Review Article

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

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Abbreviations and Acronyms

GRADE = Grading of Recommendations, Assessment, Development and Evaluation

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 and falls and fractures as a prognostic and as a causal risk factor.

Materials and Methods: We searched PubMed®, Scopus®, CINAHL (Cumulative Index to Nursing and Allied Health Literature) and abstracts of major urological meetings up to December 31, 2018. We conducted random effects meta-analyses of adjusted relative risks of falls and fractures. We applied the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach to rate the quality of evidence for nocturia as a prognostic and causal factor of falls and fractures.

Results: Among 5,230 potential reports 9 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% CI

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% CI 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, followup 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 an approximately 1.3-fold increased risk of fractures.

FALLS and fractures are common, associated with substantial health care costs and a major reason for long-term functional impairment.[1,2] Older adults are at increased risk for falls due to age related deterioration in balance and gait that is worsened by illness and medications.[3] More than 30% of people older than 65 years and living at home fall at least once a year.[3,4] Although only a minority of falls leads to fractures,[4] injuries due to falls are common and, among older adults, associated with a high risk of institutionalization.[2] Therefore, developing multifactorial fall prevention programs is a major focus in geriatric research.[5]

Nocturia is one of the most common and bothersome lower urinary tract symptoms[6,7] and according to another meta-analysis is associated with an approximately 30% increase in the risk of death.[8] Nocturia is strongly associated with advanced age.[9,10] Approximately 1 in 4 adults in their 60s and half of adults in their 80s void 2 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 nocturia and falls include older age, diabetes, cardiovascular disease, depression and physical inactivity.[12−14] However, some risk factors such as obesity may increase nocturia but decrease fractures.[15,16]

Cross-sectional studies have consistently shown 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. Therefore, we 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 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidance.[20]

Data Sources and Searches

We searched PubMed (from 1946), Scopus (from 1995) and CINAHL (from 1960) up to December 31, 2018 (supplementary Appendix 1, https://www.jurology.com). In addition, we searched annual conference abstracts of the American Urological Association, European Association of Urology, ICS (International Continence Society) and International Urogynecological Association from 2005 to 2018 for any ongoing or unpublished studies. We did not apply restrictions to language or publication status. We handsearched the reference lists of the included articles.

Eligibility Criteria

We included longitudinal studies with a followup of at least 3 months, with at least 95% of participants 18 years old or older. We included studies assessing nocturia at baseline and reporting falls or fractures at a later followup 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 1 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, followup 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 randomized controlled trials.[21] Taking into account the previous literature,[22−24] through discussion and consensus building we developed an instrument to categorize studies as low or high risk of bias. This includes the features of the included studies that could potentially bias the estimates, ie 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 categorized as low if the study met the criteria for low risk of bias in each of the 5 domains of the assessment (supplementary Appendix 2, https://www.jurology.com).

The GRADE approach includes separate criteria for rating the quality of evidence regarding a prognostic issue (is there a true association?) vs 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 (ie is nocturia associated with falls/fractures?) and, thus, in GRADE rating begins as high quality evidence. Observational studies, according to GRADE, seldom provide trustworthy evidence regarding causation (ie does nocturia cause falls/fractures?). Therefore, for causation, observational studies begin as low quality evidence. To highlight this key distinction we evaluated the quality of evidence for nocturia 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 another systematic review.[8]

Data Analysis Including Statistical Analysis
To calculate the pooled estimates of relative measures of the association of nocturia with falls and fractures we extracted relative risks (RR) or alternatively hazard ratios (HR) to be used 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 formula, $RR = OR/(1 - p + (p \times OR))$, in which p represents baseline risk, ie the fall/fracture risk in individuals without nocturia at baseline.[27] We calculated the pooled RRs 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, followup time and risk of bias. The estimates were stratified by nocturia status as a binary variable (case definitions of 2 or more vs 0 to 1 and 3 or more vs 0 to 2 voids per night) and a 3-value categorical variable (2 to 3 vs 0 to 1 and 4 or more vs 0 to 1 void per 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.

As optimal decision making requires estimates of relative and absolute effects, we illustrated the difference in the absolute annual risk of falls and fall related fractures between individuals with vs without nocturia. To assess the average risks of falls and fractures in the general elderly population the annual number of people with 1 or more falls per 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 (supplementary Appendix 3, https://www.jurology.com).[4] After calculating the 95% CIs 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, https://www.jurology.com). 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 used.[3] In estimating the prevalence of patient-important nocturia (defined as 2 or more voids per night)[11] in relevant age groups we 1) extracted the reported prevalences from studies included in a previous systematic review (supplementary Appendix 4, https://www.jurology.com),[9] 2) calculated the 95% CIs for natural logarithms of prevalence per 100 people and 3) pooled the estimates in random effects meta-analysis (supplementary fig. 3, https://www.jurology.com). Finally, to derive 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.[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 5 provided data on the association between nocturia and fractures (table 1).[29,30,36–39] Among the 5 studies assessing falls 3 confirmed the accuracy of our consensus data extraction,[32–34] 1 provided additional information[31] and 1 was unable to assist with our requests.[29] Among the 5 studies assessing fractures 3 confirmed the accuracy of our consensus data extraction,[36–38] 1 provided additional information[39] and 1 was unable to assist with our requests.[29]

Of the 5 studies assessing falls 3 were conducted in North America, 1 in Europe and 1 in Australia. Of the 5 studies assessing fractures 2 were conducted in North America, 2 in Europe and 1 in Eastern Asia. Studies included mainly older people in their 70s and predominantly men, with followup times ranging from 1 to 6 years for studies of falls and 4 to 9 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 nonspine fractures with varying followup times.[31,39] We identified 1 conference abstract,[29] which reported only death as an end point (included in another meta-analysis[8]), but access to the study raw data also provided assessments for falls and fractures (supplementary fig. 4, https://www.jurology.com).[30] Therefore, we were able to include 5 studies in the meta-analysis of falls with a total followup of 23,678 person-years and 5 studies in the meta-analysis of fractures with a total followup of 87,973 person-years.
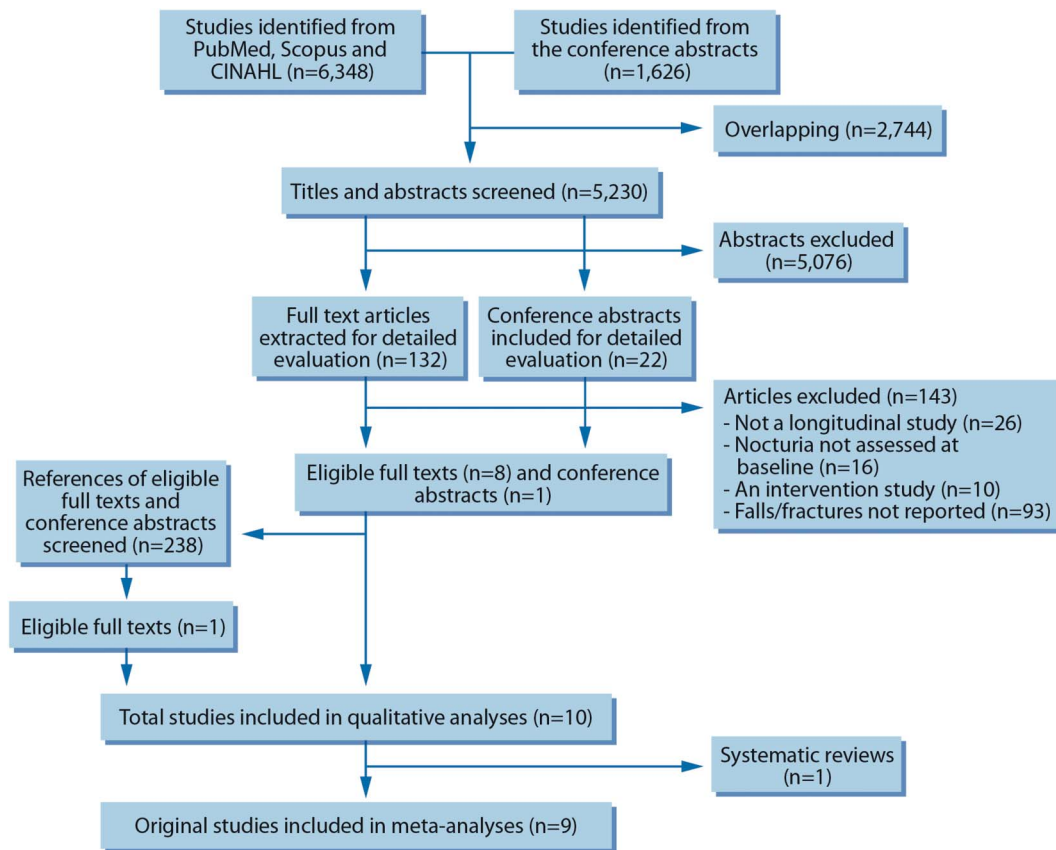
Figure 1. Study flow chart

Risk of Bias

Of the 5 studies assessing falls 4 used representative source populations,[29,31−33] 3 conducted baseline assessments of nocturia and followup assessments of falls accurately,[31,32,34] 3 had little missing data at followup[31,32,34] and 3 adequately adjusted their estimates for important prognostic risk factors for falls.[29,31,32] We considered 3 studies (assessing impact on falls) to be overall high risk of bias (fig. 2, table 1; supplementary table 1, https://www.jurology.com).

Of the 5 studies assessing fractures 3 used representative source populations,[29,37,39] 3 assessed nocturia accurately,[36,38,39] 4 assessed fractures accurately,[36−39] 3 had little missing data at followup[37−39] and 2 adequately adjusted their estimates for important prognostic risk factors for fractures.[29,39] Therefore, we considered 4 studies (assessing impact on fractures) to be overall high risk of bias (fig. 2, table 1; supplementary table 1, https://www.jurology.com).

Impact of Nocturia on Falls

In the meta-analysis of estimates adjusted for at least age and gender (5 studies, 2 low and 3 high risk of bias) the pooled relative risk of falling at least once in the followup was higher for people with vs 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, followup time, nocturia case definition or risk of bias (supplementary tables 1 and 2, https://www.jurology.com).

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 available only for men and did not differ by age, followup time, nocturia case definition or risk of bias (supplementary tables 1 and 3, https://www.jurology.com).

The absolute risk of falling at least once a year was 5.5% higher among people 65 years old with nocturia (defined as 2 or more voids per night) compared to those without nocturia (defined as 0 to 1 void per night), and 7.5% higher in people 80 years old with nocturia vs without (fig. 4, supplementary fig. 5, https://www.jurology.com).

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 followup was 32% higher in people with nocturia

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

References	Country	Sample Source	Gender	% Male	Mean Age (range)	Exclusion Criteria	Baseline Assessment of Nocturia	Followup Assessment of Falls/Fractures	Median Followup (yrs)	No. Contacted at Baseline	No. Eligible Respondents (%)
			Population Characteristics								
Fitzgerald et al[29,30,*]	Puerto Rico	Various public registries	Men	100	70 (60—99)	Institutionalized	Unvalidated questionnaire	Falls + fractures via interview, recall period 1 yr	4	1,736	Baseline 1,332 (77), 1,011 (58)
Parsons et al [31,†]	United States	Various public registries	Men	100	74 (65-100)	Physical or cognitive disability, terminal illness, bilateral hip replacement	AUA Symptom Index	Falls via repeated telephone contacts every 4 mos	1	Unclear	5,872
Temml et al[36]	Austria	Health screening	Men	100	52 (41—80)	None	International Prostate Symptom Score	Hip fractures via hospital registries	5	Unclear	1,820
Frost et al[37]	Denmark	Civil registry	Men	100	65 (60—75)	None	Unvalidated questionnaire‡	All fractures via hospital registries	5	9,314	4,696 (50)
Nakagawa et al[38]	Japan	Civil registry	Both	46	76 (70—97)	Nonmembers of National Health Insurance system	Questionnaire in accordance with ICS definitions	All fractures via National Health Insurance registry	5	2,925	784 (27)
Vaughan et al[32]	United States	National social insurance program registry (Medicare)	Both	52	75 (65—106)	Poor cooperation, institutionalized, history of falls (1 yr before baseline assessment)	Questionnaire in accordance with ICS definitions	Falls via repeated telephone contacts every 6 mos	3	2,188	Baseline 1,000 (46), followup 692 (69)
Stenhagen et al[33]	Sweden	Civil registry	Both	46	71 (60—93)	Inability to speak Swedish, history of falls (6 mos before baseline assessment)	Unclear	Falls via interview, recall period 6 mos	6	5,370	Baseline 2,535 (47), followup 1,720 (32)
Marshall et al[39,†]	United States	Various public registries	Men	100	74 (65—100)	Physical or cognitive disability, terminal illness, bilateral hip replacement	AUA Symptom Index (assessed every 2 yrs)	Nonspine fractures via mail/ telephone + medical record assessments, repeated every 4 mos	8.6	Unclear	5,989
Noguchi et al[34,35]	Australia	Electoral roll	Men	100	76 (70—99)	Institutionalized, dementia, neurological disease, poor mobility	International Prostate Symptom Score	Falls via repeated telephone contacts every 4 mos	1	3,821	1,366 (36)

* Previously unpublished analyses based on study raw data.[30]
† MrOS (Osteoporotic Fractures in Men) study cohort.
‡ Nocturia registered only for men specifying the symptom in the assessment of symptoms/diseases related to the urinary tract.

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 [29, 30]	+	−	−	−	+	High
2. Parsons 2009 [31]	+	+	+	+	+	**Low**
3. Vaughan 2010 [32]	+	+	+	+	+	**Low**
4. Stenhagen 2013 [33]	+	−	−	−	−	High
5. Noguchi 2016 [34, 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 [29, 30]	+	−	−	−	+	High
2. Temml 2009 [36]	−	+	+	−	−	High
3. Frost 2010 [37]	+	−	+	+	−	High
4. Nakagawa 2010 [38]	−	+	+	+	−	High
5. Marshall 2016 [39]	+	+	+	+	+	**Low**

Figure 2. Risk of bias of included studies

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. 5, table 2). In subgroup analyses the estimates did not differ significantly by age, gender, followup time, nocturia case definition or risk of bias (supplementary tables 1 and 4, https://www.jurology.com).

Regarding assessments on the association between nocturia and different types of fractures only 1 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 nonspine 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 (supplementary table 1, https://www.jurology.com).[38]

The absolute annual risk of fractures was 0.9% higher in people with nocturia than in those without nocturia age 65 years (fig. 4). The absolute difference in annual fracture risk among people 80 years old was 1.2% between those with vs without nocturia (supplementary fig. 5, https://www.jurology.com).

Quality of Evidence
Of the 5 studies assessing falls 3 were high risk and 2 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). Therefore, we rated the quality of evidence as moderate for nocturia as a prognostic risk factor and as very low for nocturia as a causal factor

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
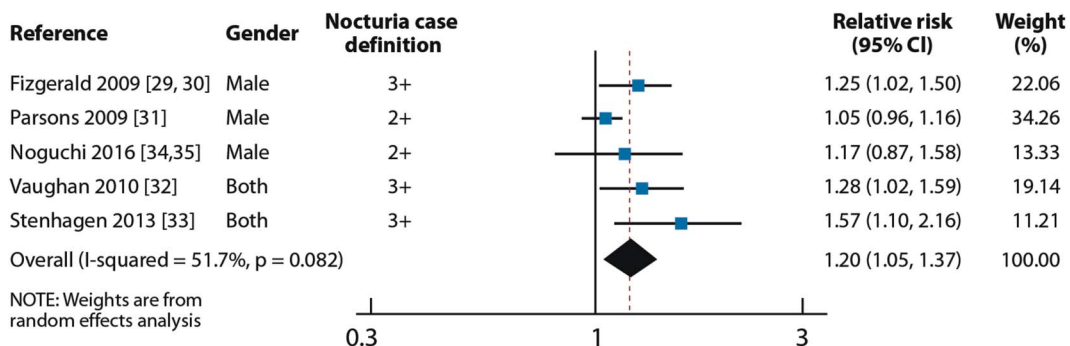
0.3   1   3

Figure 3. Forest plot of relative risks of falls in people with nocturia

Table 2. *Nocturia as a prognostic factor for falls and fractures vs as a cause of falls and fractures*

	Evidence Profile — Falls	Evidence Profile — Fractures
	Summary of findings	
No. studies (design)	5 (observational cohort)	5 (observational cohort)
No. participants:		
No nocturia	5,931	9,767
Nocturia*	4,730	4,533
Relative risk (95% CI)	1.20 (1.05—1.37)	1.32 (0.99—1.76)
Absolute risk difference (%)/yr:		
Age 65	5.5	0.9
Age 80	7.5	1.2
	Quality assessment†	
Starting quality:		
Prognosis	High	High
Causation	Low	Low
Risk of bias:‡		
Prognosis	Serious limitations	Serious limitations
Causation	Serious limitations	Serious limitations
Inconsistency, indirectness:		
Prognosis	No serious limitations	No serious limitations
Causation	No serious limitations	No serious limitations
Imprecision:		
Prognosis	No serious limitations	Serious limitations
Causation	No serious limitations	Serious limitations
Certainty in estimates:		
Prognosis	Moderate	Low
Causation	Very low	Very low

* Nocturia case definitions varied across studies.
† Based on principles of GRADE framework in which the body of observational evidence begins as high quality when used for prognosis research and as low quality when used for intervention research.
‡ Described in supplementary Appendix 2 (https://www.jurology.com) and figure 2.

for falls (table 2). Of the 5 studies assessing fractures 4 were high risk and 1 low risk of bias and, thus, we rated down for risk of bias. We also rated down for imprecision (confidence interval crossed no effect). Therefore, we rated the quality of evidence as low for nocturia as a prognostic risk factor for fractures and as very low for nocturia as a causal factor for fractures.

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 followup among people with vs without nocturia at baseline. The 20% relative risk increase corresponds with a nocturia associated increase in the absolute annual risk of falling by 5.5% among people 65 years old and by 7.5% among those 80 years old. This meta-analysis also showed a possible increased relative risk of fracture of 32% in people with nocturia compared to without nocturia after adjusting for age, gender and various comorbidities. The absolute risk of fractures was 0.9% higher in people with nocturia among those

65 years old and 1.2% higher among those 80 years old. Our findings are of moderate quality evidence for nocturia as a prognostic factor of increased fall risk, low quality for nocturia as a prognostic factor of increased fracture risk and very low quality for nocturia as a cause of falls or fractures.

Strengths and Limitations

The strengths of this review include a contemporary and comprehensive search of published and unpublished studies without language restrictions, duplicate assessment of eligibility and data extraction and risk of bias, communication with the authors of the original studies, and appraisal of the quality of evidence using the GRADE framework for prognosis and causation. To our knowledge this is the first systematic review with meta-analysis to estimate the effect of nocturia on the risk of falls and fractures. By including only population based studies and excluding the effects of any systematic intervention, our results provide the best available evidence on the association between nocturia and falls and fractures. Finally, we also provided estimates of relative and absolute risks of falls and fractures by nocturia status (to obtain absolute estimates we also performed a meta-analysis of the prevalence of nocturia; supplementary fig. 3, https://www.jurology.com).

The limitations of our review are largely those of the included studies. Due to the small numbers of events, the confidence intervals around the estimates of the association between nocturia and fractures are wide. Although the analyses showed no significant effect for nocturia case definition, the evaluation of exposure-response relationship was limited as only 2 studies of falls[31,34] and 1 study of fractures[39] provided estimates for nocturia as a discrete variable with multiple values. In addition, there was a paucity of studies including women. Estimates of the association between nocturia and falls were available only from cohorts of male or mixed gender, while none of these studies and only 1 study of fractures provided estimates separately for women. Although subgroup analyses split by median of mean age (75 years 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. As the majority of the studies were conducted in Western countries, estimates may differ in nonWestern countries. Finally, because the majority of studies were high risk of bias, quality ratings were low for prognosis of fractures and very low for causation for 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).
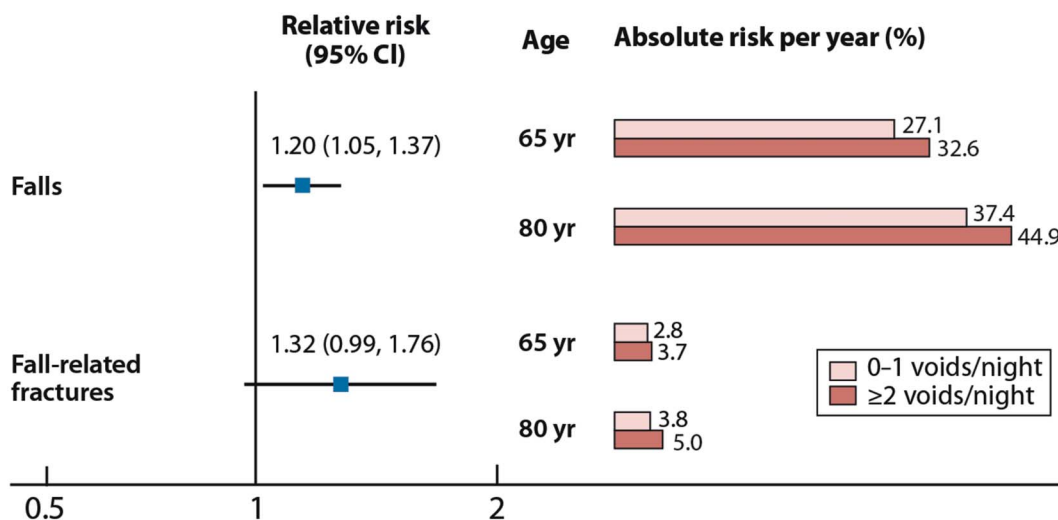
Figure 4. Absolute risk of falls and fall related fractures in older people with vs without nocturia

Relation to Prior Work

In an earlier systematic review examining the association of lower urinary tract symptoms in men with falls, injuries and fractures, nocturia was consistently associated with an increased risk of any fall.[40] This review, published in 2016, included 6 retrospective and 3 prospective studies, and all the prospective studies but not the retrospective ones were also included in our review.[31,37,38] The prior review did not include 6 studies that proved eligible in our systematic review, namely 2 conducted among men (1 full text article[36] and 1 conference abstract[29]), 2 conducted among both genders that were reported before the publication of their review,[32,33] and 2 (both conducted among men) that were published after their review appeared.[34,39] 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 lead to fractures. The decision whether to treat nocturia primarily depends on the level of bother it causes. Especially when caring for older adults reporting nocturia, treatment requires an understanding of the multifactorial etiology of nocturia.[41,42] At its worst the 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 developing safer and more effective treatments for nocturia, establishing how and when to offer the patient with nocturia 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
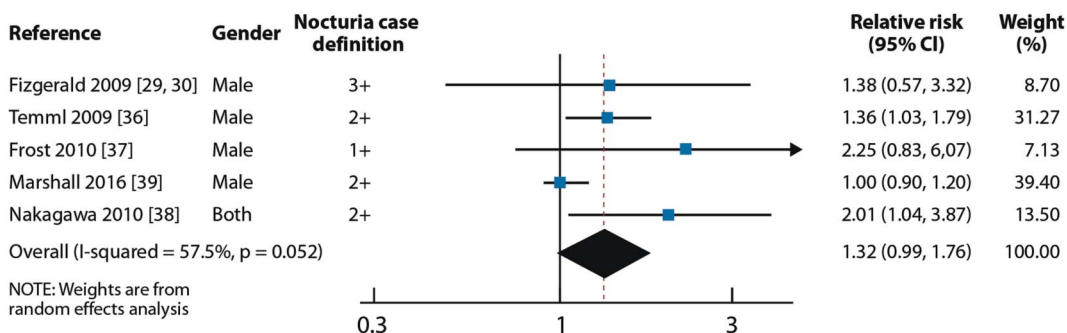

Figure 5. Forest plot of relative risks of fractures in people with nocturia

fall related fracture risk among older adults. Future investigations should address the impact of nocturia treatment on falls and fractures.

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REFERENCES

1. Burns ER, Stevens JA and Lee R: The direct costs of fatal and non-fatal falls among older adults—United States. J Safety Res 2016; **58:** 99.

2. Tinetti ME and Williams CS: Falls, injuries due to falls, and the risk of admission to a nursing home. N Engl J Med 1997; **337:** 1279.

3. 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.

4. Morrison A, Fan T, Sen SS et al: Epidemiology of falls and osteoporotic fractures: a systematic review. Clinicoecon Outcomes Res 2013; **5:** 9.

5. Gillespie LD, Robertson MC, Gillespie WJ et al: Interventions for preventing falls in older people living in the community. Cochrane Database Syst Rev 2012: CD007146.

6. Hashim H, Blanker MH, Drake MJ et al: International Continence Society (ICS) report on the terminology for nocturia and nocturnal lower urinary tract function. Neurourol Urodyn 2019; **38:** 499.

7. Agarwal A, Eryuzlu LN, Cartwright R et al: What is the most bothersome lower urinary tract symptom? Individual- and population-level perspectives for both men and women. Eur Urol 2014; **65:** 1211.

8. Pesonen JS, Cartwright R, Vernooij RWM et al: The impact of nocturia on mortality: a systematic review and meta-analysis. J Urol 2020; **203:** 486.

9. Bosch JL and Weiss JP: Prevalence and causes of nocturia. J Urol 2010; **184:** 440.

10. Pesonen JS, Cartwright R, Mangera A et al: Incidence and remission of nocturia: a systematic review and meta-analysis. Eur Urol 2016; **70:** 372.

11. Tikkinen KA, Johnson TM 2nd, Tammela TL et al: Nocturia frequency, bother, and quality of life: how often is too often? A population-based study in Finland. Eur Urol 2010; **57:** 488.

12. Fitzgerald MP, Litman HJ, Link CL et al: The association of nocturia with cardiac disease, diabetes, body mass index, age and diuretic use: results from the BACH survey. J Urol 2007; **177:** 1385.

13. Tikkinen KA, Auvinen A, Johnson TM 2nd et al: A systematic evaluation of factors associated with nocturia—the population-based FINNO study. Am J Epidemiol 2009; **170:** 361.

14. Gibson W, Hunter KF, Camicioli R et al: The association between lower urinary tract symptoms and falls: forming a theoretical model for a research agenda. Neurourol Urodyn 2018; **37:** 501.

15. Tikkinen KA, Auvinen A, Huhtala H et al: Nocturia and obesity: a population-based study in Finland. Am J Epidemiol 2006; **163:** 1003.

16. De Laet C, Kanis JA, Odén A et al: Body mass index as a predictor of fracture risk: a meta-analysis. Osteoporos Int 2005; **16:** 1330.

17. Stewart RB, Moore MT, May FE et al: Nocturia: a risk factor for falls in the elderly. J Am Geriatr Soc 1992; **40:** 1217.

18. Kim SY, Bang W, Kim MS et al: Nocturia is associated with slipping and falling. PLoS One 2017; **12:** e0169690.

19. Asplund R: Hip fractures, nocturia, and nocturnal polyuria in the elderly. Arch Gerontol Geriatr 2006; **43:** 319.

20. Moher D, Liberati A, Tetzlaff J et al: Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009; **339:** b2535.

21. Guyatt GH, Oxman AD, Vist G et al: GRADE guidelines: 4. Rating the quality of evidence—study limitations (risk of bias). J Clin Epidemiol 2011; **64:** 407.

22. Tähtinen RM, Cartwright R, Tsui JF et al: Long-term impact of mode of delivery on stress urinary incontinence and urgency urinary incontinence: a systematic review and meta-analysis. Eur Urol 2016; **70:** 148.

23. Hayden JA, van der Windt DA, Cartwright JL et al: Assessing bias in studies of prognostic factors. Ann Intern Med 2013; **158:** 280.

24. Kim SY, Park JE, Lee YJ et al: Testing a tool for assessing the risk of bias for nonrandomized studies showed moderate reliability and promising validity. J Clin Epidemiol 2013; **66:** 408.

25. Iorio A, Spencer FA, Falavigna M et al: Use of GRADE for assessment of evidence about prognosis: rating confidence in estimates of event rates in broad categories of patients. BMJ 2015; **350:** h870.

26. Guyatt GH, Oxman AD, Kunz R et al: What is "quality of evidence" and why is it important to clinicians? BMJ 2008; **336:** 995.

27. Sinclair JC and Bracken MB: Clinically useful measures of effect in binary analyses of randomized trials. J Clin Epidemiol 1994; **47:** 881.

28. Harris RJ, Bradburn MJ, Deeks JJ et al: Metan: fixed- and random-effects meta-analysis. Stata J 2008; **8:** 3.

29. Fitzgerald MP, Dávila-Roman AL, Garcia A et al: Nocturia prevalence and association with chronic medical illness, 2-year mortality in older Puerto Rican men (abstract 277). Presented at annual meeting of International Continence Society, San Francisco, California, October 3, 2009.

30. Palloni A, Dávila-Roman AL and Sanchez-Ayendez M: Puerto Rican Elderly: Health Conditions (PREHCO) Project, 2002-2003, 2006-2007 (ICPSR34596-v1). Ann Arbor, Michigan: Inter-University Consortium for Political and Social Research 2013.

31. Parsons JK, Mougey J, Lambert L et al: Lower urinary tract symptoms increase the risk of falls in older men. BJU Int 2009; **104:** 63.

32. Vaughan CP, Brown CJ, Goode PS et al: The association of nocturia with incident falls in an elderly community-dwelling cohort. Int J Clin Pract 2010; **64:** 577.

33. Stenhagen M, Ekström H, Nordell E et al: Falls in the general elderly population: a 3- and 6-year prospective study of risk factors using data from the longitudinal population study 'Good ageing in Skane'. BMC Geriatr 2013; **13:** 81.

34. Noguchi N, Chan L, Cumming RG et al: Lower urinary tract symptoms and incident falls in community-dwelling older men: the Concord Health and Ageing in Men Project. J Urol 2016; **196:** 1694.

35. Noguchi N, Chan L, Cumming R et al: Lower urinary tract symptoms and risk of falls in community-dwelling older men (abstract 47). Presented at annual meeting of International Continence Society, Montreal, Quebec, Canada, October 7, 2015.

36. Temml C, Ponholzer A, Gutjahr G et al: Nocturia is an age-independent risk factor for hip-

fractures in men. Neurourol Urodyn 2009; **28:** 949.

37. Frost M, Abrahamsen B, Masud T et al: Risk factors for fracture in elderly men: a population-based prospective study. Osteoporos Int 2012; **23:** 521.

38. Nakagawa H, Niu K, Hozawa A et al: Impact of nocturia on bone fracture and mortality in older individuals: a Japanese longitudinal cohort study. J Urol 2010; **184:** 1413.

39. Marshall LM, Lapidus JA, Wiedrick J et al: Lower urinary tract symptoms and risk of non-spine fractures among older community dwelling U.S. men. J Urol 2016; **196:** 166.

40. Noguchi N, Chan L, Cumming RG et al: A systematic review of the association between lower urinary tract symptoms and falls, injuries, and fractures in community-dwelling older men. Aging Male 2016; **19:** 168.

41. Oelke M, Anderson P, Wood R et al: Nocturia is often inadequately assessed, diagnosed and treated by physicians: results of an observational, real-life practice database containing 8659 European and US-American patients. Int J Clin Pract 2016; **70:** 940.

42. Sakalis VI, Karavitakis M, Bedretdinova D et al: Medical treatment of nocturia in men with lower urinary tract symptoms: systematic review by the European Association of Urology Guidelines Panel for Male Lower Urinary Tract Symptoms. Eur Urol 2017; **72:** 757.

43. Vaughan CP, Fung CH, Huang AJ et al: Differences in the association of nocturia and functional outcomes of sleep by age and gender: a cross-sectional, population-based study. Clin Ther 2016; **38:** 2386.

44. Chrischilles E, Rubenstein L, Chao J et al: Initiation of nonselective alpha1-antagonist therapy and occurrence of hypotension-related adverse events among men with benign prostatic hyperplasia: a retrospective cohort study. Clin Ther 2001; **23:** 727.