



Characterizing nocturia among Belgian healthy postmenopausal women: Prevalence, bother, etiology and possible risk factors for developing nocturia

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ABSTRACT

Introduction: Limited literature concerning nocturia in early postmenopausal women is available. However, due to the lack of endogenous estrogen in these women, an increased prevalence of nocturia is expected.

Material and methods: This prospective observational trial recruited 210 ‘early’ postmenopausal women consulting the Ghent University menopause clinic. Postmenopausal status was biochemically confirmed. Women fulfilled 3 questionnaires: ICI questionnaire on nocturia (ICIQ-N); ‘Targeting the individual’s Aetiology of Nocturia to Guide Outcomes’ (TANGO) and the Perceived Stress Scale (PSS). Moreover, information concerning women’s age, anthropometrics and life style were collected. Nocturia was defined as ≥ 2 nocturnal voids.

Results: Nocturia was reported in 24.8 % (52/210) of the post-menopausal women. Bother increased with every nocturnal void. Women with ≥ 2 nighttime voids were found to have significantly increased prevalence of urgency compared to women with only one ($p < 0.001$; 38.5 % VS 22.7). Troubles initiating sleep at the start of the night and insomnia during the night were significantly different in women with a different nocturnal frequency (initiating sleep: $p = 0.09$ no voids: 34.4 %, 1 void: 39.2 %, ≥ 2 voids 53.8 %; insomnia: $p < 0.001$; no voids: 1.6 %, 1 void: 22.7 %, ≥ 2 voids: 53.8 %). Next to bladder and sleep dysfunctions, waist circumference is reported as risk factor for developing nocturia (OR 1.04; 95 % CI: 1.01–1.08)

Conclusion: Nocturia is an important problem in early postmenopausal women, affecting a quarter of the questioned women. Etiology of nocturia in this population is multifactorial as estrogen withdrawal comes along with bladder and sleep dysfunctions.

1. Introduction

Nocturia, or the act of passing urine during the main sleeping period, is a common symptom in the elderly population [1]. Today, little is known about nocturia in early postmenopausal women. However, due to the lack of endogenous produced estrogen in these women, an increased prevalence of nocturia is expected. A Thai cohort study reported nocturia as the most prevalent genito-urethral symptom affecting 77.7 % of all postmenopausal women. Despite this high prevalence, only a quarter

of all affected women sought medical attention [2].

Multiple studies have shown that nocturia is an important symptom leading to severe consequences on overall health. Nocturia is an independent risk factor for depressive symptoms [3], a reduced productivity [4] and it increases the risk of falls and fractures [5,6]. Moreover, it has been found that patients with nocturia of at least two voids per night have a 23%–27% increased risk of all-cause mortality [7,8]. Nevertheless this problem needs to become more transparent, especially in postmenopausal women, as poor health is eight times more common in

Abbreviations: ADH, anti-diuretic hormone; BMI, body mass index; IQR, interquartile range; LUTS, lower urinary tract symptoms; OSAS, obstructive sleep apnea symptoms; PSS, perceived stress scale; RAAS, renin-angiotensin-aldosterone-system; TANGO, Targeting the individual’s Aetiology of Nocturia to Guide Outcomes; STRAW, Stages of Reproductive Aging Workshop; VAS, Visual Analogue Scale.

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postmenopausal women with three or more nocturnal voids [9].

As for the global population with bothersome nocturia [10], a multifactorial etiology in postmenopausal women is expected, as an impaired estrogen production exerts its effect through different mechanisms. Firstly, the depletion of estrogen leads to a higher incidence of sleep problems including trouble falling asleep and waking up repeatedly [11]. Moreover, an increase in nocturnal hot flushes is reported to induce sleep fragmentation [11,12]. Additionally, the incidence of obstructive sleep apnea syndrome (OSAS) is higher in postmenopausal women compared to premenopausal women [13,14] and lower estradiol levels are associated with OSAS [15,16]. Secondly, down regulation of the estrogen receptors, which are present in the urethra and the bladder trigonum, is seen during menopause. This down regulation will induce a higher incidence of lower urinary tract symptoms (LUTS), specifically urinary urgency and frequency of small volume voids [17–19].

Finally, lack of estrogen potentially has a stimulating effect on diuresis as it leads to a lower excretion of anti-diuretic hormone (ADH) and an impaired activation of the Renin Angiotensin Aldosterone System (RAAS), although research is limited [20]. In a normal estrogen status, secretion of ADH peaks during the night [20,21], resulting in a lower free water clearance overnight, a higher nighttime urinary osmolality and thus a decreased nighttime diuresis. Moreover, high serum levels of estrogen stimulate the function of the RAAS with an increased production of angiotensinogen II, which has a direct antidiuretic effect through increased sodium reabsorption and an indirect effect through stimulation of the aldosterone synthesis, resulting in sodium reabsorption and potassium excretion [22]. During menopause, the impaired secretion of ADH due to the withdrawal of estrogen, will thus lead to impaired nocturnal water reabsorption, resulting in a higher nighttime urine production. As for ADH, menopausal transition parallels impaired stimulation of the RAAS leading to sodium loss.

A more extensive study on the incidence, origin and impact of nocturia in postmenopausal women is important, as it may guide the professional to an optimal assessment and treatment of nocturia in the affected women. The aim of this study was threefold:

- 1) To observe the prevalence of nocturia in the healthy Belgian early postmenopausal population.
- 2) To define risk factors for developing nocturia as a postmenopausal woman.
- 3) To examine potential underlying causes of nocturia in early postmenopausal women.

2. Material & methods

2.1. Design and participants

All patients in this prospective observational trial were recruited when consulting the menopause clinic of our institution between March 2018 and June 2019. Postmenopausal state was confirmed based on biochemical assessment (estradiol, FSH, LH). All women were in 'early' postmenopausal stages +1a,+1b or +1c as defined by the 'Stages of Reproductive Aging Workshop' (STRAW) criteria [23]. Moreover, patients with the following comorbidities were excluded in this study: thyroid dysfunction, the use of antihypertensive agents, history of psychiatric or neurological disorders and a history of alcohol or drug addiction. None of the women used hormonal replacement therapy or vaginal estrogens at the time of study assessment.

2.2. Measurements

To improve participation and response rate, this research was based on validated questionnaire rather than frequency-volume-charts, as many 'healthy' women find this assessment to cumbersome and time-consuming if they are not suffering from LUTS.

Women were asked to complete the ICI questionnaire on nocturia

(ICIQ-N), which questions nocturnal frequency and the associated bother. Nighttime frequency was dichotomized as either no nocturia (0) or having nocturia (1), with nocturia defined as ≥ 2 nocturnal voids. Bother linked with nocturia was reported on a Visual Analogue Scale (VAS), with '0' defined as having no bother and '10' as having high bother. Baseline characteristics including age, weight, height, waist circumference, BMI, parity and smoking habit were collected. Subsequently, women were asked to fulfill the 'Targeting the individual's Aetiology of Nocturia to Guide Outcomes' (TANGO) screening tool to observe underlying risk factors for nocturia (comorbidities: edema, orthostatic hypotension, intake of diuretics and diabetes; sleep characteristics: self-reported sleep quality, onset insomnia 'It takes me longer than 30 min to fall asleep at night', secondary insomnia 'I have difficulty of staying asleep due to my bladder', awakening in the first 3 h of the night and sleep apnea signs 'I have been told I snore loudly OR stop breathing at night', LUTS (urgency and urge-incontinence) and self-reported health status) [24,25].

Participants also completed the Perceived Stress Scale (PSS), a psychological instrument for measuring perception of stress. This scale captures the degree to which situations in one's life are appraised as stressful. For each situation women selected a response from the options: 'never', 'almost never', 'sometimes', 'fairly often' and 'very often'. Scale items were summed. The higher this sum score, the more stress was experienced by the participants [26]. Cohen et al. designed a normative values table for this scale and reported a mean score of 16.94 in women aged between 45–54 years in 2009 [27].

2.3. Statistical analysis

SPSS version 25 was used for statistical analysis. Descriptive statistics were presented as median(s) (interquartile range). Differences in bother between different nocturnal frequencies were assessed using the non-parametric Mann-Whitney *U* test for continuous variables. Categorical variables of the TANGO were compared between 'no nocturnal voids', '1 nocturnal void' and ' ≥ 2 nocturnal voids' in 2×2 assessment using the non-parametric Chi-square test. To identify independent predictors for nocturia, a univariate and multivariate logistic regression analysis with calculation of the adjusted odds ratios was performed. A *p*-value ≤ 0.05 was considered statistically significant.

The study was approved by the Ghent University Hospital review board (EC 2018/0315). The Declaration of Helsinki was followed and conducted in accordance to the legal regulations in Belgium. Written informed consent was obtained from all participants included in the study.

3. Results

3.1. Descriptive statistics

This study recruited 210 postmenopausal women with a median age of 52 (IQR 45–56) years. The overall median weight and height was 66 (IQR 59–73) kg and 165 (IQR 162–169) cm respectively, which corresponds with a median Body Mass Index (BMI) of 23.9 (IQR 21.4–27.5) kg/m². The median waist circumference was 89 (IQR 84–96) cm. Women had a median of 2 (IQR 1–2) children. Approximately 16 % (33/206) of participants self-reported being current smokers. No baseline differences in anthropometric, lifestyle or comorbidity variables between women with differing nocturia severity were found (Table 1).

3.2. Prevalence and bother

Nocturia was reported in 24.8 % (52/210) of the postmenopausal women. Twenty-nine percent (61/210) of the women slept through the night without waking up to void. One nocturnal void was seen in 46.2 % (97/210) of the cohort, 19 % (40/210) reported 2 nocturnal voids and 5.7 % (12/210) reported more than 2 nocturnal voids. A significant

Table 1
Descriptive statistics among women with a different nocturnal frequency.

	Participants (n = 210)	≥ 2 nocturnal voids (n = 52)	1 nocturnal void (n = 97)	No nocturnal voids (n = 61)	P – value*
Age (years) (median, IQR)	52 (45.3–56.0)	53 (45.50–56)	52 (45–56)	52 (44–55)	0.7
Anthropometrics (median, IQR)					
Weight (kg)	66.0 (59.2–73.0)	68.0 (60.5–78.0)	65.0 (58.0–73.0)	67.5 (61.0–72.8)	0.3
Height (cm)	165 (162–169)	165 (162–171)	165 (160–169)	165 (162–170)	0.4
BMI (kg/m ²)	23.9 (21.4–27.5)	23.9 (21.2–27.6)	23.9 (21.0–26.7)	24.4 (21.4–27.5)	0.6
Waist circumference (cm)	89.0 (83.5–96.0)	90.0 (85.0–100.8)	88.0 (81.3–93.8)	90.0 (84.0–95.0)	0.1
Life style factors (median, IQR)					
Parity (children)	2 (1–2)	2 (1–2.5)	2 (1–2)	1 (1–2)	0.06
Caffeine consumption (units/day)	3.0 (2.0–5.0)	3.5 (2.0–5.3)	3.0 (2.0–4.0)	3.0 (2.0–4.0)	0.2
Comorbidities (%)					
Intake of diuretics	1.4 (3/210)	0 (0/52)	1.0 (1/97)	3.3 (2/61)	0.3
Orthostatic hypotension	19.0 (40/210)	19.2 (10/52)	17.5 (17/97)	21.3 (13/61)	0.8
Diabetes	0.5 (1/210)	0 (0/52)	1.0 (1/97)	0 (0/61)	0.6
Lower limb edema	23.3 (49/210)	25.0 (13/52)	20.6 (20/97)	26.2 (16/61)	0.7
Smoking	15.7 (33/206)	11.5 (1/52)	17.5 (17/96)	16.4 (10/59)	0.6

IQR = Interquartile Range.

BMI = Body Mass Index.

* A p-value < 0.05 was considered statistically significant. Differences among variables in patients with a different nocturnal frequency were assessed using the Kruskal Wallis test for continuous variables and the chi-square test for categorical dichotomic variables.

difference in bother was seen between women who had to get up once and women who voided two or more times during the night (1/10 (IQR 0/10–5/10) and 5/10 (IQR 2/10 – 7/10) respectively).

3.3. TANGO questionnaire

Fig. 1 reports statistically significant differences in onset and secondary insomnia, awaking in the first 3 h of the night and daytime urgency compared between women without nocturnal voids: with 1 and with ≥ 2 nocturnal voids assessed using the TANGO. A significant increase in the prevalence of urge-incontinence was seen when comparing

women with no and ≥ 2 nocturnal voids (p = 0.03, 4.9 % (12/97), 17.3 % (9/52) respectively). As 12.4 % (12/97) of the women with 1 nocturnal void report incontinence, no statistically significant difference could be assessed compared to women with no or ≥ 2 nocturnal voids.

Although no statistically significant differences in sleep apnea signs were observed, a higher prevalence of sleep apnea signs was seen in women with a higher nocturnal frequency (p = 0.098, 1 nocturnal void: 23.7 % (23/97), ≥ 2 nocturnal voids: 36.5 % (37/52)). Lastly, no different responses on the statements ‘My sleep quality is bad’ and ‘I report my health as bad’ were reported between patients with a different nocturnal frequency (p = 0.2 and p = 0.5 respectively).

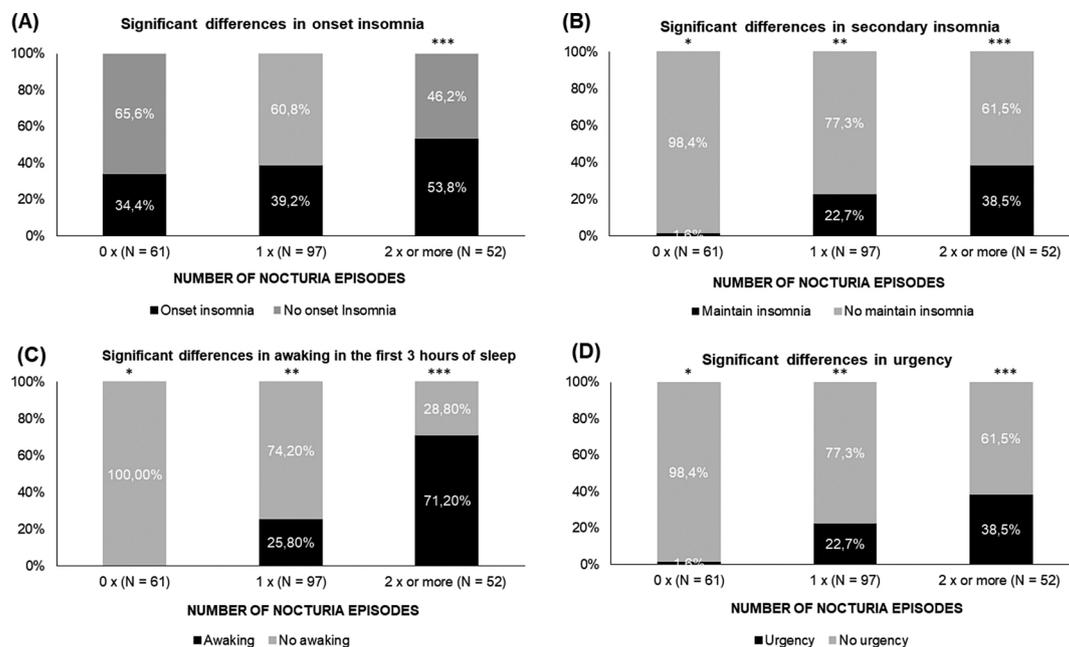


Fig. 1. Frequencies among risk factors for nocturia assessed using the TANGO questionnaire for patients with 0, 1 and 2 or more nocturia episodes: A) Differences in onset (first 30 min of the night) insomnia, B) Differences in maintaining sleep through the night (secondary insomnia), C) Differences in awakening during the first 3 h of the sleep to go to the toilet, D) Differences among daytime urgency episodes. Comparisons were assessed 2 on 2 using the chi-square test for categorical variables.

* P value < 0.05 between patients with 0 and 1 nocturia episode.

** P value < 0.05 between patients with 1 and 2 or more nocturia episodes.

*** P value < 0.05 between patients with 0 and 2 or more nocturia episodes.

However, an increased ratio of women describing their sleep quality as bad when comparing women without nocturnal voids and women with ≥ 2 ($p = 0.059$; 36.1 % (22/61) and 53.8 % (28/52) respectively). Forty-five (46.4 %) women with one nocturnal void reported their sleep quality as bad.

3.4. PSS questionnaire

Stress, measured using the PSS, did not differ between women with zero, one or two nocturnal voids ($p = 0.729$). The median stress score was 16 (IQR 14–21) for women without nocturnal voids, 18 (IQR 13–22) for those voiding one time overnight and 17.5 (IQR 14–23) for women with a nocturnal frequency of ≥ 2 .

3.5. Risk assessment

Univariate logistic regression analyses showed that waist circumference could be identified as an independent risk factor for developing nocturia (OR 1.04; 95 % CI: 1.01–1.08). Secondly, a significant association between nocturia and urgency could be observed, as patients with daytime urgency were 3 times more likely to have nocturia compared to patients without this problem (OR 3.7; CI: 1.76–7.8). Moreover, onset insomnia 'It takes me longer than 30 min to fall asleep at night' had an influence on the appearance of nocturia, as women with onset insomnia were almost two times more prone to nocturia than those without. Patients with 'secondary insomnia' and 'awaking in the first 3 h to void' had a significant higher risk for developing nocturia than patients without (Table 2).

A multivariate analysis with potential confounders for developing nocturia was tested as shown in Table 2. This multivariate model was significant, however, only secondary insomnia ($p = 0.003$, OR 3.99 (1.59–9.61)), onset insomnia ($p = 0.043$, OR 2.25 (1.03–4.99)) and urgency ($p = 0.01$, OR 3.97 (1.70–9.26)) could be defined as independent risk factors for developing nocturia after adjusting for waist circumference and sleep apnea signs.

4. Discussion

In this prospective study the prevalence of nocturnal voiding among early postmenopausal women was high, as approximately half of women in this cohort had to get up once at night to void, and a quarter of this cohort reported two or more nighttime voids. Urgency and sleep disturbances are potential etiological factors contributing to nocturia.

Large discrepancies in nocturia prevalence are reported [2,9,28,29]. Nocturia prevalence in this cohort was in line with results reported in a Taiwanese study (30.2 %) [29] and a Thai sample (77.7 % of their participants voided at least once a night) [2]. The Belgian prevalence was slightly higher than among the Japanese and Swedish populations

[9,28]. However, the Japanese study included both peri- and postmenopausal women, potentially underestimating nocturnal frequency. The Swedish study included community-based population of women between 40 and 64 years old, whereas the present study recruited participants who were consulting a menopause clinic, presumably for postmenopausal symptoms.

As previously described, getting up twice at night was associated with a significant increase in bother, a relationship seen with each increase in nocturnal frequency [30–32]. This high bother reflects the profound impact of nocturia in postmenopausal women and the need for intervention. Stress among this cohort was in line with the normative values for women between 45 and 55 years old, as reported by a US national survey in 2009 [27].

In contrast to other authors [2,22] this study did not find that age and BMI were risk factors for nocturia in postmenopausal women. However, many of the differences between these studies and our analysis can be readily explained by dissimilarities in study population. The present study was limited in age to early post-menopausal women whereas other studies included women in pre, peri and post menopause. Anthropometrics are likely to play a role in the development of nocturia in our group, as waist circumference significantly increased the risk for bothersome nocturia and a trend towards an effect of weight could be visualized.

The TANGO screening tool was used to observe different underlying aetiologies of nocturia at the same time, instead of assessing them separately without interaction to each other. Based on these results, different underlying causes for nocturia can be suggested. Daytime urgency symptoms significantly increased with each nocturia episode and women with urgency were three times more likely to have nocturia compared to women without urgency. These odds on nocturia increase even more after adjusting for other potential risk factors. Moreover, a significant increase in urge-incontinence episodes was seen, when comparing women without nocturnal voids and those with two or more. All these factors can be linked with the genitourinary syndrome of the menopause, reflecting the down regulation of oestrogen receptors in the urethra and bladder [18,19]. Moreover, a potential link between an increase in overactive bladder syndrome and the menopause is proposed in literature [34]. In-vitro studies on human bladder tissue showed that estrogen can directly activate large conductance, voltage and Ca^{2+} - activated K^+ (BK) channels, leading to a decrease in detrusor smooth muscle excitability and contractility and thus a potential effect on overactive bladder syndrome [35]. However, research observing the link between day and nighttime bladder symptoms in postmenopausal women are lacking.

In the general population, the link between OSAS and nocturia has been extensively discussed [32,33]. Although the increased prevalence of OSAS after menopausal transition has been studied [13,14], research linking nocturia and OSAS specific in postmenopausal women is lacking.

Table 2

Univariate and multivariate logistic regression analysis with nocturia (≥ 2 nocturnal voids) as a dependent, dichotomous variable.

Variable	Univariate		Multivariate	
	Odds (95 % CI)	P - value*	Odds (95 % CI)	P - value*
Age	1.00 (0.99–1.02)	0.7		
Weight	1.02 (0.99–1.05)	0.1		
BMI	6.8×10^{145} (0.00 –)	0.3		
Waist circumference	1.04 (1.00–1.07)	0.038	1.02 (0.98–1.06)	0.3
Lower limb edema	1.13 (0.55–2.34)	0.7		
< 5 h of sleep	1.05 (0.52–2.14)	0.9		
Onset insomnia	1.96 (1.04–3.69)	0.038	2.25 (1.03–4.92)	0.043
Secondary insomnia	3.67 (1.80–7.48)	<0.001	3.99 (1.58–9.61)	0.003
Awakening in first 3 h of sleep to void	13.12 (6.28–27.40)	<0.001		
Urgency	3.69 (1.80–7.48)	<0.001	3.97 (1.70–9.26)	0.001
Urge-incontinence	2.00 (0.82–4.88)	0.1		
Sleep apnea signs	1.81 (0.93–3.56)	0.08	1.62 (0.67–3.89)	0.3

* A p-value of < 0.05 was considered statistically significant and are highlighted in bold. CI: Confidence Interval.

In this cohort, no significant differences in sleep apnea signs were reported. However, a trend towards a higher prevalence of sleep apnea signs could be visualized in women with a higher nocturnal frequency. Sleep apnea signs were questioned using the following statement: 'I have been told I snore loudly OR stop breathing at night'. Potentially, an underestimation of the prevalence of OSAS is seen, as most women with OSAS present with vague complaints (insomnia, nightmares or depression) instead of snoring [35–38]. Insert references 36 en 37. In addition, not all women have a (bed)partner, to confirm apnea symptoms.

Significant increased odds for insomnia (both onset and maintained) linked with an increase of nighttime voids is found. Moreover, a multivariate model found both parameters to increase the risk on nocturia by two and four times respectively, compared to women without this sleeping disorder. This finding is in line with the results of the Japanese cohort, who found that women with difficulties initiating sleep were 1.5 times more likely to develop nocturia compared to women without [28]. This finding seems logical, however it could be that this association is the other way around with insomnia inducing an early night toilet visit, as sleep disturbances are frequently present in postmenopausal women. Assessing if insomnia leads to nocturia or nocturia leads to insomnia is a crucial question which is difficult to examine. In addition, it is not possible to determine whether the women considered nocturia correctly, as every nightly toilet visit should be preceded and followed by sleep. Misinterpretation of this finding can be a possible declaration of the high incidence of onset insomnia in this cohort.

Lastly, the proportion of women who awaking during the first 3 h of sleep showed a linear relationship with increase in nocturnal frequency. This early nighttime voiding can be due to a high fluid intake in the evening, impaired secretion of ADH resulting in an increased water diuresis overnight or in combination with a low bladder capacity. Unfortunately, information about bladder capacity, overnight diuresis and timing of voids was not available.

To our knowledge, this prospective study is the first to assess several potential causative factors of nocturia in early postmenopausal women using validated questionnaires. This analysis shows that nocturia in this population is multifactorial, as the withdrawal of estrogen secretion has an impact on different contributors including sleep and bladder conditions. Potentially, an effect of estrogen withdrawal on water and salt diuresis can be suspected, suggesting an important impact of the kidney on the development of nocturia in this group as well. However, this remains an hypothesis. Further research including frequency volume charts, fluid assessment and sleep observation is necessary. Moreover, a renal function profile observing water and salt diuresis during 24 h can be helpful to clarify the effect of oestrogen loss on ADH secretion and RAAS activity.

This prospective study has some limitations. Firstly, a selection bias can be withhold, as women were recruited at the gynecological department, and are thus potentially not reflecting the general population of women during early post menopause. However, all women included in this analysis were healthy without intake of medication or comorbidities. Secondly, the assessment of nocturia and its potential risk factors was based on validated questionnaires rather than voiding dairies or frequency volume charts. For this reason, the ratio of postmenopausal women reporting nocturnal polyuria could not be determined. Lastly, it was difficult to specify if patients woke up due to the need to urinate or where awake as a results of other factors (f. e. hot flushes or pain).

5. Conclusion

Nocturia is an important problem in early postmenopausal women, which should not be underestimated. In this Belgian cohort 24.8 % of the participants report nocturia, with each nocturnal void leading to a significant increase in bother.

Waist circumference, daytime urgency and trouble falling asleep during the first 30 min of the night were identified as risk factors for

developing nocturia in the early post-menopause.

The menopausal estrogen withdrawal resulted in a significant increase in bladder and sleep dysfunctions, suggesting a multifactorial etiology of nocturia in the early postmenopausal women with interplay of multiple contributors. However, more research concerning the impact of estrogen withdrawal on diuresis is necessary.

Disclosures

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Conflict of interest

The authors report no declarations of interest.

Ethical statement

The study was approved by the Ghent University Hospital review board (EC 2018/0315). The Declaration of Helsinki was followed and conducted in accordance to the legal regulations in Belgium. Written informed consent was obtained from all participants included in the study.

This statement was made in the Material and Methods section of the manuscript.

CRediT authorship contribution statement

Kim Pauwaert: Conceptualization, Writing - original draft, Writing - review & editing. **An-Sofie Goessaert:** Conceptualization, Writing - original draft, Writing - review & editing. **Lynn Ghijssels:** Writing - original draft, Writing - review & editing. **Wendy Bower:** Writing - review & editing. **Herman Depypere:** Conceptualization, Writing - review & editing. **Karel Everaert:** Conceptualization, Writing - review & editing.

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