent analysis) – Study IV.

	Unadjusted		Adjusted					
			Urgency		Frequency		Nocturia	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Urgency	1.71	1.36-2.14	1.19	0.94-1.50	-	-	-	-
Frequency	1.95	1.52-2.49	-	-	1.42	1.11-1.83	-	-
Nocturia	2.31	1.79-2.98	-	-	-	-	1.38	1.07-1.79
Age in 1994 (vs. 50 yrs)								
60 yrs	1.93	1.52-2.47	1.80	1.40-2.32	1.82	1.41-2.34	1.79	1.38-2.30
70 yrs	7.14	5.67-8.99	6.81	5.23-8.88	6.83	5.25-8.90	6.69	5.13-8.73
Marital status (vs. married)								
Single/divorced	1.98	1.60-2.46	2.39	1.91-2.98	2.38	1.90-2.98	2.35	1.88-2.94
Widowed	2.31	1.72-2.46	1.20	0.89-1.63	1.21	0.90-1.64	1.21	0.90-1.64
BMI (vs. ≤25)								
25-30	0.70	0.58-0.85	0.77	0.64-0.94	0.76	0.63-0.93	0.77	0.63-0.94
>30	0.85	0.67-1.09	0.97	0.74-1.26	0.94	0.72-1.23	0.96	0.74-1.25
Current smoking	1.51	1.22-1.86	1.98	1.58-2.49	1.95	1.56-2.45	2.01	1.60-2.52
Alcohol intake >150 g/week	0.85	0.65-1.09	1.16	0.89-1.52	1.17	0.90-1.54	1.16	0.89-1.53
Medical conditions								
Diabetes	1.90	1.51-2.38	1.66	1.31-2.11	1.66	1.31-2.10	1.68	1.33-2.13
Hypertension	1.20	1.01-1.43	1.12	0.93-1.34	1.11	0.92-1.34	1.11	0.93-1.34
Cardiac disease	2.58	2.16-3.08	1.54	1.27-1.86	1.52	1.26-1.84	1.54	1.27-1.86
Pulmonary disease	1.78	1.42-2.24	1.35	1.07-1.70	1.33	1.06-1.68	1.34	1.06-1.68
Cerebrovascular disease	1.96	1.45-2.64	1.43	1.05-1.93	1.42	1.04-1.92	1.43	1.06-1.94
Cancer	2.37	1.87-3.02	1.77	1.38-2.27	1.76	1.37-2.25	1.73	1.35-2.22
Neurological disease	2.00	1.43-2.80	1.65	1.17-2.33	1.70	1.21-2.39	1.67	1.18-2.35

Appendix 26. Unadjusted and adjusted associations of LUTS and covariables with all-cause mortality in the follow-up of 21 years - Cox regression analyses with variable values fixed to the baseline assessment of 1994 (fixed analysis) – Study IV.

	Unadjusted		Adjusted					
			Urgency		Frequency		Nocturia	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Urgency	1.52	0.86-2.69	0.94	0.52-1.68	-	-	-	-
Frequency	1.43	1.11-1.84	-	-	1.09	0.84-1.42	-	-
Nocturia	2.56	1.81-3.63	-	-	-	-	1.41	0.99-2.02
Age in 1994 (vs. 50 yrs)								
60 yrs	1.93	1.52-2.47	1.92	1.49-2.48	1.91	1.49-2.46	1.91	1.48-2.46
70 yrs	7.14	5.67-8.99	8.18	6.31-10.62	8.12	6.26-10.53	8.00	6.17-10.38
Marital status (vs. married)								
Single/divorced	1.78	1.44-2.22	2.09	1.67-2.63	2.09	1.67-2.63	2.06	1.64-2.59
Widowed	3.02	2.10-4.34	1.87	1.30-2.71	1.89	1.31-2.72	1.88	1.31-2.72
BMI (vs. ≤25)								
25-30	0.88	0.72-1.06	0.92	0.75-1.12	0.92	0.75-1.12	0.92	0.76-1.12
>30	1.00	0.77-1.28	1.03	0.79-1.35	1.03	0.79-1.34	1.02	0.78-1.33
Current smoking	1.66	1.37-2.03	2.44	1.96-3.03	2.41	1.94-3.00	2.46	1.98-3.05
Alcohol intake >150 g/week	1.20	0.98-1.48	1.42	1.14-1.77	1.42	1.14-1.76	1.40	1.12-1.74
Medical conditions								
Diabetes	2.12	1.62-2.77	1.78	1.35-2.34	1.77	1.34-2.34	1.74	1.32-2.30
Hypertension	1.42	1.19-1.71	1.21	1.00-1.47	1.21	1.00-1.47	1.21	1.00-1.47
Cardiac disease	2.64	2.18-3.19	1.49	1.22-1.83	1.49	1.22-1.83	1.49	1.22-1.83
Pulmonary disease	1.91	1.49-2.45	1.39	1.08-1.80	1.39	1.07-1.79	1.38	1.07-1.78
Cerebrovascular disease	2.00	1.42-2.80	1.42	1.00-2.02	1.41	0.99-2.00	1.42	1.00-2.02
Cancer	2.57	1.76-3.74	2.21	1.50-3.26	2.24	1.52-3.30	2.26	1.53-3.32
Neurological disease	1.67	1.01-2.74	2.00	1.21-3.32	2.00	1.21-3.31	1.99	1.20-3.29

Appendix 27. *P*-values of interaction terms in regression analyses of the association of LUTS with all-cause mortality – Study IV.

	Urgency	Daytime frequency	Nocturia
	***p*-value**	***p*-value**	***p*-value**
Year of birth	0.882	0.050	0.704
Marital status	0.474	0.335	0.594
BMI	0.370	0.398	0.992
Current smoking	0.017	0.778	0.920
Alcohol intake	0.227	0.374	0.264
Diabetes	0.121	0.499	0.644
Hypertension	0.599	0.261	0.561
Cardiac disease	0.041	0.823	0.701
Pulmonary disease	0.505	0.605	0.472
Cerebrovascular disease	0.172	0.295	0.499
Cancer	0.631	0.900	0.643
Neurological disease	0.943	0.185	0.696

ORIGINAL PUBLICATIONS

PUBLICATION I

Incidence and remission of nocturia: a systematic review and meta-analysis

Pesonen JS, Cartwright R, Mangera A, Santti H, Griebling TL, Pryalukhin AE, Riikonen J, Tähtinen RM, Agarwal A, Tsui JF, Vaughan CP, Markland AD, Johnson TM 2nd, Fonsell-Annala R, Khoo C, Tammela TL, Aoki Y, Auvinen A, Heels-Ansdell D, Guyatt GH, Tikkinen KA

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Voiding Dysfunction

Incidence and Remission of Nocturia: A Systematic Review and Meta-analysis

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Abstract

Context: Although vital for decision-making about management, the natural history of nocturia remains uncertain. A systematic review would clarify the issue, but because natural history reviews are uncommon it would require methodological innovations.
Objective: To estimate the incidence and remission of nocturia, and refine methods for meta-analyses assessing natural history.
Evidence acquisition: We conducted a comprehensive search of PubMed, Scopus, and Cumulative Index of Nursing and Allied Health Literature databases and abstracts of major urologic meetings as far as August 31, 2015. Random effects meta-analyses addressed incidence/remission rates of nocturia; meta-regression explored potential determinants of heterogeneity. Studies were categorized as either low or high risk of bias using a novel instrument specifically designed for longitudinal symptom studies aimed at the general population.
Evidence synthesis: Of 4165 potentially relevant reports, 16 proved eligible. Pooled estimates from 13 studies (114 964 person-years of follow-up) demonstrated that annual incidence was strongly associated with age: 0.4% (0–0.8%) for adults aged $<$ 40 yr; 2.8% (1.9–3.7%) for adults aged 40–59 yr; and 11.5% (9.1–14.0%) for adults aged $\geq$ 60 yr. Of those with nocturia, each year 12.1% (9.5–14.7%) experienced remission.
Conclusions: The available evidence suggests that nocturia onset is strongly associated with age, with much higher rates in those over 60 yr; remission occurs in approximately 12% each year. These estimates can aid with management decisions and counseling related to nocturia.

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Patient summary: We reviewed all previous studies of progression of night-time urination (nocturia). We found that in any given year 0.4% of adults aged < 40 yr, 3% of adults aged 40–59 yr, and 12% of adults aged ≥ 60 yr will develop nocturia, while overall 12% of those with nocturia will improve. These findings may be helpful in making decisions about coping with or treating nocturia.

1. Introduction

Nocturia (waking from sleep at night to void) [1] is one of the most common and bothersome urinary symptoms [2]. Nocturia is associated with impaired quality of life, and is a significant cause of sleep disruption. Nocturia may increase fracture and mortality risk [3,4]. Cross-sectional studies suggest that older age increases the risk of nocturia [5], and studies have identified additional risk factors, suggesting a multifactorial etiology [6]. Little is known, however, about patterns of progression and remission of nocturia over time, knowledge of which would facilitate shared decision-making about the initiation and continuation of therapeutic options between patients and healthcare providers [7].

Conventional systematic reviews that compare one treatment against another or against a nontreatment control are common and the methods are well established [8]. However, systematic reviews and meta-analyses addressing natural history or prognosis of symptoms are rare, and require methodological innovation. Although investigators have conducted longitudinal studies addressing nocturia, summarizing the data is challenging, with variation between assessment tools, case definitions, and analytic strategies [6]. The primary aim of this systematic review was to explore and compare, using different analytical methods and definitions, the average annual cumulative incidence and remission of nocturia. We also aimed to examine progression of nocturia, and further develop methods for systematic reviews and meta-analyses assessing natural history and prognosis of symptoms.

2. Evidence acquisition

We registered the review protocol (PROSPERO: CRD42012001985), and followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidance [9]. No ethical approval was required.

2.1. Data sources and searches

An experienced research librarian (M.A.) collaborated in planning the search strategy, performed up to 31 August, 2015, in PubMed (from 1946 to present), Scopus (1995 to present), and Cumulative Index of Nursing and Allied Health Literature (1960 to present) without search limits or language restrictions. As increasing evidence suggests the benefits of inclusion of grey literature to the systematic reviews [10], we also searched abstracts published in the annual meetings of the American Urological Association, European Association of Urology, International Continence Society, and International Urogynecological Association from the past 10 yr (2005–2015) for ongoing and unpublished studies. Supplementary Appendix 1 provides the search strategy. We also hand searched reference lists of all included articles.

2.2. Eligibility criteria

We included longitudinal studies with a follow-up of at least 3 mo reporting the incidence, progression, remission, or change in prevalence in a primarily non-care seeking adult population. We excluded studies in which the aim was to assess the effect of any intervention, including those with untreated control arms. We also excluded studies assessing lower urinary tract symptoms (LUTS) in patients with any specific health disorder. Finally, we excluded studies assessing the impact of pregnancy or delivery on LUTS if the baseline LUTS assessment was carried out either during pregnancy or in the 1st postpartum year.

2.3. Study selection and data extraction

We developed standardized, pilot-tested forms together with detailed instructions for screening of abstracts and full texts, risk of bias assessments, and data extraction. The reviewers conducted pilot screening and data extraction exercises to achieve a high level of agreement. Pairs of reviewers, independently and in duplicate, screened study reports for eligibility, assessed risk of bias, and collected data from each eligible study. Reviewers resolved disagreements through discussions; one of two adjudicators resolved remaining disagreements.

When more than one report provided data from the same study, we used the most complete report, and additionally combined data from less complete reports where possible. We recorded the country/source of study sample, age and sex distribution, exclusion criteria used in individual studies, assessment tools used for nocturia, follow-up time, sample size including response rate, as well as incidence and remission rates of nocturia.

2.4. Assessment of risk of bias

One challenge for a systematic review of symptom prognosis is that risk of bias criteria, as well as criteria for overall certainty in estimates, although well established for reviews of therapeutic trials, are controversial in observational studies [11]. Through iterative discussion and consensus building, and informed by prior literature

[12,13], we developed a novel instrument to categorize studies as either low or high risk of bias, evaluating the representativeness of the source populations, accuracy of the outcome assessment, and the proportion of missing data (Supplementary Appendix 2) [14].

2.5. Data analysis, including statistical analysis

We used three different analytic definitions to assess the incidence of nocturia: (1) any new nocturia case (≥1 voids/night) at follow-up for individuals without nocturia at baseline, (2) any new case of ≥2 voids/night for individuals with no or one void per night at baseline, and (3) any new case of ≥3 voids/night for individuals with two or less voids per night at baseline. Similarly, we used three analytic definitions for nocturia remission: (1) one or more voids per night resolving to no nocturia, (2) two or more nocturia episodes resolving to no or one void per night, and (3) three or more nocturia episodes resolving to two or less voids per night. Epidemiological studies have suggested that difference of at least one void per night is patient-important [15,16].

For cumulative incidence and remission rates, person-years were calculated by multiplying the number of individuals without/with nocturia (for incidence and remission, respectively) at the follow-up by follow-up time (simple cumulative incidence methodology). Standard errors and 95% confidence intervals were calculated for natural logarithms of incidence/remission rates per 1000 person-years of follow-up. In the case of zero events, a correction of 0.5 was added to observed events and person-years to enable calculation of confidence intervals. Finally, we also used actuarial cumulative incidence methodology for sensitivity analyses (Supplementary Appendix 3).

We calculated pooled rates of incidence and remission of nocturia using the DerSimonian–Laird random effects inverse variance method. Rates were expressed as observed events per 1000 person-years of follow-up. If a study provided more than one definition for incidence/remission of nocturia, when pooling data, we preferred nocturia estimates using a definition of two or more voids/night. Analyses were also carried out for three age groups (18–39 yr, 40–59 yr, and 60 yr and over) as earlier research suggest substantial differences between individuals in young adulthood, middle age, and in older age [5]. Finally, we measured estimates stratified by sex and across the three nocturia case definitions (defined as ≥1, ≥2, or ≥3 voids/night).

We employed prespecified hypotheses to examine heterogeneity using meta-regression analysis weighted by the inverse of the variance in a random effects model. Separately for each nocturia case definition (≥1, ≥2, or ≥3 voids/night), we examined the following variables as potential sources of heterogeneity: (1) mean age, (2) sex distribution, (3) length of follow-up, and (4) risk of bias. For incidence, we had prespecified hypotheses that effect estimates would be higher for: (1) older age, (2) higher proportion of male population, (3) shorter follow-up time, and (4) lower risk of bias. For remission, we had prespecified hypotheses that effect estimates would be higher for: (1) younger age, (2) higher proportion of female population, (3) shorter follow-up time, and (4) lower risk of bias.

To illustrate the relation of nocturia incidence and remission with nocturia prevalence, we estimated the (baseline) prevalence of nocturia ≥1, ≥2 and ≥3 episodes/night using a previous comprehensive systematic review addressing the prevalence of nocturia [5].

We narratively summarized the studies on progression of nocturia but did not pool estimates because too few studies on progression were included in our meta-analysis. Statistical analyzes were performed using metan and metareg in Stata 12.1 (StataCorp, College Station, TX, USA) [17].

3. Evidence synthesis

3.1. Literature search and study characteristics

We screened 4165 abstracts and retrieved 74 full texts and two eligible conference abstracts (Fig. 1). Sixteen studies provided usable data from 15 142 men and 18 726 women (Table 1). From these 16 studies, two provided proportional measures of progression and remission of nocturia among all persons in follow-up but did not report actual number of incident or remitting cases [18,19]. Similarly, one study provided only periodic prevalences of nocturia but not data of incident or remitting cases [20]. We were therefore able to include 13 studies (114 964 person-years) in meta-analyses of incidence and remission rates of nocturia [21–33].

Table 1 provides a description of the 16 studies. Ten (62%) were conducted in Europe, three (19%) in North America, and three (19%) in Asia. The studies varied widely, including sex and age distributions, as well as in follow-up times (median 4.5 yr; range, 6 mo to 16 yr). Fifteen studies (94%) used symptom questionnaires and one (6%) used frequency-volume charts.

3.2. Risk of bias

Of the 16 included studies, 10 (62%) were at high risk and six (38%) at low risk of bias (Fig. 2). Of these 16 studies, 14 (88%) accurately assessed nocturia both at baseline and at follow-up, nine (56%) had little missing data in the follow-up, and eight (50%) used representative source populations.

3.3. Incidence

In meta-analyses of the incidence rates of nocturia (12 studies, five low and seven high risk of bias), the pooled average annual cumulative incidence was 4.9% (95% confidence interval 4.1–5.8, $I^2 = 98.6\%$; no difference between simple and actuarial cumulative incidence methodology; Fig. 3; Supplementary Fig. 1). With age stratification, annual incidence increased with increasing age: 0.4% (0–0.8%, $I^2 = 65.1\%$) for adults aged < 40 yr, 2.8% (1.9–3.7%, $I^2 = 98.1\%$) for adults aged 40–59 yr, and 11.5% (9.1–14.0%, $I^2 = 98.8\%$) for adults aged ≥ 60 yr (Fig. 3). Pooled incidence

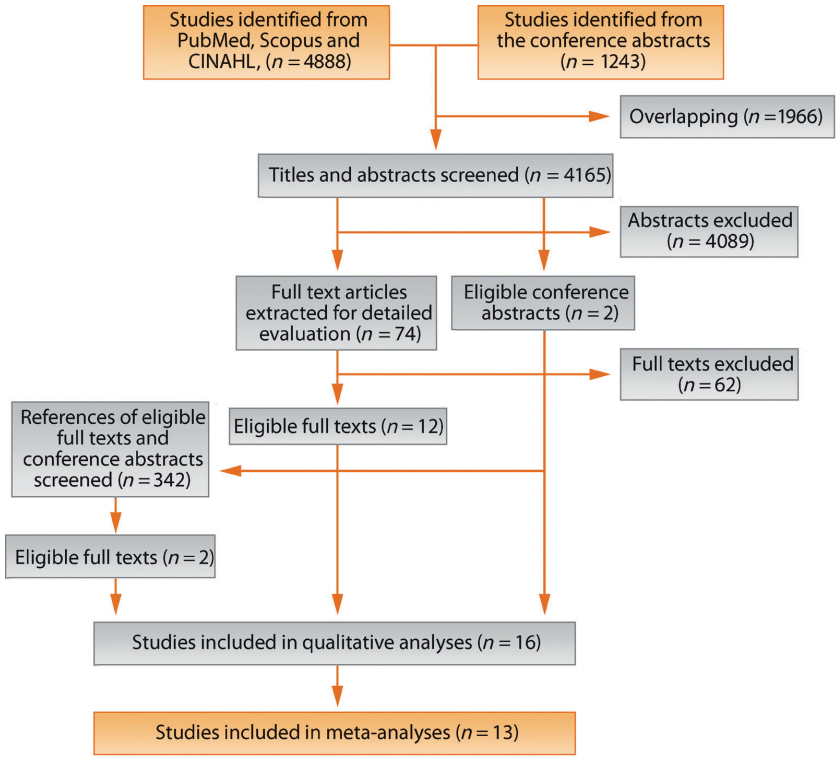

Fig. 1 – Study flow chart.
CINAHL = Cumulative Index to Nursing and Allied Health Literature.

rates did not significantly differ by nocturia case definition (4.1% (3.0–5.2%) for ≥1 episode per night, 4.4% (3.6–5.2%) for ≥2 episodes per night, and 3.7% (2.4–5.1%) for ≥3 episodes per night; Supplementary Table 1).

In multivariable meta-regression, (borderline) significant predictor for higher incidence was older age (4.7% increase/decade for ≥1 voids/night, −1.4 to 10.8, $p = 0.12$, 2.5% increase/decade for ≥2 voids/night, 0.1–4.9, $p = 0.04$; and 2.6% increase/decade for ≥3 voids/night, −0.2 to 5.4, $p = 0.06$). Follow-up time, sex distribution, or risk of bias were not strongly suggestive of higher or lower incidence of nocturia (Supplementary Table 2).

3.4. Remission

In meta-analyses of remission rates of nocturia (12 studies, five low and seven high risk of bias), the pooled average annual cumulative remission was 12.1% (9.5–14.7%, $I^2 = 97.8\%$; no difference between simple and actuarial cumulative remission methodology; Fig. 4; Supplementary Fig. 2). With age stratification, annual remission rates did not differ by age: 11.1% (3.7–18.5%, $I^2 = 0.0\%$) for adults aged < 40 yr, 9.4% (6.2–12.6%, $I^2 = 94.1\%$) for adults aged 40–59 yr, and 13.9% (9.0–18.8%, $I^2 = 98.8\%$) for adults aged ≥ 60 yr (Fig. 4). Pooled remission rates for nocturia increased with higher nocturia case definition: 6.7% (4.5–8.9%) for ≥1 voids/night, 15.5% (10.4–20.6%) for ≥2 voids/night, and 22.3% (13.2–31.3%) for ≥3 voids/night (Supplementary Table 1).

In multivariable meta-regression, age, sex distribution, follow-up time, or risk of bias were not consistently suggestive of higher or lower remission of nocturia (Supplementary Table 3).

3.5. Relation between incidence and remission rates with baseline prevalence of nocturia

Figure 5 illustrates the relation of baseline prevalence (of having or not having nocturia) with (average annual) cumulative incidence and remission. For instance, baseline prevalence is 5% for ≥3 nocturia episodes. Therefore, 5% of population are "at risk" of nocturia remission and 95% are "at risk" of nocturia incidence. According to our meta-analyses (Supplementary Table 1), cumulative incidence is 3.7% (2.4–5.1%) and cumulative remission is 22.3% (13.2–31.3%) for ≥3 nocturia episodes. However, due to the baseline prevalence, indeed more incident than remittent nocturia cases emerge annually and the prevalence therefore grows with age (Fig. 5).

Table 1 – Characteristics of the studies included in qualitative analyses

Study	Country	Source of sample	Population characteristics[a]	Exclusion criteria	Assessment tool for nocturia	Follow-up time (yr)	No. of contacted at the baseline	No. of eligible respondents	
								Baseline	Follow-up
Bulpitt et al 1976 [21] [18]	England	GP registry	Both sex, 38% men, mean age 53 yr (range, 32–69 yr)	Hypertension	A symptom questionnaire for hypertensive patients (validated)	0.8	173	88 (51%)	55 (63%)
Lee et al 1998 [18] [b]	Scotland	GP registries	Men, mean age 56 yr (range, 40–79 yr)	Treatment/disease affecting lower urinary tract	AUA-SI	5	3094	1994 (64%)	1159 (58%)
Møller et al 2000 [22]	Denmark	Civil registry	Women, mean age 50 yr (range, 40–60 yr)	None	BFLUTS	1	4000	2860 (72%)	2284 (80%)
Temml et al 2003 [19] [b]	Austria	Health screening	Men, mean age 55 yr (range, 40–84 yr)	Treatment affecting lower urinary tract	IPSS	5	2096	854 (41%)	456 (53.4%)
Johnson et al 2005 [23]	USA	Marketing list vendor	Both sex, 40.7% men, mean age 71yr (range, 60+ yr)	Institutionalized	MESA questionnaire (validated)	1	1956	1632 (83%)	1105 (68%)
Häkkinen et al 2006 [24]	Finland	Civil registry	Men, mean age 62 yr (range, 50–70 yr)	None	DAN-PSS	5	3143	2198 (70%)	1683 (77%)
Chen et al 2007 [25]	Taiwan	Health screening	Women, mean age 60 yr (range, 40–79 yr)	None	Unvalidated questionnaire	2	1149	862 (75%)	314 (36%)
Viktrup and Lose 2008 [26]	Denmark	Department of obstetrics	Primiparous women, mean age 35 yr (range, 17–41 yr)[c]	None	A questionnaire in accordance with definitions by ICS (validated)	7	Unclear	305	226
Wennberg et al 2009 [27]	Sweden	Civil registry	Women, mean age 56 yr (range, 20–98 yr)	None	IPSS	16	2911	2248 (77%)	1081 (37%)
Malmsten et al 2010 [20] [b]	Sweden	Civil registry	Men, mean age 62 yr (45–99 yr)	None	IPSS	11	10458	7763 (74%)	3257 (42%)
Heidler et al 2011 [28]	Austria	Health screening	Women, mean age 57 yr (range, 21–81 yr)	Urinary tract infection, surgery for urinary incontinence	BFLUTS	6.5	1166	925 (79%)	386 (42%)
Van Doorn et al 2011 [29]	The Netherlands	Civil registry	Men, mean age 62 yr (range, 50–78 yr)	Surgery/condition affecting lower urinary tract, poor health	FVC (frequency-volume chart)	2.1	3398	1122 (33%)	698 (62%)
Aoki et al 2012 [30]	Japan	Health screening	Both sex, 30.8% men, mean age 68 yr (range, 23–95 yr)	None	Unvalidated questionnaire	4	Unclear	23 126	13 536
Hunter et al 2012 [31]	USA	Home support registries	Women receiving home support, mean age 84 yr (range, 70–103 yr)	Poor health	ICIQ-FLUTS	0.5	203	100 (49%)	75 (75%)
Hirayama et al 2013 [32]	Japan	Health screening	Both sex, 50.7% men, mean age 73 yr (range, 65–93 yr)	Poor health, institutionalized	IPSS	1	4427	3915 (88%)	3685 (94%)
Araujo et al 2014 [33]	USA	Street lists	Both sex, 38.9% men, mean age 52 yr (range, 30–79 yr)	Poor health	AUA-SI	5	9602	5502 (57%)	4144 (75%)

[a] Mean age at the midpoint of the follow-up; to estimate the mean age at the moment of nocturia incidence/remission in the study population, half of the duration of the follow-up time was added to the mean age at the baseline.
[b] Three studies were not included in the meta-analyses.
[c] Age information at the time of delivery. We used data from nocturia observations that were collected between the 7th and 12th postpartum years.
AUA-SI = American Urological Association Symptom Index; BFLUTS = The Bristol Female Lower Urinary Tract Symptoms; DAN-PSS = The Danish Prostatic Symptom Score; ICIQ-FLUTS = International Consultation on Incontinence Questionnaire-Female Lower Urinary Tract Symptoms; ICS = International Continence Society; IPSS = International Prostate Symptom Score; MESA = Medical, Epidemiologic and Social Aspects of Aging questionnaire.

Reference	Risk of bias criteria			Overall risk of bias
	Representativity of the source population	Assessment of the outcome	Missing data	
Bulpitt et al 1976 [21]	−	+	−	High
Lee et al 1998 [18]	+	+	−	High
Møller et al 2000 [22]	+	+	+	**Low**
Temml et al 2003 [19]	−	+	−	High
Johnson et al 2005 [23]	+	+	+	**Low**
Häkkinen et al 2006 [24]	+	+	+	**Low**
Chen et al 2007 [25]	−	−	−	High
Viktrup and Lose 2008 [26]	+	+	+	**Low**
Wennberg et al 2009 [27]	+	+	+	**Low**
Malmsten et al 2010 [20]	+	+	+	**Low**
Heidler et al 2011 [28]	−	+	−	High
Van Doorn et al 2011 [29]	+	+	−	High
Aoki et al 2012 [30]	−	−	+	High
Hunter et al 2012 [31]	−	+	−	High
Hirayama et al 2013 [32]	−	+	+	High
Araujo 2014 et al [33]	−	+	+	High

Fig. 2 – Risk of bias of the included studies.

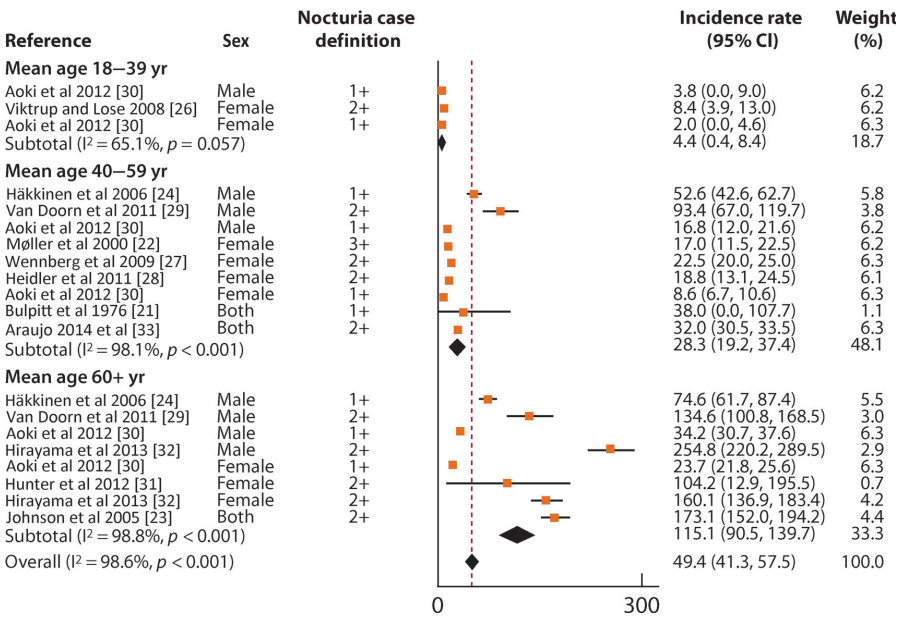

Fig. 3 – Forest plot of incidence rates of nocturia per 1000 person-years of follow-up.
CI = confidence interval.

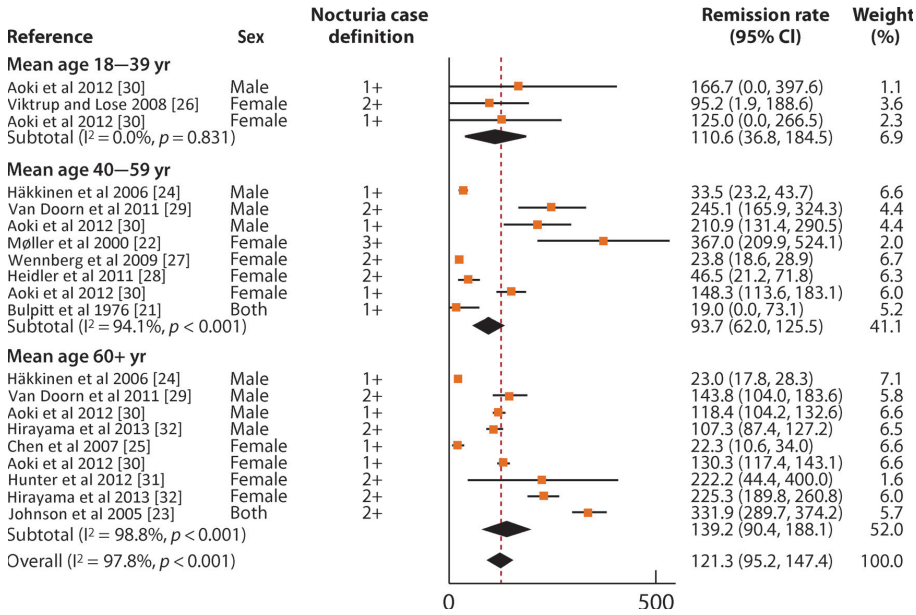

Fig. 4 – Forest plot of remission rates per 1000 person-years of follow-up.
CI = confidence interval.

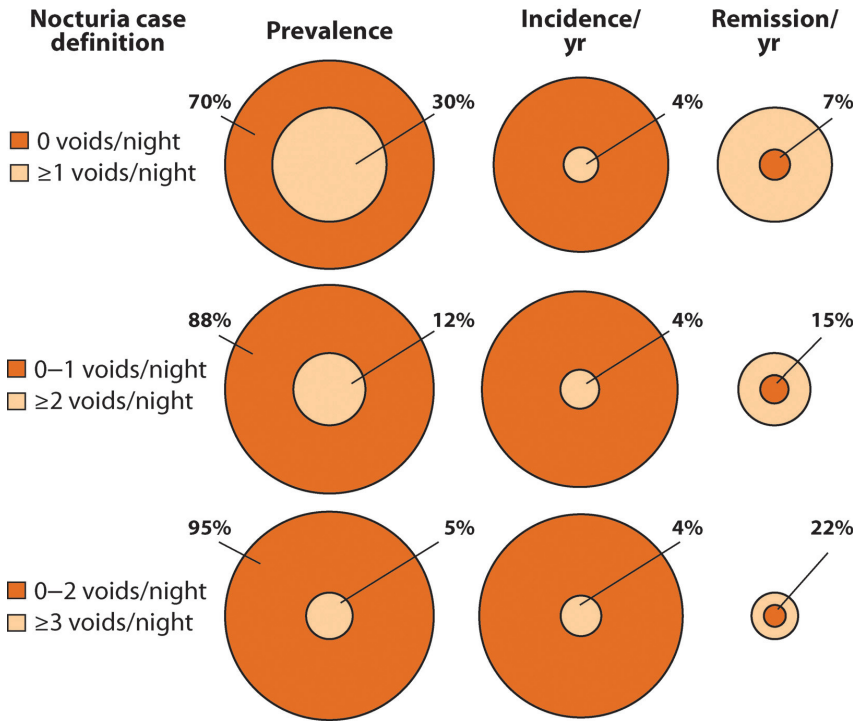

Fig. 5 – Relation of annual incidence and remission rates of nocturia to baseline prevalence of at least one void per night (30%), at least two voids per night (12%), and at least three voids per night (5%).

3.6. Progression of nocturia

Three studies provided proportional measures for progression/remission of nocturia [18,19,28]. In a Scottish study conducted among middle-aged and elderly men [18], progression of nocturia occurred in 40% and remission in 10%, whereas in 50% of men nocturia remained unchanged after 5-yr follow-up. In an Austrian study also conducted among middle-aged and elderly men [19], progression occurred in 28%, remission in 27%, while in 45% of men nocturia symptoms were unchanged. An Austrian study conducted among women of all adult ages [28], reported after 6.5-yr follow-up, progression from one void to at least two voids per night occurred in 21% of women with one void per night at the baseline, and remission to one void per night in 23% of women with at least two voids per night at the baseline.

3.7. Strengths

To our knowledge, this is the first systematic review assessing the natural history of nocturia. The strengths of this review include a contemporary and comprehensive search of both published and unpublished studies without language restrictions, the duplicate assessment of eligibility and data extraction, and the appraisal of risk of bias. Although randomized trials provide estimates of treatment effect with the lowest risk of bias, populations enrolled are likely to differ from general populations in a variety of ways, making their application to general populations limited [34]. Hence, we chose to provide estimates from observational studies of unselected patients; such studies are likely to be the best source of estimates of prognosis. We used appropriate statistical methods to generate pooled estimates, followed a prespecified data analysis plan, and employed a limited number of important and plausible hypotheses to explore potential determinants of heterogeneity, and applied novel approaches to risk of bias assessment [14]. Finally, sensitivity analyses did not change results appreciably.

3.8. Limitations

The limitations of our review are largely the weaknesses of the eligible studies. Firstly, included studies use several different instruments for assessment with different definitions of nocturia. Secondly, variation in follow-up times makes comparison of estimates for incidence and remission rates of nocturia challenging because of the fluctuating nature of this symptom [35]. Pooling the rates from studies with follow-up times varying from 6 mo to 16 yr (Table 1) necessarily involves some approximation when trying to estimate average annual incidence and remission. These studies have included some people with interventions and are therefore somewhat limited as not entirely representing the "natural" history. Another important limitation is the very wide differences between rates of both incidence and remission across studies, differences that could be partially explained by age. Differences in age distributions and follow-up times between male and female studies limited the comparability of the estimates between sexes. Finally, although identified studies include both men and women of all adult ages, there is paucity of studies including younger adults.

3.9. Implications for clinical practice and future research

Besides being useful in counseling patients with nocturia, these results highlight the burden of nocturia among older men and women compared with younger adults. Those aged over 60 yr were nearly four times more likely to develop nocturia compared with adults aged 40–59 yr. Also, while one out of every eight persons with nocturia reported remission annually, for clinicians and patients, nocturia remains a challenging condition to treat [6,36]. With the aging of populations worldwide and the well-recognized negative health impact of frequent nocturia [15,37], development of novel treatment strategies that are well-tolerated should remain a research priority.

4. Conclusions

Our study summarizes the incidence and remission of nocturia in a general population using data from five low and eight high risk of bias studies. Across all available studies, the incidence of nocturia is 0.4% per year among adults aged $<$ 40 yr, 2.8% among those aged 40–59 yr, and 11.5% among those aged $\geq$ 60 yr, while overall remission is 12.1% per year; estimates, however, varied considerably among studies. These estimates can aid with management decisions and counseling related to 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: Pesonen, Cartwright, Tikkinen.
Acquisition of data: Pesonen, Cartwright, Mangera, Santti, Griebling, Pryalukhin, Riikonen, Tähtinen, Agarwal, Tsui, Vaughan, Markland, Johnson, Fonsell-Annala, Khoo, Aoki, Tikkinen.
Analysis and interpretation of data: Pesonen, Cartwright, Auvinen, Heels-Ansdell, Guyatt, Tikkinen.
Drafting of the manuscript: Pesonen, Cartwright, Tikkinen.
Critical revision of the manuscript for important intellectual content: Pesonen, Cartwright, Mangera, Santti, Griebling, Pryalukhin, Riikonen, Tähtinen, Agarwal, Tsui, Vaughan, Markland, Johnson, Fonsell-Annala, Khoo, Tammela, Aoki, Auvinen, Heels-Ansdell, Guyatt, Tikkinen.
Statistical analysis: Pesonen, Cartwright, Heels-Ansdell, Guyatt, Tikkinen.
Obtaining funding: Tikkinen.
Administrative, technical, or material support: Tammela.
Supervision: Cartwright, Guyatt, Tikkinen.
Other: None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eururo.2016.02.014.

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PUBLICATION II

The impact of nocturia on mortality: a systematic review and meta-analysis

Pesonen JS, Cartwright R, Vernooij RWM, Aoki Y, Agarwal A, Mangera A, Markland AD, Tsui JF, Santti H, Griebling TL, Pryalukhin AE, Riikonen J, Tähtinen RM, Vaughan CP, Johnson TM 2nd, Auvinen A, Heels-Ansdell D, Guyatt GH, Tikkinen KAO

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The Impact of Nocturia on Mortality: A Systematic Review and Meta-Analysis

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ABSTRACT

Purpose: Nocturia (waking from sleep at night to void) is a common cause of sleep disruption and associated with increased comorbidity and impaired quality of life. However, its impact on mortality remains unclear. We performed a systematic review and meta-analysis to evaluate the association of nocturia with mortality, both as a prognostic and causal risk factor.

Materials and Methods: We searched PubMed, Scopus, CINAHL and major conference abstracts up to December 31, 2018. Random effects meta-analyses addressed adjusted relative risks (RR) of mortality for people with nocturia and a meta-regression explored potential determinants of heterogeneity, including risk of bias. We applied the GRADE framework to rate the quality of evidence for nocturia as a prognostic risk factor for mortality and, separately, as a cause of mortality.

Results: Of 5230 identified reports, 11 observational studies proved eligible. For the assessment of nocturia, ten studies used symptom questionnaires and one frequency-volume charts. Nocturia was defined as ≥2 episodes/night in six (55%), and as ≥3 episodes/night in five (45%) studies. Pooled estimates demonstrated a risk ratio of 1.27 (95% confidence interval 1.16-1.40; I^2=48%; absolute 5-year mortality difference 1.6% and 4.0% in people aged 60 and 75 years, respectively). The pooled estimates of relative risk did not differ significantly across varying age, gender, follow-up time, nocturia case definition, risk of bias, or study region. We rated the quality of evidence for nocturia as a prognostic factor as moderate and as a cause of mortality as very low.

Conclusions: Nocturia is probably associated with an approximately 1.3-fold increased risk of death.

Keywords: epidemiology; meta-analysis; mortality; nocturia; systematic review

INTRODUCTION

Nocturia (waking from sleep at night to void) is one of the most common and bothersome lower urinary tract symptoms (LUTS) [1,2]. The incidence of nocturia increases markedly with age in both women and men [3]. Besides being a common cause of sleep disruption and impaired quality of life, nocturia is associated with comorbidities such as diabetes, cardiovascular diseases, chronic respiratory diseases, neurological diseases and malignancies [4-6]. An accompanying meta-analysis demonstrates that nocturia is associated with a 1.2-fold risk of falls and 1.3-fold risk of fractures [7]. Suggesting a number of possible causal pathways, some authors have postulated that nocturia may increase the risk of death [8].

As people with nocturia tend to be older and are more likely to have comorbid conditions, the relevance of using nocturia as a mortality risk factor must consider the effect of various confounders of the association between nocturia and mortality (i.e. we would not want to attribute to nocturia an association with death that can be completely explained by older age). To optimally assess the impact of nocturia on mortality, one must also take into account fluctuation of nocturia, as well as follow-up time (time interval after initial assessment) [3]. Furthermore, investigators should use a validated nocturia assessment method, and to further minimize the risk of bias, reliably register all deaths during follow-up.

The primary aim of our systematic review and meta-analysis is to clarify the association with, and the possible impact of nocturia on mortality, addressing possible effect modification by age, gender, follow-up time, varying nocturia definitions, and different sources of bias on the relative measures of association (i.e. possible variation in the

extent of association by age, gender, and other factors). We therefore tested the relation of nocturia with mortality, both as a prognostic risk factor and causal agent.

MATERIALS AND METHODS

We registered the review protocol (PROSPERO: CRD42016051132), and followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidance [9].

Data sources and searches

We searched the databases of PubMed (from 1946), Scopus (from 1995), and Cumulative Index of Nursing and Allied Health Literature (CINAHL) (from 1960) up to December 31, 2018. Additionally, we searched the conference proceedings of the American Urological Association (AUA), European Association of Urology (EAU), International Continence Society (ICS), and International Urogynecological Association (IUGA) annual conferences from 2005 to 2018 for any ongoing or unpublished studies. We did not apply any restrictions to language or publication status. Finally, we hand-searched the reference lists of the included articles. Supplementary Appendix 1 provides the search strategy.

Eligibility criteria

We included longitudinal studies with a follow-up (study duration) of at least three months with at least 95% of the participants being adults (aged ≥18 years), assessing nocturia at baseline and reporting death during follow-up (after an initial assessment). We excluded studies that evaluated the effect of any intervention, including cohorts of untreated control arms.

Study selection and data extraction

We employed standardized, pilot-tested forms with detailed instructions for screening of abstracts and full texts, risk of bias assessments, and data extraction. Pairs of two reviewers independently screened study reports for eligibility, assessed risk of bias of eligible studies, and abstracted data. The reviewers resolved disagreements through discussion and, if necessary, consulted clinician-methodologist adjudicators. When more than one report provided data of the same study, we extracted relevant data from all reports after excluding overlap. We recorded the country/source of the study sample, age and sex distribution, exclusion criteria, assessment tools used for nocturia, follow-up time, sample size, exclusion criteria and response rate, and adjustment variables (for the mortality effect estimates). We contacted the authors of primary studies for confirmation and clarification of our data extraction.

Assessment of the quality of evidence and risk of bias

According to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework, for assessments of prognosis, a body of observational studies begins as high-quality evidence. Several categories of limitations may, however, reduce evidence quality, including risk of bias, imprecision, inconsistency and indirectness [10]. In contrast, in the GRADE approach for studies of interventions, a body of observational studies begins as 'low-quality' evidence, and may be rated down to 'very low' by the same limitations as in intervention studies, but may also be rated up by factors such as a large effect size or a dose-response gradient [11]. Therefore, in this review, which includes only observational studies, the evidence can provide trustworthy inferences about prognosis (i.e. is nocturia associated with mortality) but not causation (i.e. does nocturia cause an increase in deaths). To formally compare the certainty of the

pooled estimates for nocturia both as a prognostic factor (synonymous with risk factor) and as a cause of mortality, we assessed the quality of evidence with the GRADE framework for both prognostic and intervention research [10,11].

The methods for risk of bias evaluation for longitudinal cohort studies are less developed than the methods for randomised controlled trials [12]. Through discussion and consensus building, and taking previous literature into account [3, 13-15], we developed an instrument to categorise studies as either low or high risk of bias (Supplementary Appendix 2). This includes the features of the included studies that could potentially bias the estimates: representativeness of the sample to the general population, confidence in the assessments of nocturia and mortality, proportion of missing data and adjustments for important potential confounders/risk factors of mortality.

Data analysis, including statistical analysis

To calculate the pooled estimates for relative measures of association of nocturia with mortality, we extracted hazard ratios (HR), or alternatively relative risks (RR) to be used interchangeably with HRs. To minimize confounding, from the reported regression models we selected those with maximum adjustments. If a study reported only an odds ratio (OR) instead of HR or RR we, acknowledging the high prevalence of nocturia, converted the OR into RR using the following formula:

$$RR = OR / (1 - p + (p \times OR))$$

in which p represents the baseline risk i.e. the risk of death in people without nocturia at the baseline [16]. We calculated the pooled RRs using the DerSimonian–Laird random effects inverse variance method. When raw data were available, to take account of the

effect of potential confounders including age and comorbidities, we derived adjusted RRs from multivariable logistic regression models.

To address the effect of age and the natural history of nocturia on the relative measures of association, we stratified the analyses by three age groups (18-49 yr, 50-69 yr and ≥70 yr). We adjusted for gender, follow-up time (<10 vs. ≥10 yr), risk of bias and study region and examined these variables as possible effect modifiers using chi-square tests. We stratified estimates by nocturia status in terms of a binary variable (case definitions of ≥2 vs. 0-1; and ≥3 vs. 0-2 voids/night) and a three-value categorical variable (2 vs. 0-1 and ≥3 vs. 0-1 voids/night), using the latter to explore exposure-response relationship of nocturia with mortality.

We complemented our subgroup analyses using chi-square tests with meta-regression analysis weighted by the inverse of the variance in a random effects model employing pre-specified hypotheses. We examined the following variables as potential sources of heterogeneity: (1) gender, (2) age, (3) length of follow-up, (4) nocturia case definition, and (5) risk of bias. We pre-specified hypotheses that the effect of nocturia on mortality would be higher for: (1) male vs. female or mixed gender, (2) younger age (<70 vs. ≥70 yr), (3) shorter follow-up time (<10 vs. ≥10 yr), (4) higher nocturia case definition (≥3 vs. ≥2 voids/night), and (5) high vs. low risk of bias. We set a threshold of p value less than 0.05 as a minimum criterion for a credible subgroup effect.

We report the association of nocturia with mortality in terms of both relative and absolute estimates, presenting five-year absolute risks of death among men and women aged 60 years and older — an age group commonly affected by nocturia [3]. When

calculating the baseline risks, we first estimated the average five-year death rates from the reported annual death rates for people aged 55-64 and 75-84 yr in the USA for 2016 [17]. Then, for the average estimates on the prevalence of nocturia of two or more voids per night [18] in desired age groups, we extracted the reported prevalences from studies included in a previous comprehensive systematic review [19] (Supplementary Appendix 3), calculated the 95% confidence intervals (CI) for natural logarithms of prevalences per 100 people and pooled the estimates in random-effects meta-analysis (Supplementary Fig. 1). Finally, to derive the baseline risks in the absence and presence of nocturia, we divided the average death rates in proportions based on the prevalence of nocturia and pooled relative risks for the desired age groups. Statistical analyses were performed using metan and metareg in Stata 12.1 (StataCorp, College Station, TX, USA) [20].

RESULTS

Literature search and study characteristics

We screened 5 230 abstracts and retrieved 132 potentially eligible full text reports and 22 conference abstracts (Fig. 1). Ten original full text articles and one conference abstract provided data on nocturia-associated death, including 19 590 men and 14 241 women with a total follow-up of 297 379 person-years (Table 1) [21-32]. Five (45%) of the 11 authors confirmed the accuracy of our data extraction [22,25,27,29,31]; two (18%) corrected some errors or provided additional information [26,32] and four (36%) were unable respond to our requests for data checks and clarifications [21,23,28,30].

Studies were conducted on three continents, in male and mixed gender populations that varied widely in their age distributions and follow-up times (Table 1). Nocturia was defined as ≥2 episodes per night in six (55%), and as ≥3 episodes per night in five (45%) studies. Reflecting the differences in study populations, as well as variations in symptom assessment methods, the baseline prevalence of nocturia in the study populations varied widely, with ranges of 8-34% based on a case definition of ≥2 (vs. 0-1 voids/night) and 2.5-35% with a case definition of ≥3 (vs. 0-2 voids/night) in adults aged <70 yr; in adults aged ≥70 yr, the range was 35-49% in the broader case definition and 8-38% in the more restrictive (Supplementary Table 1).

Risk of bias

To identify eligible individuals, two studies used electoral rolls [22,27], two household registries [23,26] and three civil registries [25,29,32]. One study used a combination of hospital and primary care registries [28], one recruited patients from a hospital's diabetes clinic [30] and one used primary care registries for White and zip code lists for Black participants [31]. We considered the cohorts of seven studies to adequately represent general populations with a satisfactory participation rate [21-23,26-28,32] (Fig. 2, Table 1). For assessment of nocturia at baseline, ten studies used symptom questionnaires and one used frequency-volume charts. We considered eight studies (73%) to have assessed nocturia accurately [25-32] (Fig. 2, Table 1). Five studies (45%) collected mortality data from a national death registry, and five (45%) used linkage to registries of different health care institutions. We considered that ten studies (91%) assessed mortality accurately through registry data [21-23,25-30,32]. Eight studies (73%) had little missing data [22,25-29,31,32]. Six studies (55%) adequately performed

adjustments for their estimates [22,25,26,29,31,32] (Fig. 2, Table 1, Supplementary Table 1).

Impact of nocturia on mortality

The pooled relative risk of death in 11 studies (2 low and 9 high risk of bias) proved higher in people with nocturia compared to those without nocturia (RR 1.27; 95% CI 1.16-1.40; heterogeneity: I^2=48.3%; moderate quality evidence for prognosis and very low quality evidence for causality) (Fig. 3, Table 2).

In subgroup meta-analyses, the pooled estimates for association between nocturia and mortality did not differ significantly for samples stratified by age, gender, follow-up time, nocturia case definition, risk of bias, or study region (Supplementary Tables 1-3). This was also true for the multivariable-adjusted meta-regression analyses (Supplementary Table 4).

Based on the mean death rates in the USA among people aged 60 and 75 yr with respective age-specific prevalences of nocturia (≥2 episodes per night) of approximately 20% and 40% (Supplementary Fig. 1), the nocturia-associated increase in the overall five-year absolute death risk were 1.6% and 4.0% among people aged 60 and 75 yr, respectively (Fig. 4, Supplementary Fig. 2).

The quality of evidence

We identified 11 studies: 2 low and 9 high risk of bias (Figure 2). We rated down the quality due to the high risk of bias (to which the majority of the included studies were susceptible). We therefore rated the quality of evidence (certainty in estimates) as

moderate for nocturia as a prognostic risk factor for mortality, and as very low quality for nocturia as a causal factor for mortality (Table 2).

DISCUSSION

This meta-analysis showed a 27% increase in relative risk of death in people with nocturia (defined as either ≥2 or ≥3 episodes/night) compared to those without nocturia after adjustment for age, gender and various comorbidities. This correspondents with nocturia-associated increase in the overall five-year absolute death risk by 1.6% among aged 60 yr and 4.0% among aged 75 yr. The magnitude of the association did not differ across a number of predictor variables. Our finding is of moderate-quality evidence for nocturia as prognostic factor of increased risk of death but only very low-quality evidence for nocturia as a cause of mortality.

Strengths and limitations

The strengths of this review include a comprehensive search of both published and unpublished studies without language restrictions; duplicate assessment of eligibility, risk of bias, and data extraction; checking of data accuracy with the authors of the original studies; and appraisal of the quality of evidence using the GRADE approach for inferences regarding nocturia both as a prognostic factor and as a causal factor for mortality. Besides the novel approaches in establishing the best available evidence on the topic, to our knowledge, our study is the first to provide absolute effects in addition to relative estimates on the association between nocturia and mortality (for this purpose, we also meta-analyzed the prevalence of nocturia; this information is likely of interest itself, see Supplementary Figure 3).

The limitations of our review are largely those of the eligible studies. No study was free of risk of bias and limitations related to non-representativeness of source populations, inaccuracy in assessments of nocturia or mortality, missing data or inadequately adjusted analyses were common (Figure 2). Second, although the analyses showed no effect for nocturia case definition, only three studies provided estimates for nocturia as a discrete variable with multiple values (number of voids). Third, only one study [26], provided data on the association between nocturia and mortality specifically for women. Fourth, none of the studies addressed causes of death; and we were therefore unable to assess mortality from specific causes. Fifth, no detailed data from bladder diaries were available, and we were therefore unable to differentiate the effects of nocturia on mortality when appearing as an isolated symptom or accompanied by other LUTS, or if nocturia was due to global/nocturnal polyuria, reduced bladder capacity or mixed etiology [1]. Sixth, there was paucity of studies assessing sleep disorders as potential comorbid conditions with nocturia, and thus, we were unable to differentiate between the roles of insomnia symptoms as potential confounders vs. mediators for mortality (nocturia caused by primary insomnia vs. insomnia secondary to nocturia) [33]. Given that, especially among the older people, nocturia is one of the leading causes of sleep disruption, which has further been shown to prognosticate mortality, analyses to test effect modification by sleep disorders would be highly relevant [34-36]. Accordingly, in the two available studies exploring the role of sleep disruption as one of the potential mediators between nocturia and mortality, both conducted in Western male populations and the other excluded from our review for being an interventional study (a randomized trial of dutasteride for prostate cancer chemoprevention), the association between nocturia and mortality turned non-significant after controlling the estimates for sleep disorders and other comorbidities [31,36]. Seventh, none of the studies utilized more

sophisticated analytical techniques, such as structural equation modeling, to identify potential causal pathways between nocturia and mortality [37]. Eighth, although the meta-regression analysis failed to show an influence of duration of follow-up, lack of repeated assessments during the follow-up and, therefore, failure to take into account the effect of incident and remittent nocturia on the estimates limits that analysis. Finally, results provide only very low-quality evidence regarding nocturia as a cause of the increased death rate associated with the exposure.

Relation to prior work

Only one earlier systematic review with meta-analysis has been published examining the impact of nocturia on mortality [38]. This systematic review published in 2015, reported a pooled HR of 1.23 (1.07-1.42), comparable to our best estimate. The review included seven studies, all included in our review [18,19,22,23,24-26], but failed to include four studies that proved eligible in our systematic review: one full text article [30] and one conference abstract [23] that were reported before the publication of their review and apparently met their eligibility criteria, and two studies that were published after their review appeared [31,32]. In their subgroup analyses (no adjustments used or meta-regression performed), shorter follow-up time (<10 yr vs. >10 yr), larger sample size (>5000 vs. ≤5000 people) and more restrictive nocturia case definition (≥3 vs. ≥2 voids per night) predicted mortality. With comprehensive adjustments and inclusion of four additional studies [23,30,31,32], none of these subgroup effects remained significant in our meta-analysis. To rate the risk of bias, the authors reported that they used or planned to use an instrument designed for observational studies [39]; they did not, however, present the results. The review also lacked any assessment of nocturia-associated

absolute effects on mortality and included no assessment of quality of evidence for prognosis or causation.

Implications of findings

Clinicians and patients should be aware that nocturia occurring at least twice per night may be a marker of ill health. Although urological treatments have potential to improve quality of life of patients with nocturia, clinicians should focus not only on treating the symptom, but also exploring patients' general health taking into account the relevant risk factors for each individual [40,41]. The association between nocturia and mortality likely reflects chronic illness as a cause of both nocturia and mortality. For instance, it is not difficult to imagine how diabetes could cause both nocturia and premature death. It is less likely, but still possible, that nocturia is in the causal pathway leading to premature death. For instance, impaired sleep as a result of nocturia could impair physiological night-time blood pressure dipping, increase sympathetic activity [42], and thus increase cardiovascular deaths. In addition, fractures and other injuries may result from falls or other accidents related to frequent night-time toileting and daytime fatigue [7], and complications of these events could result in premature death. Indeed, the companion review to this article documents an association between nocturia and falls and fractures. These causal pathways are, however, speculative, and we have concluded that there is only very low-quality evidence supporting nocturia as a causal factor in premature death [7].

CONCLUSIONS

Moderate-quality evidence suggests that nocturia (defined as either ≥2 or ≥3 episodes/night) is associated with a 1.3-fold increased risk of death. Future investigations should address the impact of treatment for nocturia on mortality.

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Figure (and supplementary material) legends

Table 1. Characteristics of the original studies included in analyses.

Table 2. Evidence profile: nocturia as a prognostic factor for mortality versus as a cause of mortality.

Figure 1. Study flow chart.

Figure 2. Risk of bias of the included studies.

Figure 3. A forest plot of the relative risks of death in people with nocturia.

Figure 4. Relative and absolute risk of death in five years between people with and without nocturia.

Table 1. Characteristics of the original studies included in analyses.

Study	Country	Source of sample	Population characteristics	Exclusion criteria	Assessment of nocturia	Assessment of mortality	Median follow-up time	No. of contacted at the baseline	No. of eligible respondents
Asplund 1999 [21]	Sweden	Pensioners' association registry	Both sex, 40% men, mean age 73 yr (range 53-92 yr)[a]	None	Unvalidated	National death registry	4.5 yr	10216	6143 (60%)
Bursztyn 2006 [22]	Israel	Electoral records	Both sex, 55% men, all aged 70 yr	None	Unvalidated	National death registry	12 yr	759	456 (60%)
Fitzgerald 2009 [23,24][b]	Puerto Rico	Various public registries	Men, mean age 71 yr (range 60-99 yr)	Institutionalized	Unvalidated	National death registry	2 yr	1736	1480 (85%)
Nakagawa 2010 [25]	Japan	Civil registry	Both sex, 46% men, mean age 76 yr (range 70-97 yr)	Non-members of NHI system	In accordance with IPSS/AUA-SI	NHI registry	5 yr	2925	784 (27%)
Kupelian 2011 [26]	USA	Various public registries	Both sex, 47% men, mean age 49 yr (range 20-90 yr)	Institutionalized	In accordance with IPSS/AUA-SI	NHCS Linked Mortality Files	8.8 yr	39695	15988 (69%)
Galizia 2012 [27]	Italy	Electoral rolls	Both sex, 45% men, mean age 74 yr (range 65+ yr)	None	In accordance with IPSS/AUA-SI	GP registries, death certificates	12 yr	1780	1288 (72%)
Lightner 2012 [28]	USA	Medical records from various health care units	Men, mean age 54 yr (range 40-79 yr)	Surgery/condition affecting lower urinary tract	AUA-SI (assessed every 2 yrs)	Multiple sources incl. death certificates and autopsy reports	17 yr	3874	2115 (55%)[c]
Van Doorn 2012 [29]	The Netherlands	Civil registry	Men, mean age 61 yr (range 50-78 yr)	Surgery/condition affecting lower urinary tract, poor health	FVC (frequency-volume chart)	GP registries	13.4 yr	3398	1114 (33%)
Chung 2014 [30]	Taiwan	Hospital diabetic clinic	Both sex, 52% men, mean age 63 yr (range 32-94 yr)[a]	Treatment for type 2 diabetes for less than 1 yr	OABSS	National death registry	2.5 yr	1715	1301 (76%)
Endeshaw 2016 [31]	USA	Medicare beneficiares, designated zip code areas	Men, mean age 74 yr (range 70-79 yr)	None	IPSS	Clinic visits, telephone contacts, death certificates	9 yr	Unclear	1478
Åkerla 2019 [32]	Finland	Civil registry	Men, mean age 58 yr (range 50-70 yr)	None	DAN-PSS (assessed every five years)	National death registry	21 yr	3143	1332 (42%)[d]

AUA-SI = American Urological Association Symptom Index, DAN-PSS = Danish Prostatic Symptom Score, GP = general practice, IPSS = International Prostate Symptom Score, LUTS = lower urinary tract symptoms, NHCS = National Center for Health Statistics, NHI = National Health Insurance, OABSS = Overactive Bladder Symptom Score

[a] Age range approximated by using the reported standard deviation (SD) for mean age (mean age ± 3SD).

[b] Previously unpublished analyses based on the study raw data [21].

[c] To replace men who either died or dropped out, additional 332 men were recruited during the first four years of follow-up.

[d] Response available for every assessment of LUTS (while alive).

Table 2. Evidence profile: nocturia as a prognostic factor for mortality versus as a cause of mortality.

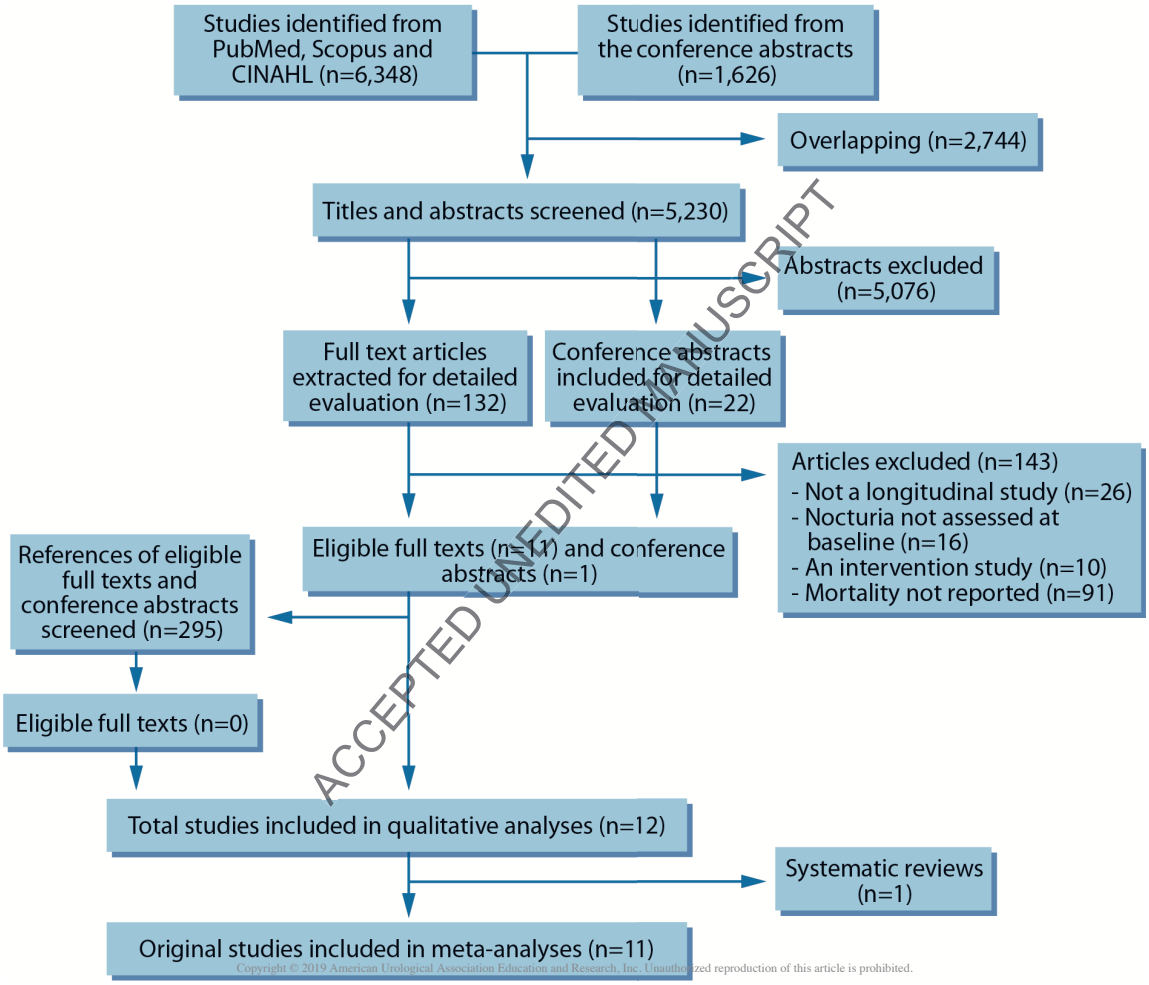
Summary of findings						Quality assessment					
No. of studies (design)	No. of participants[a]		Relative risk (95% CI)	Absolute risk difference	Prognosis vs. causation[b]	Starting quality	Risk of bias[c]	Inconsis-tency	Indirectness	Imprecision	Certainty in estimates
	No nocturia	Nocturia									
11 (observational cohort)	26763	7048	1.27 (1.16-1.40) [c]	Age 60 yr: 1.6% per 5 yr Age 75 yr: 4% per 5 yr	Prognosis	High	Serious limitations	No serious limitations	No serious limitations	No serious limitations	Moderate
					Causation	Low	Serious limitations	No serious limitations	No serious limitations	No serious limitations	Very low

GRADE = Grades of Recommendation, Assessment, Development, and Evaluation

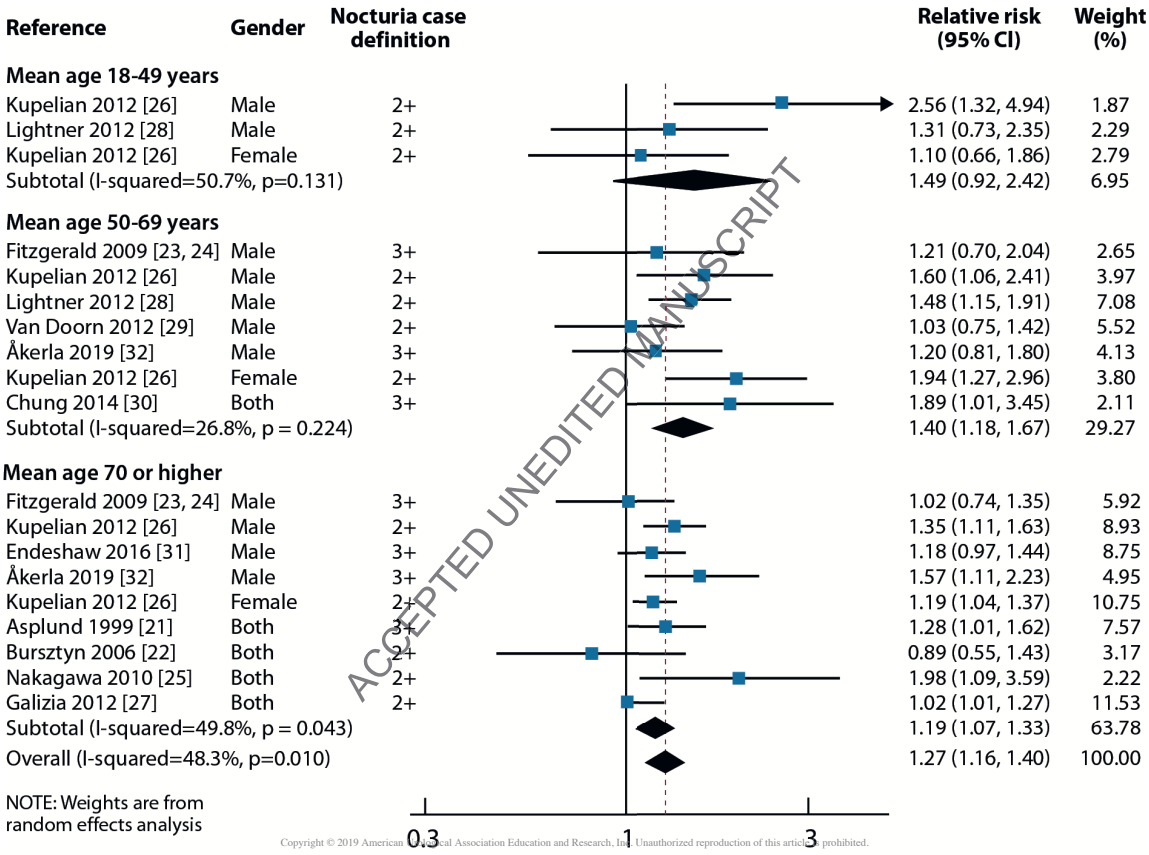
[a] Some studies reported the number of exposed participants for several nocturia case definitions. In these cases, the number of participants with ≥ 2 and 0-1 voids/night was included in the total count of exposed and unexposed participants.

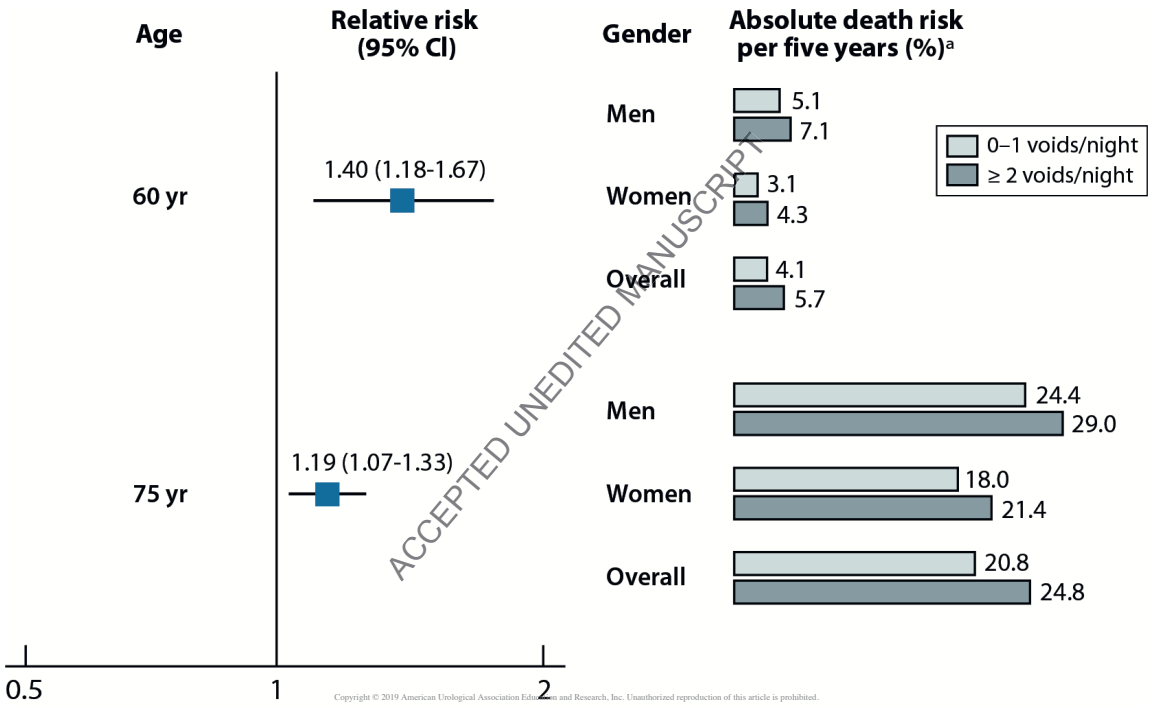
[b] Assessment based on the principles of the GRADE framework where the body of observational evidence begins as high quality when used for prognosis research and as low quality when used for intervention research.

[c] Assessment described in Supplementary Appendix 2 and Fig. 2.



Reference	Risk of bias criteria					Overall risk of bias
	Representativity of the source population	Assessment of nocturia	Assessment of mortality	Missing data	Adjustment	
Asplund 1999 [21]	+	−	+	−	−	High
Bursztyn 2006 [22]	+	−	+	+	+	High
Fitzgerald 2009 [23,24]	+	−	+	−	−	High
Nakagawa 2010 [25]	−	+	+	+	+	High
Kupelian 2011 [26]	+	+	+	+	+	**Low**
Galizia 2012 [27]	+	+	+	+	−	High
Lightner 2012 [28]	+	+	+	+	−	High
Van Doorn 2012 [29]	−	+	+	+	+	High
Chung 2014 [30]	−	+	+	−	−	High
Endeshaw 2016 [31]	−	+	−	+	+	High
Åkerla 2019 [32]	+	+	+	+	+	**Low**





PUBLICATION III

The impact of nocturia on falls and fractures: a systematic review and meta-analysis

Pesonen JS, Vernooij RWM, Cartwright R, Aoki Y, Agarwal A, Mangera A, Markland AD, Tsui JF, Santti H, Griebling TL, Pryalukhin AE, Riikonen J, Tähtinen RM, Vaughan CP, Johnson TM 2nd, Auvinen A, Heels-Ansdell D, Guyatt GH, Tikkinen KAO

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The Impact of Nocturia on Falls and Fractures: A Systematic Review and Meta-Analysis

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Keywords: falls; fractures; meta-analysis; nocturia; systematic review

ABSTRACT

Purpose: Although nocturia is associated with various comorbidities, its impact on falls and fractures remains unclear. We performed a systematic review and meta-analysis to evaluate the association between nocturia with falls and fractures, both as a prognostic and causal risk factor.

Materials and Methods: We searched PubMed, Scopus and CINAHL and abstracts of major urologic meetings up to December 31, 2018. We conducted random effects meta-analyses of adjusted relative risks (RR) of falls and fractures. We applied the GRADE approach to rate the quality of evidence for nocturia as a prognostic and causal factor of falls and fractures.

Results: Of 5230 potential reports, nine observational longitudinal studies provided data on the association between nocturia and falls or fractures (1 for both, 4 for falls, 4 for fractures). Pooled estimates demonstrated a risk ratio of 1.20 (95% confidence interval 1.05-1.37; I^2=51.7%; annual risk difference 7.5% among the elderly) for association between nocturia and falls and 1.32 (95% confidence interval 0.99-1.76; I^2=57.5%; annual risk difference 1.2%) for association between nocturia and fractures. Subgroup analyses showed no significant effect modification by age, gender, follow-up time, nocturia case definition or risk of bias. We rated the quality of evidence for nocturia as a prognostic factor as moderate for falls and low for fractures, and as very low as a cause of falls/fractures.

Conclusions: Nocturia is probably associated with an approximately 1.2-fold increased risk of falls and possibly with an approximately 1.3-fold increased risk of fractures.

INTRODUCTION

Falls and fractures are common, associated with substantial healthcare costs, and are a major reason for long-term functional impairment [1,2]. Older adults are at an increased risk of falling due to the age-related deterioration in balance and gait, which is worsened by illness and medications [3]. Over 30% of people aged over 65 years and living at home fall at least once per year [3,4]. Although only a minority of falls lead to fractures [4], injuries due to falls are common and, among older adults, are associated with a high risk of institutionalisation [2]. Developing multifactorial fall prevention programs therefore represents a major focus in geriatric research [5].

Nocturia is one of the most common and bothersome lower urinary tract symptoms (LUTS) [6,7], and according to an accompanying meta-analysis [8] (*parallel submission to The Journal of Urology*), associated with an approximately 30% increase in the risk of death. Nocturia is strongly associated with advanced age [9,10]. Approximately one in four adults in their sixties and half of adults in their eighties void two times per night [9] – a level that typically causes bother and is associated with impaired quality of life [11]. The etiology of nocturia is multifactorial, including age-related changes in the lower urinary tract, as well as alterations in renal function and sleep quality due to various medical conditions and lifestyle factors [12,13].

The relationship between nocturia and falls and fractures is complex as they are each associated with multiple comorbidities that could confound or mediate associations. Common factors associated with both nocturia and falls include older age, diabetes, cardiovascular diseases, depression and physical inactivity [12-14]. Some risk factors,

such as obesity, may however, increase nocturia but decrease fractures (e.g. obesity) [15,16].

Cross-sectional studies have consistently found an association of nocturia with falls [17,18] but less consistently an association with fractures [17,19]. However, in cross-sectional studies one can never be sure of the temporal relation between exposure and outcome. We therefore undertook a systematic review of longitudinal studies to explore the impact of nocturia on the risk of falls and fractures in a general population.

MATERIALS AND METHODS

We registered the review protocol (PROSPERO CRD42016051525), and followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidance [20].

Data sources and searches

We searched the databases of PubMed (from 1946 to present), Scopus (from 1995 to present), and Cumulative Index of Nursing and Allied Health Literature (CINAHL) (from 1960 to present) up to December 31, 2018 (Supplementary Appendix 1), and annual conference abstracts of the American Urological Association (AUA), the European Association of Urology (EAU), the International Continence Society (ICS), and the International Urogynecological Association (IUGA) from 2005 to 2018 for any ongoing or unpublished studies. We did not apply restrictions to language or publication status. We hand-searched the reference lists of the included articles.

Eligibility criteria

We included longitudinal studies with a follow-up of at least three months, with at least 95% of the participants aged ≥18 years. We included studies assessing nocturia at baseline and reporting falls or fractures at a later follow-up time. We excluded studies that evaluated the effect of any intervention, including cohorts of untreated control arms.

Study selection and data extraction

Pairs of reviewers, independently and in duplicate, screened the references for eligibility, assessed risk of bias using a pilot-tested standardized form, and extracted data from eligible studies. Reviewers resolved disagreements through discussion and, if necessary, consulted a clinician-methodologist adjudicator. When more than one report provided data from the same study, we extracted data from all reports after excluding overlap. We recorded the country/source of the study sample, age and sex distribution, exclusion criteria of the cohorts, assessment tools used for nocturia, follow-up time, sample size including response rate, and variables used to adjust for falls/fractures in the presence/absence of nocturia. We contacted the authors of primary studies for confirmation and clarification of our data extraction.

Risk of bias and quality of evidence assessment

The methods for risk of bias evaluation for longitudinal cohort studies are less well developed than the methods for randomised controlled trials [21]. Taking the previous literature into account [22-24], through discussion and consensus building, we developed an instrument to categorise studies as either low or high risk of bias. This includes the features of the included studies that could potentially bias the estimates:

the comparability of source populations, confidence in the assessment of nocturia and falls/fractures, proportion of missing data, and adjustments for important potential confounders/risk factors for falls and fractures. The overall risk of bias was categorised low if the study met criteria for low risk of bias in each of the five domains of the assessment (Supplementary Appendix 2).

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach includes separate criteria for rating the quality of evidence regarding a prognostic issue (is there a true association) versus a causal issue (is an exposure causally related to an outcome). With respect to prognosis, GRADE stipulates that observational studies can often provide trustworthy inferences (i.e. is nocturia associated with falls/fractures) and thus in GRADE rating begin as high-quality evidence. Observational studies, according to GRADE, seldom provide trustworthy evidence regarding causation (i.e. does nocturia cause falls/fractures) and therefore, for causation, observational studies begin as low-quality evidence. To highlight this key distinction, we evaluated the quality of evidence for nocturia both as a prognostic factor (synonymous with risk factor) and as a cause of falls/fractures [21,25,26]. More information on the rationale is available in the accompanying systematic review [8].

Data analysis, including statistical analysis

To calculate the pooled estimates for relative measures of association of nocturia with falls and fractures, we extracted relative risks (RR), or alternatively hazard ratios (HR) to use interchangeably with RRs. From the reported regression models, we selected the estimates with the highest level of adjustments to minimize the effect of

confounding. If a study reported only an odds ratio (OR) instead of HR or RR we converted the OR into RR using the following formula:

$$RR = OR / (1 - p + (p \times OR))$$

in which p represents the baseline risk i.e. the fall/fracture risk in individuals without nocturia at the baseline [27]. We calculated the pooled RRs by using the DerSimonian–Laird random effects inverse variance method. For studies providing access to the raw data, we derived new adjusted RRs from multivariable logistic regression models to take account of the effect of potential confounders.

To explore the association of nocturia with falls and fractures in subgroups, we stratified the estimates by age, gender, follow-up time and risk of bias. The estimates were stratified by nocturia status as a binary variable (case definitions of ≥2 vs. 0-1 and ≥3 vs. 0-2 voids/night) and a three-value categorical variable (2-3 vs. 0-1 and ≥4 vs. 0-1 voids/night), using the latter to explore exposure-response relationship of nocturia with falls and fractures. Additional subgroup-analyses with similar stratifications were conducted for studies reporting recurrent falls as an outcome.

As optimal decision-making requires estimates of both relative and absolute effects, we illustrated the difference in the absolute annual risk of falls and fall-related fractures between individuals with and without nocturia. To assess the average risks of falls and fractures in the general elderly population, the annual number people with ≥1 falls/year and the proportion of those who fell and sustained a fracture were extracted from prospective Western population-based studies included in a previous systematic review [4] (Supplementary Appendix 3). After calculating the 95% confidence intervals for natural logarithms of incidence rates of fallers per 100

person-years and proportions of individuals with a fall-related fracture per 100 fallers, the estimates were pooled in random-effects meta-analyses (Supplementary Figs. 1 and 2). To stratify the pooled estimates of average annual fall and fall-related fracture rates by age, coefficients from another systematic review, assessing various risk factors for falls, were utilized [3]. For estimating the prevalence of patient-important nocturia (defined as two or more voids per night) [11] in relevant age groups, we i) extracted the reported prevalences from studies included in a previous systematic review [9] (Supplementary Appendix 4), ii) calculated the 95% confidence intervals (CI) for natural logarithms of prevalence per 100 people, and iii) pooled the estimates in random-effects meta-analysis (Supplementary Fig. 3). Finally, to derive the baseline risks in the absence and presence of nocturia, we divided the average annual fall and fracture rates in proportions based on the prevalence of nocturia and pooled relative risks for the desired age groups. Statistical analyses were performed using metan and metareg in Stata 12.1 (StataCorp, College Station, TX, USA) [28].

RESULTS

Literature search and study characteristics

We screened 5 230 abstracts and retrieved 132 potentially eligible full text articles and 22 conference abstracts (Fig. 1). Five studies provided data on the association between nocturia and falls [29-35] and five on nocturia and fractures [29,30,36-39] (Table 1). Of the five studies assessing falls, three of the five authors confirmed the accuracy of our consensus data extraction [32-34], one provided additional information [31] and one was unable to assist with our requests [29]. Of the five studies assessing fractures, three of the five authors confirmed the accuracy of our

consensus data extraction [36-38], one provided additional information [39] and one was unable to assist with our requests [29].

Of the five studies assessing falls, three were conducted in North America, one in Europe and one in Australia. Of the five studies assessing fractures, two were conducted in North America, two in Europe and one in Eastern Asia. Studies included mainly older people in their seventies and predominantly men, with follow-up times varying from one to six years for studies of falls and four to nine years for studies of fractures (Table 1). Two studies were conducted in the same base population of older men with separate reports on falls and non-spine fractures with varying follow-up times [31,39]. We identified one conference abstract [29], which reported only death as an endpoint (was included in the accompanying meta-analysis [8]) but access to the study raw data provided assessments also for both falls and fractures [30] (Supplementary Fig. 4). We were therefore able to include five studies in the meta-analysis of falls with a total follow-up of 23 678 person-years and five studies in the meta-analysis of fractures with a total follow-up of 87 973 person-years.

Risk of bias

Of the five studies assessing falls, three used representative source populations [32-34], three conducted the baseline assessments of nocturia and follow-up assessments of falls accurately, three had little missing data at the follow-up [32,33,35], and three adequately adjusted their estimates for important prognostic risk factors for falls [31-33]. We judged three studies (assessing impact on falls) to be at overall high risk of bias (Fig. 2, Table 1, Supplementary Table 1).

Of the five studies assessing fractures, three used representative source populations [31,37,39], three assessed nocturia accurately [36,38,39], four assessed fractures accurately [36-39], three had little missing data at the follow-up [37-39], and two adequately adjusted their estimates for important prognostic risk factors for fractures [31,39]. We therefore considered four studies (assessing impact on factures) to be at overall high risk of bias (Fig. 2, Table 1, Supplementary Table 1).

Impact of nocturia on falls

In the meta-analysis of estimates adjusted at least for age and gender (5 studies: 2 low and 3 high risk of bias), the pooled relative risk of falling at least once in the follow-up was higher in people with nocturia compared to those without nocturia at baseline (RR 1.20; 95% CI 1.05-1.37; heterogeneity: I^2=52%; moderate quality evidence for prognosis and very low quality for causality) (Fig. 3, Table 2). In the subgroup analyses, the estimates did not differ by age, gender, follow-up time, nocturia case definition, or risk of bias (Supplementary Tables 1 and 2).

In the additional analysis of studies reporting recurrent falls as an outcome (3 studies: 1 low and 2 high risk of bias), the pooled, adjusted relative risk was 38% higher in people with nocturia at the baseline (RR 1.38; 95% CI 1.11-1.71; I^2=54.7%). The estimates were available only for men and did not differ by age, follow-up time, nocturia case definition, or risk of bias (Supplementary Tables 1 and 3).

The absolute risk of falling at least once a year was 5.5% higher among people aged 65 yr with nocturia (defined as ≥2 voids/night) compared to people without (defined

as 0-1 voids/night), and 7.5% higher in people aged 80 yr with nocturia compared to people without (Fig. 5, Supplementary Fig. 5).

Impact of nocturia on fractures

In the meta-analysis of estimates adjusted for at least age and gender (5 studies: 1 low and 4 high risk of bias), the pooled relative risk of having a fracture at follow-up was 32% higher in people with nocturia compared to those without nocturia at baseline (RR 1.32; 95% CI 0.99-1.76; heterogeneity: I^2=57.5%; low quality evidence for prognosis and very low quality for causality) (Fig. 4, Table 2). In subgroup analyses, the estimates did not differ significantly by age, gender, follow-up time, nocturia case definition or risk of bias (Supplementary Tables 1 and 4).

Regarding assessments on the association between nocturia and different types of fractures, only one estimate was available for each specific association with RRs of 1.36 (95% CI 1.03-1.79) for hip fractures in men [36], 1.00 (95% CI 0.90-1.20) for non-spine fractures in men [39], 1.37 (95% CI 0.19-9.86) for osteoporotic fractures in men [37] and 2.20 (95% CI 1.04-4.68) for specifically fall-related fractures in a mixed gender population [38], respectively (Supplementary Table 1).

The absolute annual risk of fractures was 0.9% higher in people with nocturia compared to people without among people aged 65 yr (Fig. 5). The absolute difference in annual fracture risk among people aged 80 yr was 1.2% between people with and without nocturia. (Fig. 5, Supplementary Fig. 5).

The quality of evidence

Of the five studies assessing falls, three were high and two low risk of bias (Fig. 2). We rated down due to high risk of bias (to which the majority of the included studies were susceptible). We therefore rated the quality of evidence as moderate for nocturia as a prognostic risk factor and as very low quality for nocturia as a causal factor for falls (Table 2). Of the five studies assessing fractures, four were high and one low risk of bias. We therefore rated down for risk of bias. We also rated down for imprecision (confidence interval crossed no effect). We therefore rated the quality of evidence as low for nocturia as a prognostic risk factor for fractures, and as very low quality for nocturia as a causal factor of fractures (Table 2).

DISCUSSION

This meta-analysis, based on best available evidence conducted predominantly among older adults, showed a probable excess relative risk of 20% for falling at least once, and an excess relative risk of 38% for falling recurrently during follow-up among people with nocturia compared to those without nocturia at baseline. The 20% relative risk increase corresponds with nocturia-associated increase in the absolute annual risk of falling by 5.5% among people aged 65 and by 7.5% among people aged 80. This meta-analysis also showed a possible increased relative risk of fracture of 32% in people with nocturia compared to people without nocturia after adjustment for age, gender and various comorbidities. The absolute risk of fractures was 0.9% higher in people with nocturia compared to people without among aged 65 yr, and 1.2% higher among aged 80 yr. Our findings are of moderate quality evidence for nocturia as a prognostic factor of increased risk of falls, low quality for nocturia as a prognostic

294 factor of increased risk of fractures, and very low quality for nocturia as a cause of
295 falls or fractures.
296
297 **Strengths and limitations**
298 The strengths of this review include a contemporary and comprehensive search of
299 both published and unpublished studies without language restrictions; the duplicate
300 assessment of eligibility and data extraction and risk of bias; the communication with
301 the authors of the original studies; and the appraisal of the quality of evidence, using
302 the GRADE framework for both prognosis and causation. This is the first systematic
303 review with meta-analysis to estimate the effect of nocturia on the risk of falls and
304 fractures. By including only population-based studies and excluding the effects of any
305 systematic intervention, our results provide the best available evidence on the
306 association between nocturia and falls and fractures. Finally, we also provided
307 estimates of both relative and absolute estimates of the risks of falls and fractures by
308 nocturia status (to get absolute estimates, we also meta-analyzed the prevalence of
309 nocturia; Supplementary Fig. 3).
310
311 The limitations of our review are largely those of the included studies. Firstly, because
312 of the small numbers of events, the confidence intervals around the estimates of the
313 association between nocturia and fractures are wide. Second, although the analyses
314 showed no significant effect for nocturia case definition, the evaluation of exposure-
315 response relationship was limited as only two studies of falls [31,34] and one study of
316 fractures [39] provided estimates for nocturia as a discrete variable with multiple
317 values. Third, there was a paucity of studies included women. Estimates of the
318 association between nocturia and falls were available only from cohorts of male or

mixed gender, while none of these studies and only one study of fractures, provided estimates separately for women. Fourth, although subgroup analyses split by median of mean age (75 yr for falls and 70 for fractures), showed no significant differences between the estimates, because of limited age-specific data, our pooled estimates can be used only to roughly estimate the differences in fall and fracture risks in different age groups. Fifth, as majority of the studies were conducted in Western countries, estimates may differ in non-Western countries. Finally, because the majority of studies were at high risk of bias, quality ratings were low for prognosis of fractures and very low for causation for both falls and fractures (indeed no data are available on whether successful treatment of nocturia prevents falls or fractures, evidence that would be required to be confident of a causal relationship).

Relation to prior work

One earlier systematic review examined the association of lower urinary tract symptoms in men with falls, injuries and fractures, and found that nocturia was consistently associated with increased risk of any fall [40]. This review published in 2016 included six retrospective and three prospective studies; all the prospective studies – but not the retrospective – studies were also included in our review [31,37,38]. The prior review did not include six studies that proved eligible in our systematic review: two studies conducted among men (one full text article [36] and one conference abstract [29]) and two studies [32,33] conducted among both genders that were reported before the publication of their review; and two studies [34,39] (both conducted among men) that were published after their review appeared. The prior review did not conduct a meta-analysis, nor did the authors provide estimates of

the impact of nocturia on the absolute risks of falls or fractures, or assess the quality of evidence.

Implications of findings

Clinicians and patients should be aware that nocturia is a marker of increased risk of falls, which may perhaps lead to fractures. The decision whether to treat or not to treat nocturia, primarily depends on the level of bother it causes. Especially when managing older adults reporting nocturia, the treatment requires understanding of the multifactorial etiology of nocturia [41,42]. At its worst, medical treatment of nocturia by manipulating diuresis, sleep or lower urinary tract function, can cause more harm than benefit [43,44]. Future research priorities include development of safer and more effective treatments for nocturia, establishment of how and when to offer the nocturia patient further evaluation, including when to refer to other specialties, such as geriatrics or sleep medicine, and including falls as an outcome in randomized trials of nocturia management.

CONCLUSIONS

Moderate quality evidence suggests that nocturia is associated with an excess relative risk of 20% for falls and low quality evidence suggests that nocturia is associated with an excess relative risk of 32% for fractures indicating an increase of more than 7% in the absolute annual fall risk and approximately 1% in fall-related fracture risk among the older adults. Future investigations should address the impact of treatment for nocturia on falls and fractures.

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Figure legends

Table 1. Characteristics of the original studies included in analyses.

Table 2. Evidence profile: nocturia as a prognostic factor for falls and fractures versus as a cause of falls and fractures.

Figure 1. Study flow chart.

Figure 2. Risk of bias of the included studies.

Figure 3. A forest plot of the relative risks of falls in people with nocturia.

Figure 4. A forest plot of the relative risks of fractures in people with nocturia.

Figure 5. Absolute risk of falls and fall-related fractures between older people with and without nocturia.

Table 1. Characteristics of the original studies included in analyses.

Study	Country	Source of sample	Population characteristics	Exclusion criteria	Assessment of nocturia at the baseline	Assessment of falls/fractures in the follow-up	Median follow-up time	No. of contacted at the baseline	No. of eligible respondents
Fitzgerald 2009 [29,30] [a]	Puerto Rico	Various public registries	Men, mean age 70 yr (range 60-99 yr)	Institutionalized	Unvalidated questionnaire	Falls and fractures via an interview, recall period of 1 yr	4 yr	1736	Baseline: 1332 (77%) Follow-up: 1011 (58%)
Parsons 2009 [31] [b]	USA	Various public registries	Men, mean age 74 yr (range 65-100 yr)	Physical or cognitive disability, terminal illness, bilateral hip replacement	AUA-SI	Falls assessed via repeated telephone contacts every 4 months	1 yr	Unclear	5872
Temml 2009 [36]	Austria	Health screening	Men, mean age 52 yr (range 41-80 yr)	None	IPSS	Hip fractures via hospital registries	5 yr	Unclear	1820
Frost 2010 [37]	Denmark	Civil registry	Men, mean age 65 yr (range 60-75 yr)	None	Unvalidated questionnaire [c]	All fractures via hospital registries	5 yr	9314	4696 (50%)
Nakagawa 2010 [38]	Japan	Civil registry	Both sex, 46% men, mean age 76 yr (range 70-97 yr)	Non-members of NHI system	A questionnaire in accordance with definitions by ICS	All fractures via NHI registry	5 yr	2925	784 (27%)
Vaughan 2010 [32]	USA	National social insurance program registry (Medicare)	Both sex, 52% men, mean age 75 yr (range 65-106 yr)	Poor co-operation, institutionalized, history of falls (1 yr prior to the baseline assessment)	A questionnaire in accordance with definitions by ICS	Falls assessed via repeated telephone contacts every 6 months	3 yr	2188	Baseline: 1000 (46%) Follow-up: 692 (69%)
Stenhagen 2013 [33]	Sweden	Civil registry	Both sex, 46% men, mean age 71 yr (range 60-93 yr)	Inability to speak Swedish, history of falls (6 mo prior the baseline assessment)	Unclear	Falls via an interview, recall period of 6 months	6 yr	5370	Baseline: 2535 (47%) Follow-up: 1720 (32%)
Marshall 2016 [39] [b]	USA	Various public registries	Men, mean age 74 yr (range 65-100 yr)	Physical or cognitive disability, terminal illness, bilateral hip replacement	AUA-SI (assessed every 2 yrs)	Nonspine fractures via post/telephone and medical record assessments, repeated every 4 months	8.6 yr	Unclear	5989
Noguchi 2016 [34,35]	Australia	Electoral roll	Men, mean age 76 yr (range 70-99 yr)	Institutionalized, dementia, neurological disease, poor mobility	IPSS	Falls assessed via repeated telephone contacts every 4 months	1 yr	3821	1366 (36%)

AUA-SI = American Urological Association Symptom Index, GP = general practice, ICS = International Continence Society, IPSS = International Prostate Symptom Score, NHI = National Health Insurance, NHS = National Health Service, OABSS = Overactive Bladder Symptom Score

[a] Previously unpublished analyses based on the study raw data [30].

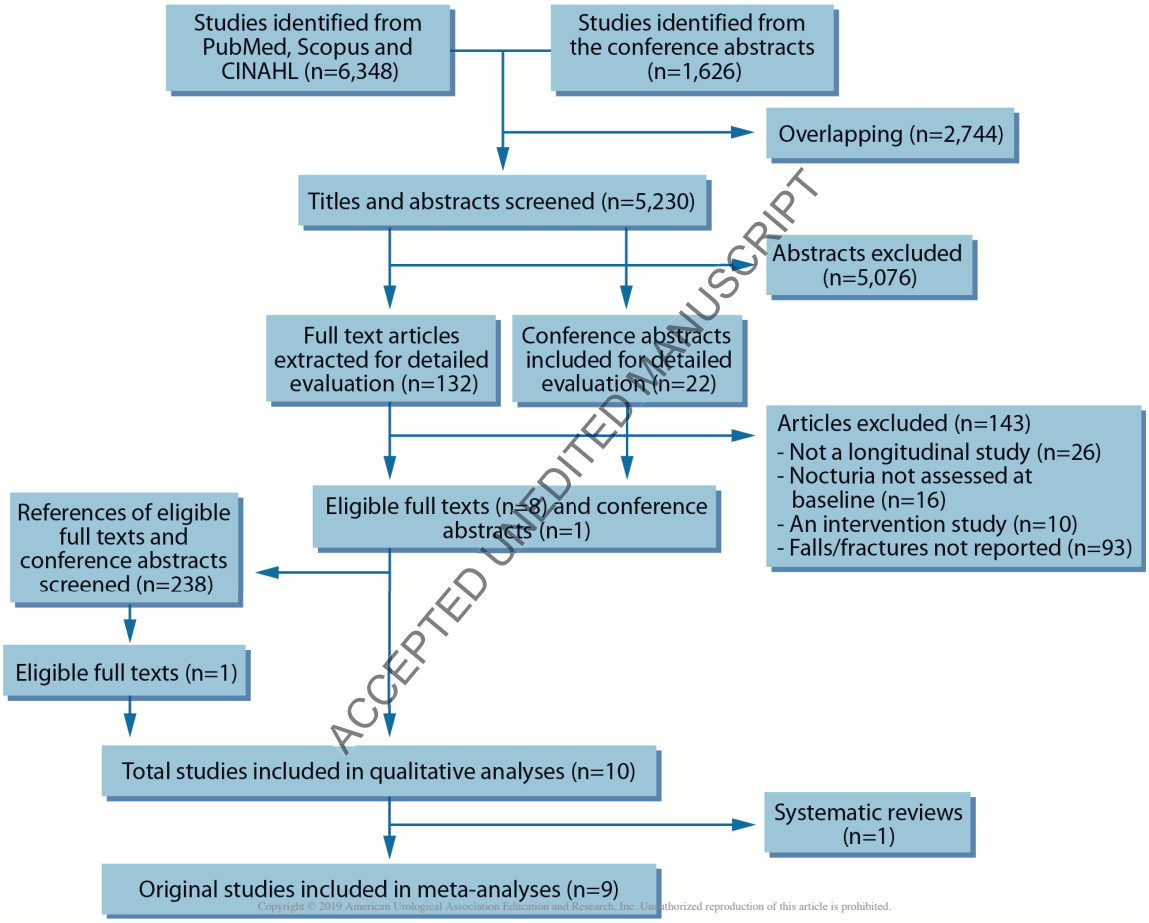
[b] Osteoporotic Fractures in Men Study (MrOS) cohort.

[c] Nocturia registered only for men specifying the symptom in the assessment of symptoms/diseases related to urinary tract.

Table 2. Evidence profile: nocturia as a prognostic factor for falls and fractures versus as a cause of falls and fractures.

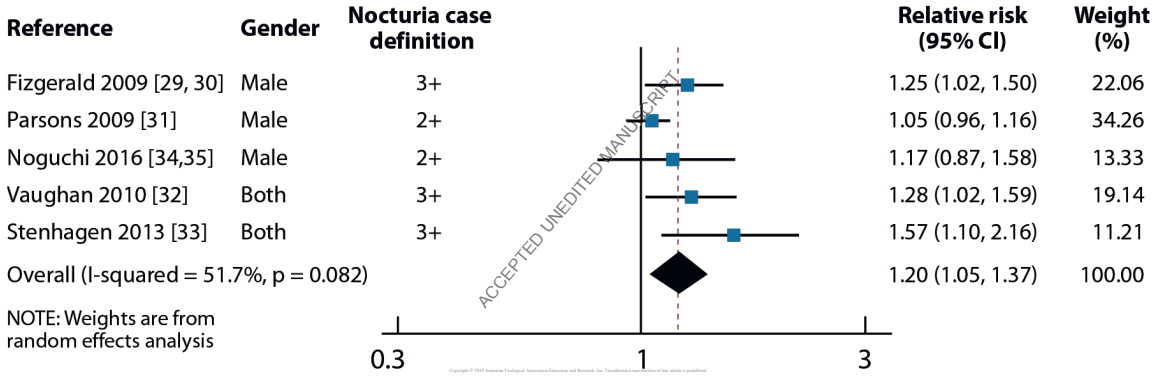
Summary of findings					Quality assessment						
No. of studies (design)	No. of participants: No nocturia	No. of participants: Nocturia[a]	Relative risk (95% CI)	Absolute risk difference per year	Prognosis vs. causation[b]	Starting quality	Risk of bias[c]	Inconsis-tency	Indirectness	Imprecision	Certainty in estimates
Evidence profile – Falls											
5 (observational cohort)	5931	4730	1.20 (1.05-1.37)	Age 65 yr: 5.5% Age 80 yr: 7.5%	Prognosis	High	Serious limitations	No serious limitations	No serious limitations	No serious limitations	Moderate
					Causation	Low	Serious limitations	No serious limitations	No serious limitations	No serious limitations	Very low
Evidence profile – Fractures											
5 (observational cohort)	9767	4533	1.32 (0.99-1.76)	Age 65 yr: 0.9% Age 80 yr: 1.2%	Prognosis	High	Serious limitations	No serious limitations	No serious limitations	Serious limitations	Low
					Causation	Low	Serious limitations	No serious limitations	No serious limitations	Serious limitations	Very low

GRADE = Grades of Recommendation, Assessment, Development, and Evaluation
[a] Nocturia case definitions varied across the studies.
[b] Assessment based on the principles of the GRADE framework where the body of observational evidence begins as high quality when used for prognosis research and as low quality when used for intervention research.
[c] Assessment described in Suppl. Appendix 2 and Fig. 2.



Reference - Falls	Risk of bias criteria - Falls					Overall risk of bias
	Representativity of the source population	Assessment of nocturia	Assessment of falls	Missing data	Adjustment	
1. Fitzgerald 2009 [31,40]	+	−	−	−	+	High
2. Parsons 2009 [32]	+	+	+	+	+	**Low**
3. Vaughan 2010 [33]	+	+	+	+	+	**Low**
4. Stenhagen 2013 [34]	+	−	−	−	−	High
5. Noguchi 2016 [35]	−	+	+	+	−	High

Reference - Fractures	Risk of bias criteria - Fractures					Overall risk of bias
	Representativity of the source population	Assessment of nocturia	Assessment of fractures	Missing data	Adjustment	
1. Fitzgerald 2009 [31,40]	+	−	−	−	+	High
2. Temml 2009 [36]	−	+	+	−	−	High
3. Frost 2010 [37]	+	−	+	+	−	High
4. Nakagawa 2010 [38]	−	+	+	+	−	High
5. Marshall 2016 [39]	+	+	+	+	+	**Low**


Reference
Gender
Nocturia case definition
Relative risk (95% CI)
Weight (%)
Fizgerald 2009 [29, 30] Male 3+ 1.25 (1.02, 1.50) 22.06
Parsons 2009 [31] Male 2+ 1.05 (0.96, 1.16) 34.26
Noguchi 2016 [34,35] Male 2+ 1.17 (0.87, 1.58) 13.33
Vaughan 2010 [32] Both 3+ 1.28 (1.02, 1.59) 19.14
Stenhagen 2013 [33] Both 3+ 1.57 (1.10, 2.16) 11.21
Overall (I-squared = 51.7%, p = 0.082) 1.20 (1.05, 1.37) 100.00
NOTE: Weights are from random effects analysis
0.3
1
3
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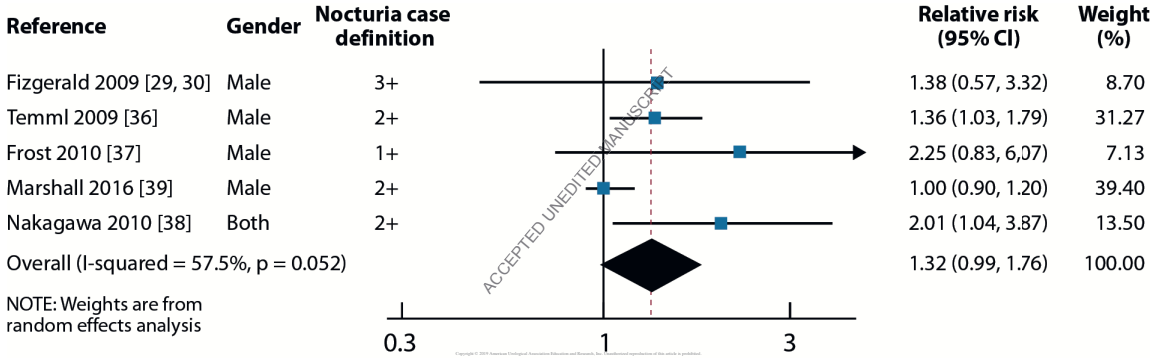
Reference
Gender
Nocturia case definition
Relative risk (95% CI)
Weight (%)
Fizgerald 2009 [29, 30] Male 3+ 1.38 (0.57, 3.32) 8.70
Temml 2009 [36] Male 2+ 1.36 (1.03, 1.79) 31.27
Frost 2010 [37] Male 1+ 2.25 (0.83, 6,07) 7.13
Marshall 2016 [39] Male 2+ 1.00 (0.90, 1.20) 39.40
Nakagawa 2010 [38] Both 2+ 2.01 (1.04, 3.87) 13.50
Overall (I-squared = 57.5%, p = 0.052) 1.32 (0.99, 1.76) 100.00
NOTE: Weights are from random effects analysis
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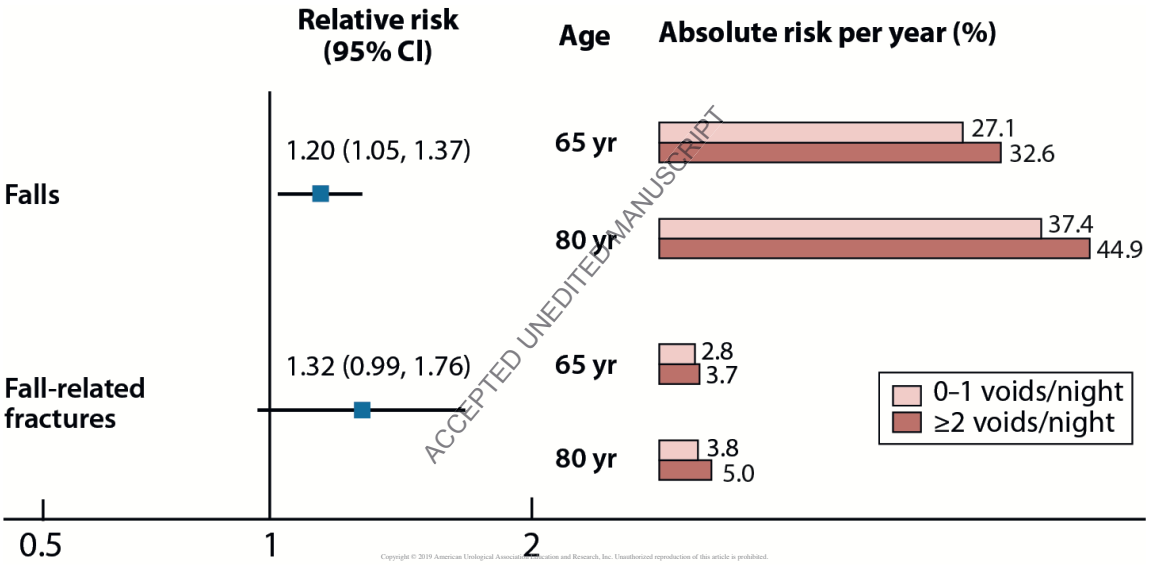

PUBLICATION IV

Impact of lower urinary tract symptoms on mortality: a 21-year follow-up among middle-aged and elderly Finnish men

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ARTICLE

Clinical

Impact of lower urinary tract symptoms on mortality: a 21-year follow-up among middle-aged and elderly Finnish men

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Abstract

Background The usefulness of lower urinary tract symptoms (LUTS) as mortality risk factors remains unclear. Repeated assessments are required to take into account symptom fluctuation and de novo symptom appearance. The study objective was to evaluate mortality in relation to three urinary storage symptoms—urgency, daytime frequency, and nocturia—in middle-aged and elderly men, considering also other time-varying factors during follow-up.

Methods A mail survey of a population-based cohort of men initially aged 50, 60, and 70 years was conducted in Finland in 1994, 1999, 2004, and 2009. The questionnaire included assessments of LUTS based on the Danish Prostatic Symptom Score and comorbidities. The men were followed up for mortality through the population registry through 2014. LUTS-related hazard ratios (HR) were analyzed with time-dependent Cox regression adjusted for the year of birth and comorbidities using variable values updated every 5 years. Sensitivity analyses were conducted using values of all variables fixed to the baseline assessment of 1994.

Results Of the 1332 eligible men with data on LUTS from each preceding survey, 514 (38.6%) died during the 21-year follow-up. In time-dependent analyses, daytime frequency, and nocturia were significantly associated with increased mortality: the adjusted HR was 1.42 (95% CI 1.11–1.83) for daytime frequency, 1.38 (1.07–1.79) for nocturia and 1.19 (0.94–1.50) for urgency. In sensitivity analyses with fixed baseline characteristics, only nocturia was suggestively associated with an increased risk of death: the adjusted HR was 1.09 (0.84–1.42) for daytime frequency, 1.41 (0.99–2.02) for nocturia and 0.94 (0.52–1.68) for urgency.

Conclusions Among aging men, LUTS are more accurate predictors of short-term than longer-term mortality risk. Repeated assessments are needed to detect clinically relevant and persistent symptoms, often associated with ill health. Accordingly, men with daytime frequency or nocturia exhibit a 1.4-fold risk of death and therefore, should be evaluated for underlying comorbidity.

Introduction

The number of patients presenting with lower urinary tract symptoms (LUTS) is increasing as the population ages. LUTS are divided into two broad categories: storage symptoms (daytime urinary frequency, nocturia, urgency, urinary

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incontinence) and voiding symptoms (incomplete emptying, intermittency, slow stream, and hesitancy). An important factor for male LUTS is bladder outlet obstruction (BOO), typically caused by benign prostatic hyperplasia (BPH)—a condition affecting more than half of men aged over 50 years [1]. Although various interventions can alleviate bothersome LUTS, persistent or recurrent symptoms are frequent despite treatments such as surgery for BOO [2, 3]. This is explained by the multifactorial etiology of LUTS: age-related physiological changes, various lifestyle factors and medical conditions affect lower urinary tract and renal function. Of the various LUTS, comorbidities are particularly important for urinary storage symptoms [4, 5].

As men with LUTS tend to be older and are more likely to have comorbidities than asymptomatic men, they are potentially at a higher risk of death. To reliably assess the impact of LUTS on mortality, careful consideration of various confounding factors is warranted. Longitudinal studies have suggested LUTS to predict development of cardiovascular diseases, albeit with some inconsistency [6, 7]. In previous longitudinal studies, LUTS have commonly been assessed either by using pre-defined cutoff values of various symptom scores or by retrospectively screening medical records for diagnosis codes without distinguishing individual symptoms. In the case of nocturia—the only symptom for which an association with mortality has been addressed in several earlier studies—the heterogeneity among previous results may reflect variation in methods, follow-up times and age distributions [8], as the natural course of LUTS may vary considerably between populations [9–11]. Hypothetically, the confidence of the estimates on LUTS-related mortality could be strengthened by taking into account the incidence and remission of symptoms and comorbidities in the course of follow-up. Therefore, the aim of this study is to analyze the impact of three common storage LUTS—urinary urgency, daytime frequency, and nocturia—on all-cause mortality during 21 years of follow-up utilizing repeated assessments in a population-based cohort of middle-aged and elderly men.

Subjects and methods

Tampere aging male urologic study

A population-based cohort study focusing on urological symptoms and sexual functioning among middle-aged and elderly men was launched in Pirkanmaa County, Finland in 1994, with repeat rounds in 1999, 2004, and 2009. Study details have been published previously [12, 13]. Briefly, a sample of 3143 men was identified from the Finnish Population Register in 1994, comprising all men born in 1924, 1934, or 1944 residing in the study area at the baseline. Self-administered questionnaires were mailed to the men in the study population at all rounds. Non-responders were reminded with a second mailing after 3 months. The questionnaire comprised items on frequency and bother of LUTS, major health conditions and medications, as well as sociodemographic, anthropometric, and lifestyle factors. An exemption from ethical review was granted by the ethics committee of the Pirkanmaa Hospital District (tracking number 99050).

Measures

The frequencies of LUTS were assessed using the Danish Prostatic Symptom Score (DAN-PSS-1) [14], consistent with the International Continence Society definitions [15]. An exception was made in 1994 in the assessment of urgency, where a modified question translated back from Finnish to English was as follows: "Is your need to urinate so urgent that it is difficult to hold it back until you reach the toilet?", which was since modified and used at subsequent the rounds in 1999, 2004, and 2009 as "Do you experience an imperative (strong) urge to urinate?". The response options were never—rarely—often—always. The question concerning daytime frequency was "What is the longest interval between each voiding, from when you wake up until you go to bed?" with response options of more than 3 h—2–3 h—1–2 h—less than 1 h. The question concerning nocturia was "How many times do you have to urinate per night?" with response alternatives of none—1 or 2 times—3 or 4 times—5 times or more. The preceding 4-week period was used as the reference time frame for the questions. For the analysis, each symptom was recoded into a binary variable: no or mild vs. moderate or severe symptoms (the first two versus the two latter options). The men were followed up for mortality through the population registry until the end of 2014. Information on the time and cause of death was obtained by a deterministic linkage with the unique personal identification number as the key.

Statistical analyses

For analyses of mortality, we included men who had answered questions for LUTS at every survey in 1994–2009 (while alive) and for comorbidities at least in the 1994 survey. To adjust the analyses for confounders, variables with well-established prognostic importance were selected for regression analyses. These variables, of which many are also known to be associated with LUTS, included age, marital status (married or cohabiting versus single or widowed), body mass index (BMI, ≤25 versus >25 kg/m^2), current smoking (yes/no), alcohol consumption (≤150 g/week vs. >150 g/week), previous diagnosis of diabetes, hypertension, cardiac disease, pulmonary disease, cerebrovascular disease, cancer, and neurological disease.

Table 1 Characteristics of men with and without urgency, daytime frequency and nocturia at the follow-up midpoint (2004)

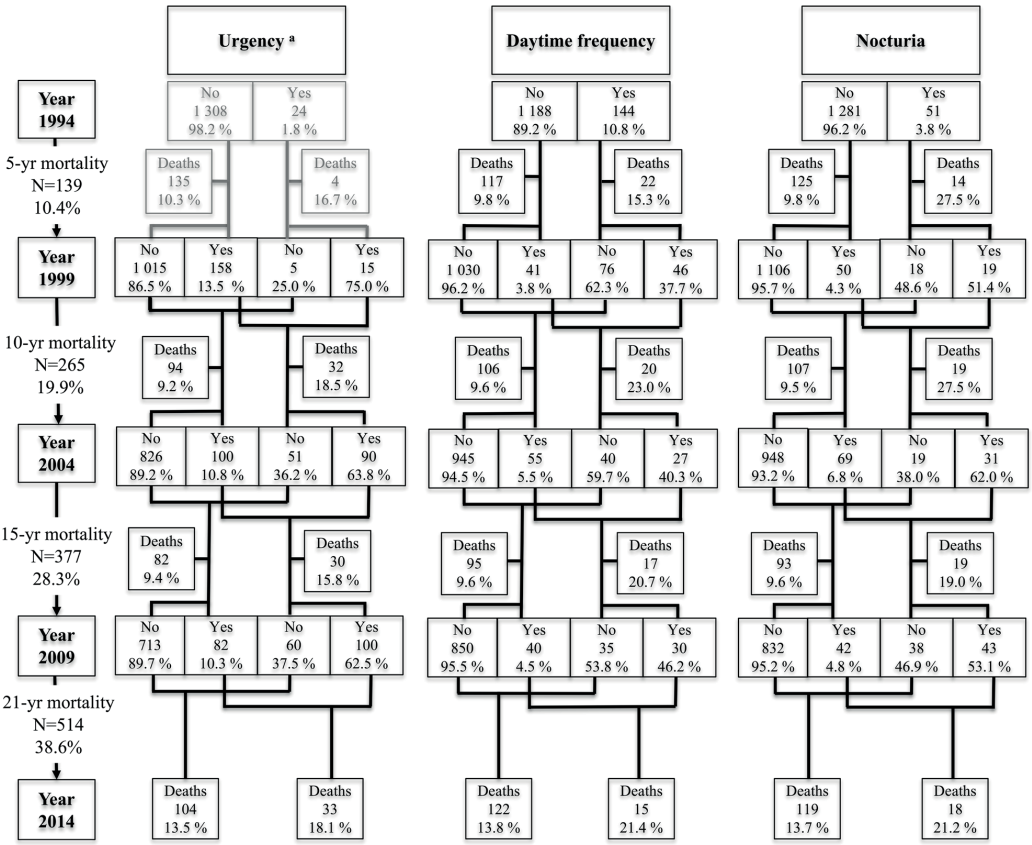
	Urgency				Daytime frequency				Nocturia			
	Yes		No		Yes		No		Yes		No	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Number of men	190		877		82		985		100		967	
Year of birth												
1944	66	34.7	432	49.5	34	41.5	464	47.1	25	25.0	473	48.9
1934	84	44.2	328	37.4	33	40.2	379	38.5	44	44.0	368	38.1
1924	40	21.1	117	13.3	15	18.3	142	14.4	31	31.0	126	13.0
Marital status												
Married/cohabiting	148	77.9	717	81.8	63	76.8	802	81.4	81	81.0	784	81.1
Single/divorced	33	17.4	111	12.7	15	18.3	129	13.1	15	15.0	129	13.3
Widowed	9	4.7	49	5.6	4	4.9	54	5.5	4	4.0	54	5.6
BMI												
≤25	60	31.6	289	33.0	21	25.6	328	33.3	36	36.0	313	32.4
25–30	89	46.8	431	49.1	39	47.6	481	48.8	51	51.0	469	48.5
>30	41	21.6	157	17.9	22	26.8	176	17.9	13	13.0	185	19.1
Current smoking	28	14.7	121	13.8	9	11.0	140	14.2	12	12.0	137	14.2
Alcohol intake >150 g/week	38	20	134	15.3	8	9.8	164	16.6	8	8.0	164	17.0
Medical conditions												
Diabetes	35	18.4	93	10.6	15	18.3	113	11.5	15	15.0	113	11.7
Hypertension	101	53.2	391	44.6	47	57.3	445	45.2	46	46.0	446	46.1
Cardiac disease	60	31.6	188	21.4	26	31.7	222	22.5	32	32.0	216	22.3
Pulmonary disease	27	14.2	99	11.3	8	9.8	118	12.0	19	19.0	107	11.1
Cerebrovascular disease	16	8.4	48	5.5	9	11.0	55	5.6	8	8.0	56	5.8
Cancer	22	11.6	79	9.0	8	9.8	93	9.4	18	18.0	83	8.6
Neurological disease	13	6.8	27	3.1	5	6.1	35	3.6	6	6.0	34	3.5

Univariate Cox regression analysis was performed for each potential prognostic variable. All variables were included in the multivariable analyses to assess their independent effects on each LUTS. All characteristics were treated as time-dependent categorical variables in the regression model. "Last observation carried forward" method [16] was used for comorbidities with missing values in the following rounds. Parallel analyses were made for each LUTS to provide time-varying hazard ratios using variable values updated every 5 years (time-dependent analysis). To further examine the effect of fluctuation of LUTS and associated comorbidities, and for easier comparison to previous studies, sensitivity analyses were conducted using values of all variables fixed to the baseline assessment (1994) and Kaplan–Meier curves were used to graphically represent these associations. Furthermore, interaction terms were evaluated in the regression models of the association of each LUTS with mortality, and subgroup analyses were conducted for the variables with a significant interaction. For all statistical analyses, SPSS version 23 was used.

Results

A total of 2198 questionnaires (70%) were returned in 1994, 2133 (75%) in 1999, 1905 (76%) in 2004, and 1424 (66%) in 2009 of whom 1332 were eligible for the study by providing sufficient data for the analyses, i.e. having answered questions regarding LUTS at every survey (while alive). Regarding the age distribution of the included men, the proportions were 41%, 36 and 23% for men aged 50, 60, and 70 at the baseline, respectively. Men with LUTS were generally older than those without LUTS and virtually all medical conditions were more frequent among men with LUTS (Table 1, Suppl. Table 1).

The symptoms showed substantial fluctuation with a decreasing trend for daytime frequency with a prevalence of 10.8% at the baseline and 7.3% at 15 years and an increasing trend for nocturia, with prevalence 3.8% at the baseline and 8.9% at 15 years. Reflecting the modified question in the assessment of urgency in 1994, its prevalence was materially lower at the baseline (1.8%) compared to the subsequent rounds (14.5% at 5, 17.8% at 10, and 19.1% at 15 years) (Fig. 1).



[a]Assessed with a modified question in 1994.

Fig. 1 Flow chart of mortality rates of men in relation to baseline prevalences and periodic incidence and remission rates of urinary urgency, frequency and nocturia

Analyses of mortality

During the 21-year follow-up, 514 men died, of whom 139 during the first, 126 during the second and 112 during the third 5-year period and 137 during the last period of 6 years. The overall mortality was 10.4% at 5 years, 19.9% at 10 years, 28.3% at 15 years, and 38.6% at 21 years. Mortality was higher among men with LUTS at every stage of follow-up (Fig. 1). In unadjusted time-dependent analyses, each of the studied storage symptoms was strongly associated with an increased risk of death: the HR was 1.71 (95% CI 1.36–2.14) for urgency, 1.95 (1.52–2.49) for daytime frequency and 2.31 (1.79–2.98) for nocturia (Table 2). In unadjusted analyses with fixed baseline characteristics, daytime frequency and nocturia were significantly associated with an increased risk of death, while urgency showed no significant association: HR 1.43 (1.11–1.84) for daytime frequency, 2.56 (1.81–3.63) for nocturia and 1.52 (0.86–2.69) for urgency (Fig. 2, Table 2).

In multivariable-adjusted time-dependent analyses, daytime frequency, and nocturia remained significantly associated with an increased risk of death, while urgency showed only a suggestive association: the adjusted HR was 1.42 (1.11–1.83) for daytime frequency, 1.38 (1.07–1.79) for nocturia and 1.19 (0.94–1.50) for urgency (Table 2, Suppl. Table 2). In multivariable-adjusted analyses with fixed baseline characteristics, only nocturia was suggestively associated with an increased risk of death: the adjusted HR was 0.94 (0.52–1.68) for urgency, 1.09 (0.84–1.42) for daytime frequency and 1.41 (0.99–2.02) for nocturia (Table 2, Suppl. Table 3).

In the regression analysis, a significant interaction was found between smoking and urgency ($p = 0.02$), as well as between previously diagnosed cardiac disease and urgency (p

Table 2 Unadjusted and adjusted association of LUTS with all-cause mortality in Cox regression analyses using variable values updated every 5 years (time-dependent analysis) and values fixed to the baseline assessment of 1994 (fixed analysis) during 21-year follow-up

		Urgency		Frequency		Nocturia	
		HR	95% CI	HR	95% CI	HR	95% CI
Time-dependent analysis	Unadjusted	1.71	1.36–2.14	1.95	1.52–2.49	2.31	1.79–2.98
	Adjusted[a]	1.19	0.94–1.50	1.42	1.11–1.83	1.38	1.07–1.79
Fixed analysis	Unadjusted	1.52	0.86–2.69	1.43	1.11–1.84	2.56	1.81–3.63
	Adjusted[b]	0.94	0.52–1.68	1.09	0.84–1.42	1.41	0.99–2.02

[a]A regression model including the year of birth and following categorical variables with time-varying values: LUTS, marital status, BMI, smoking, alcohol consumption, diabetes, hypertension, cardiac disease, pulmonary disease, cerebrovascular disease, neurological disease and cancer. "Last observation carried forward" method [14] used for comorbidities with missing values in the follow-up rounds

[b]All above-mentioned variables treated as fixed categorical variables in the regression model i.e. the variable values fixed to the baseline assessment of 1994

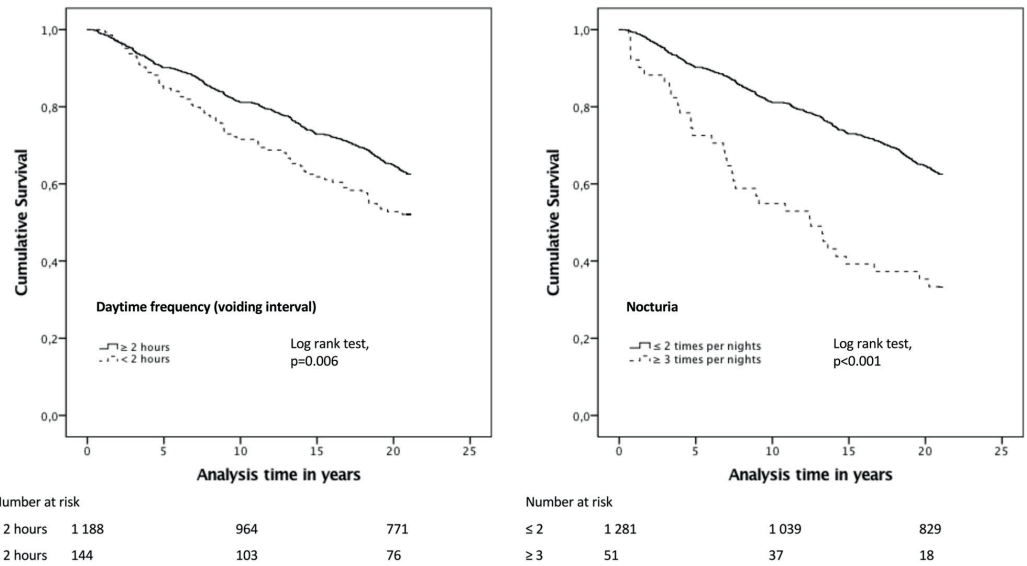


Fig. 2 Kaplan–Meier curves for men with and without daytime frequency and nocturia at the baseline (1994)

= 0.04). The effect of urgency was suggestively stronger among non-smokers compared to smokers (HR 1.46, 1.12–1.91 vs. 0.73, 0.45–1.20) and among those without a diagnosed cardiac disease compared to those with a diagnosis (HR 1.30, 0.95–1.79 vs. 1.04, 0.73–1.48) (Table 3). The effects of daytime frequency and nocturia showed no significant differences between any subgroups. (Suppl. Table 4).

Discussion

Due to the fluctuating nature of the symptoms and related comorbidities, the impact of LUTS as predictors of mortality has not been well-established. The influence of short-term fluctuating symptoms can mask the effect of clinically relevant longer-term symptoms, compromising the reliability of the observed association of baseline LUTS on subsequent morbidity. To provide more robust estimates, we explored the impact of LUTS on mortality utilizing repeated assessments of these symptoms and associated comorbidities. Our results showed that men with nocturia or daytime frequency have increased mortality, even after adjustment for behavioral risk factors and comorbidities. However, the associations were significant only in analyses where the symptoms and comorbidities were updated every 5 years indicating that the baseline assessments of LUTS are reliable only in predicting short-term mortality risk while repeated assessments are needed to predict longer term risk.

The crude death rates were higher in men with LUTS throughout the follow-up. After adjusting for age and comorbidities, daytime frequency, and nocturia remained associated with mortality compared with men free of these

Table 3 Subgroup analyses for variables with significant interaction in the regression models: association of urinary urgency with mortality among smoking and non-smoking men and among men with and without previously diagnosed cardiac disease

	Unadjusted		Adjusted[a]	
	HR	95% CI	HR	95% CI
Current smoking				
Yes	0.95	0.60–1.51	0.73	0.45–1.20
No	2.09	1.61–2.71	1.46	1.12–1.91
Cardiac disease				
Yes	1.20	0.86–1.69	1.04	0.73–1.48
No	2.11	1.55–2.86	1.30	0.95–1.79

[a]A regression model including the year of birth and following categorical variables with time-varying values: LUTS, marital status, BMI, smoking, alcohol consumption, diabetes, hypertension, cardiac disease, pulmonary disease, cerebrovascular disease, neurological disease and cancer. "Last observation carried forward" method [14] used for comorbidities with missing values in the follow-up rounds

symptoms. Although an association with mortality was more apparent for daytime frequency and nocturia than urgency, there was indication of an association of urinary urgency with an elevated death risk confined to non-smokers. In men with urinary urgency, and lacking the confounding effect of smoking—a commonly recognized risk factor for several illnesses, such as cardiovascular diseases—the mortality risk was nearly 1.5-fold. Furthermore, we found an indication of urgency being related to increased mortality in men without a history of cardiac disease, which suggests that urgency might deserve attention as a potential indicator of latent heart disease.

Our study provides three important improvements to previous reports of longitudinal associations of LUTS with mortality. First, we are not aware of any former study utilizing repeated assessments and thus taking into account the fluctuation and development of symptoms and comorbidities during follow-up. Second, our follow-up is longer than in any previous study on the topic, and covers more than 500 deaths (including >70 deaths among men with each of the LUTS examined). Third, although some previous studies have assessed the impact of nocturia and urgency on mortality [8, 17], we are not aware of any earlier study assessing mortality in relation to daytime frequency. Our effect size for mortality associated with nocturia is consistent with most previous studies showing, on average, a 1.3-fold risk [8]. Similarly, the magnitude of risk associated with urgency is fairly consistent with a previous Finnish study of elderly men reporting a 1.9-fold mortality at 10-year follow-up [17].

Regarding the limitations of the study, the nocturia question in DAN-PSS-1 does not distinguish one void from two voids per night. Because one nocturnal voiding is often considered normal, one or two voids/night are unlikely to distinguish meaningful nocturia and thus, ≥3 voids/night was considered a more robust indicator of important nocturia. Accordingly, a previous study suggested a gradient in risk of death with nocturia severity [18]. Furthermore, although incidence of nocturia is independent of nocturia case definition (≥1, ≥2, or ≥3 voids/night), remission frequency increases with more stringent criteria [9]. Due to a more stringent case definition in our analyses, remission over time is more likely and repeated assessments are therefore crucial.

Due to the relatively small number of deaths related to specific symptoms, our study did not have adequate statistical power to analyse the impact of multiple LUTS in combination. However, previous findings suggest that storage symptoms frequently overlap and various LUTS are often concomitant [19]. Furthermore, we were unable to assess the effect of treatments of LUTS on death. However, few men seek treatment for their LUTS [19, 20] and response to treatment can be unsatisfactory particularly for storage symptoms [2, 3, 21]. Finally, some residual confounding in our results is likely in spite of extensive adjustments with various medical conditions and lifestyle factors.

Although urinary symptoms are common in aging men, they may also be markers of ill health. Investigations for underlying comorbidity are warranted particularly in cases of persistent and treatment-resistant symptoms. The multifactorial etiology of LUTS includes various medical conditions and behavioral factors, besides age-related changes in the lower urinary tract such as development of BPH. Although LUTS share common etiologic factors, distinction between specific symptoms is important due to the different pathophysiologic mechanisms, especially in nocturia, which has been recently recognized as a separate clinical entity [22]. The proposed etiologies underlying various LUTS include vascular insufficiency of the pelvic floor due to atherosclerosis [23, 24], systemic inflammation in metabolic syndrome [25], neurogenic dysfunction related to diabetes [26], fluid shifts caused by hypertension and cardiac failure [27] as well as increased sympathetic activity caused by hyperinsulinemia or sleep problems [26, 28]. These complex pathways may explain the association of LUTS with increased mortality. However, the evidence on the usefulness of various LUTS as causal risk factors for mortality is lacking: there is no data available on whether treatment of LUTS would decrease mortality e.g. by preventing injuries or cardiovascular events to occur [6, 7, 29].

In conclusion, LUTS are more accurate predictors of short-term than longer-term mortality risk among aging men. Repeated assessments are needed to identify clinically relevant and persistent symptoms, often associated with ill health. Accordingly, middle-aged and elderly men presenting with daytime frequency or nocturia are potentially at a 1.4-fold increased risk of death. Therefore, the management of men with LUTS should focus not only on treating the symptoms, but also assessing their general health, risk factors and major comorbidities, including pre-clinical conditions.

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Compliance with ethical standards

Conflict of interest J.A. has attended scientific congress as a guest for Sanofi. J.P. has received an unrestricted grant from Ferring, a lecture honorarium from Astellas, Merck and Orion and attended scientific congresses as a guest for Astellas, Novartis, and Orion. J. H. has attended scientific congresses as a guest for Astellas and Orion. T.L.J.T. worked as a consultant for Astellas, Orion Pharma, Bayer AG, Jansse-Cilag and as an investigator in clinical trials sponsored by Medivation, Orion Pharma, Bayer AG, Pfizer, Janssen-Cilag and Lidds Ab. A.A. has been expert advisor for Epid Research Inc.

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