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

Jori S. Pesonen[a,b], Rufus Cartwright[c,d], Robin W.M. Vernooij[e], Yoshitaka Aoki[f], Arnav Agarwal[g], Altaf Mangera[h], Alayne D. Markland[i,j], Johnson F. Tsui[k], Henrikki Santti[l], Tomas L. Griebling[m], Alexey E. Pryalukhin[n,o], Jarno Riikonen[b], Riikka M. Tähtinen[p], Camille P. Vaughan[j,q], Theodore M. Johnson 2[nd] [j,q], Anssi Auvinen[r], Diane Heels-Ansdell[s], Gordon H. Guyatt[s,t], Kari A.O. Tikkinen[l,u*]

For affiliations see end of article.

* Corresponding author: Departments of Urology and Public Health, University of Helsinki and Helsinki University Hospital, Haartmaninkatu 4, Helsinki 00029, Finland. Tel. +358-50-5250971. E-mail address: kari.tikkinen@gmail.com (Kari A.O. Tikkinen).

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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.

Authors's affiliations

[a] Department of Urology, Päijät-Häme Central Hospital, Lahti, Finland.

[b] Department of Urology, Tampere University Hospital, and Faculty of Medicine and Life Science, University of Tampere, Tampere, Finland

[c] Department of Epidemiology and Biostatistics, Imperial College, London, UK.

[d] Department of Urogynaecology, Oxford University Hospitals NHS Trust, Oxford, UK.

[e] Department of Research, Netherlands Comprehensive Cancer Organization, Utrecht, The Netherlands.

[f] Department of Urology, University of Fukui, Fukui, Japan.

[g] Department of Medicine, University of Toronto, Toronto, ON, Canada.

[h] Department of Urology, Sheffield Teaching Hospitals, Sheffield, UK.

[i] Department of Medicine and Division of Gerontology, Geriatrics and Palliative Care, University of Alabama - Birmingham UAB School of Medicine, Birmingham, AL, USA

[j] Department of Veterans Affairs, Birmingham/Atlanta Geriatric Research Education and Clinical Center, Atlanta, GA, USA.

[k] Department of Urology, Hackensack University Medical Center, New Jersey, NY, USA.

[l] Department of Urology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland.

[m] Department of Urology and The Landon Center On Aging, University of Kansas, Kansas City, KS, USA.

[n] Department of Urology, North-Western State Medical University named after I.I. Mechnikov, Saint Petersburg, Russia.

[o] Department of Pathology, University Hospital of Bonn, Bonn, Germany.

[p] Department of Obstetrics and Gynecology, Tampere University Hospital, Tampere, Finland.

[q] Department of Medicine, Division of General Medicine and Geriatrics, Emory University School of Medicine, Atlanta, GA, USA

[r] Faculty of Social Sciences, University of Tampere, Tampere, Finland.

[s] Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, ON, Canada.

[t] Department of Medicine, McMaster University, Hamilton, ON, Canada.

[u] Department of Public Health, University of Helsinki, Helsinki, Finland.

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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.

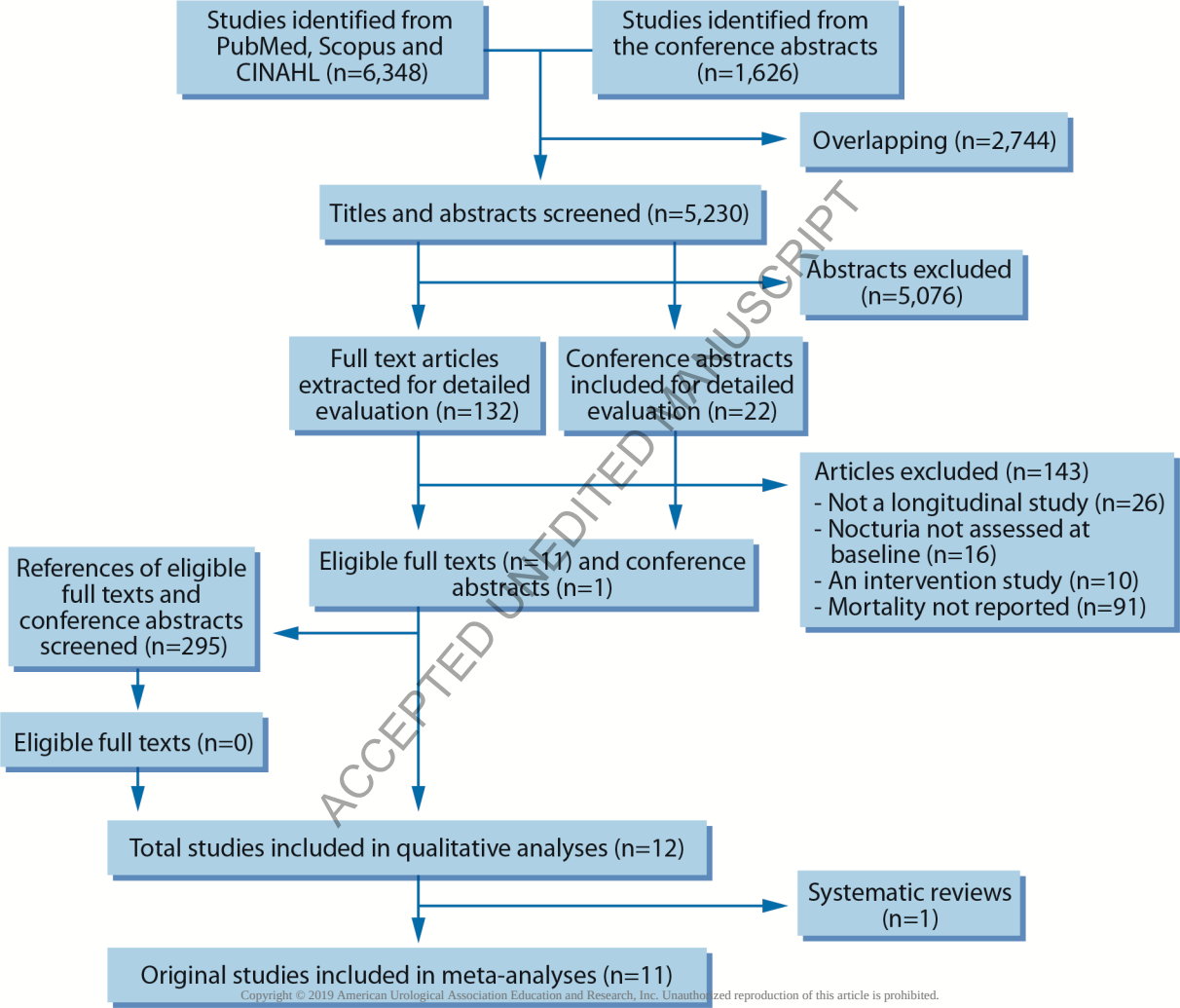
Summary of findings						Quality assessment					
No. of studies (design)	**No. of participants[a]**		**Relative risk (95% CI)**	**Absolute risk difference**	**Prognosis vs. causation[b]**	**Starting quality**	**Risk of bias[c]**	**Inconsis-tency**	**Indirectness**	**Imprecision**	**Certainty in estimates**
	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**