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Permalink

<https://escholarship.org/uc/item/4pm927zc>

Journal

Clinical Therapeutics, 38(11)

ISSN

0149-2918

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Publication Date

2016-11-01

DOI

10.1016/j.clinthera.2016.09.009

Peer reviewed



Published in final edited form as:

Clin Ther. 2016 November ; 38(11): 2386–2393.e1. doi:10.1016/j.clinthera.2016.09.009.

Differences in the Association of Nocturia and Functional Outcomes of Sleep by Age and Gender: a Cross-sectional, Population-Based Study

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Abstract

Purpose—Nocturia is associated with poor sleep quality; however, little is known about the relationship between nocturia and sleep quality across different workforce-relevant age groups of adults. This has implications for developing new treatment strategies that are well tolerated across populations.

Materials and Methods—We conducted a cross-sectional study involving merged data from the 2005-2006 and 2007-2008 waves of the National Health and Nutrition Examination Survey. Participants responded to validated questions on nocturia frequency and sleep, the Functional Outcomes of Sleep Questionnaire General Productivity subscale (FOSQ-gp, range 1-4). Analyses included multivariable linear regression with stratification by gender to examine associations

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Conflict of Interest: C.V.: no relevant disclosures

C.F.: no relevant disclosures

A.H.: no relevant disclosures

T.J.: no relevant disclosures

A.M.: no relevant disclosures

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between nocturia frequency (higher worse) and the FOSQ-gp scores (lower scores indicating worse daytime function related to sleep disturbance).

Findings—Of 10,512 adults aged ≥ 20 who completed the survey, 9,148 (87%) had complete nocturia and FOSQ-gp data. The population age-adjusted prevalence of nocturia at least twice nightly was 21.1% among men and 26.6% among women ($p < 0.001$), and nocturia increased with age ($p < 0.001$). Compared to those with no or one episode of nocturia, those with nocturia at least twice nightly reported lower mean FOSQ-gp scores (3.65 (95% CI: 3.61-3.69) vs. 3.19 (95% CI: 3.09-3.31) for men; 3.52 (95% CI: 3.48-3.56) vs. 3.09 (95% CI: 3.02-3.16) for women). Older adults (age > 65 years) with greater nocturia frequency reported worse FOSQ-gp scores compared to younger adults with similar nocturia frequency ($p < 0.001$ among men and women).

Implications—In a population-based sample of community-dwelling men and women, the association between nocturia and worsened functional outcomes of sleep was greater among adults older than 65 years - a group more vulnerable to drug side effects and in whom nocturia is typically multifactorial. Additionally, these analyses demonstrate that the association between nocturia and functional outcomes of sleep is stronger with increasing age among men. Effective treatment strategies that are well tolerated by older adults such as multicomponent treatments that simultaneously address the combined effects of lower urinary tract and sleep dysfunction are needed.

Keywords

nocturia; sleep; older adults; aging; epidemiology

Introduction

Nocturia (*waking from sleep at night to void*¹) is associated with disrupted sleep at night, and evidence suggests that frequent nocturia leads to daytime napping and impaired work productivity²⁻⁴. Previous studies among older adults have demonstrated that both sleep dysfunction and nocturia increase substantially in prevalence as adults age⁵⁻⁸. Less is known about the association of nocturia frequency and sleep disruption among different age groups of adults, with one study suggesting that the negative impact of nocturia to interfere with sleep is greater among younger women versus older women⁹.

Evaluating the relative impact of nocturia on important functional outcomes such as those related to poor sleep among different age groups is important for developing targeted therapies. Older adults are more vulnerable to the side effects of available pharmacologic therapy for nocturia, particularly antimuscarinic bladder relaxants, alpha-blockers and antidiuretic therapy¹⁰. Older adults are also more likely to experience side effects from sedative-hypnotic medications that may be used for sleep dysfunction¹⁰. If older adults are disproportionately impacted by combined effects of sleep dysfunction and nocturia, this has implications for the study of new treatment strategies.

The National Health and Nutrition Examination Survey (NHANES) is a cross-sectional population-based survey in the United States (U.S.). The goals of this study were to characterize the relationship between nocturia and functional outcomes of sleep and to

assess the relationship between nocturia and functional outcomes of sleep across different age groups of men and women.

Methods

The NHANES program consists of cross-sectional, national health surveys conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (<http://www.cdc.gov/nchs/nhanes.htm>). The NHANES uses a complex, stratified, multi-stage, probability cluster design that oversamples persons aged 60 years or older and racial/ethnic minority groups (Non-Hispanic Black, Mexican American, and low-income Non-Hispanic White) to provide more reliable estimates for these groups. The NCHS Ethics Review Board approved the protocol, and all participants provided written informed consent¹¹. As a secondary analysis of publicly available NHANES data, these analyses were granted exemption from review by the Institutional Review Board at the University of Alabama at Birmingham.

Participants were interviewed in person in mobile examination centers and then underwent standardized physical examination, including measured height and weight. To assess nocturia frequency, respondents were asked, “During the past 30 days, how many times per night did you most typically get up to urinate, from the time you went to bed at night until the time you got up in the morning?”; response options included 0, 1, 2, 3, 4, or “5 or more”. Nocturia was evaluated both as an ordinal variable and dichotomized as 0-1 episodes per night and 2 or more episodes per night based upon literature suggesting 2 or more episodes of nocturia represents clinically relevant nocturia¹².

The impact of sleep disturbance was assessed using the validated Functional Outcomes of Sleep Questionnaire General Productivity weighted subscale (FOSQ-gp). (Specific questionnaires can be found at: http://www.cdc.gov/nchs/nhanes/nhanes_questionnaires.htm.) The FOSQ-gp queries if the participant had difficulty with eight different daily tasks such as concentrating, finishing a meal, financial affairs or homework, because of feeling sleepy or tired with four response options ranging from 1 = ‘extreme difficulty’ to 4 = ‘no difficulty’. A weighted mean FOSQ-gp score is calculated based upon the total number of answered items for each participant¹³. Total FOSQ-gp scores range from 1-4 with lower scores indicating worse daytime function related to sleep disturbance.

Participants self-reported their race/ethnicity, which was then categorized as non-Hispanic white, non-Hispanic Black, Hispanic - Mexican American, Hispanic (not including Mexican American) and other/mixed race ethnicity. For this investigation, race/ethnicity was then dichotomized as Non-Hispanic White versus all other racial/ethnic groups. Because many of the tasks queried by the FOSQ-gp revolve around the completion of daily tasks such as employment, volunteer work or attending school, the authors determined age categorization that evaluated working ages would be more informative for interpreting the results than traditional categorization based upon age-decade. Because many of the tasks queried by the FOSQ-gp revolve around the completion of daily tasks such as employment, volunteer work or attending school, the authors determined age categorization that evaluated working ages

would be more informative for interpreting the results than traditional categorization based upon age-decade. Age was categorized to broadly define different workforce-relevant age groups of *young adults*, *middle adults*, and *older adults* (ages 20-45 years, ages 46-65 years and ages 66 years and older). Body mass index (BMI) was calculated from measured height and weight and categorized as less than 25.0 (underweight/normal weight), 25.0 to 29.9 (overweight), and 30.0 or more (obese) kg/m².

Chronic conditions were categorized as osteoarthritis, chronic lung disease (emphysema, chronic bronchitis, asthma), coronary heart disease (coronary artery disease, angina or heart attack), diabetes, and stroke. These conditions were ascertained using the self-report question, “*Has a doctor or other health professional told you that you had [condition]?*”¹⁴. Participants who reported taking insulin and/or diabetic pills were classified as having diabetes even if they did not self-report a prior diagnosis of this condition. The cumulative number of positive responses to any self-reported chronic condition was divided into four categories: 0, 1, 2, and 3 or more. Sleep apnea was self-reported based upon a positive response to the query, “*Have you ever been told by a doctor or other health professional that you have a sleep disorder?*” followed by listing ‘sleep apnea’ as the diagnosed sleep disorder. Self-reported benign prostate enlargement (BPE) and was queried only among men 40 years of age or older. The investigators did not include BPE in the final model because the reduced sample size (decreased by one third) prevented the evaluation of the association between nocturia and sleep across all age groups of men. Depression was assessed using the validated Patient Health Questionnaire–9 (PHQ-9). The PHQ-9 yields scores from 0 to 27 and scores ≥ 10 are used to define major depression.¹⁵

The 2005-06 and 2007-08 survey data for women and men were combined. Analyses were conducted separately by gender based on previous research suggesting different correlates of nocturia among men and women^{16,17}. Prevalence estimates and 95% confidence intervals (CIs) were calculated using STATA 12.1 (STATA Corp. College Station, Texas), which incorporates the appropriate sample weights, as well as the stratification and clustering of the complex NHANES sample design. The sample weights adjust for unequal probabilities of selection and nonresponse. Analyses included weighted prevalence estimates of clinically relevant nocturia according to gender and age categories. After stratification by gender, Pearson's χ^2 test or a t-test as appropriate were used to assess the association between clinically relevant nocturia (0-1 vs. ≥ 2 episodes per night) and demographic and medical characteristics. Estimates with relative standard errors greater than 30% were identified as statistically unreliable. Variables which might confound the association between nocturia (ordinal value) and functional sleep outcomes were included in gender stratified multivariable linear regression models. The ordinal rather than the dichotomized nocturia variable was used to permit a more informative presentation of the association of increasing frequency of nocturia and FOSQ-gp scores. Starting with models stratified by gender and including age category, race, chronic disease, and BMI, additional variables, including sleep apnea and depression, were evaluated in a stepwise fashion to determine a final model including those characteristics that led to at least a 10% change in the estimate or 95% confidence interval for nocturia. Effect modification according to the previously specified workforce-relevant age categories was explored in the full model, prior to stepwise evaluation, to assess the association between nocturia and the FOSQ-gp among different age

groups of men or women. A p -value of ≤ 0.05 defined significant effect modification for the interaction term of workforce-relevant age category and nocturia when included in the full model. Additional analyses were performed to assess for differences between those with complete data and those who were excluded. We also calculated the number of proxy interviews performed for NHANES participants with complete data for FOSQ-gp and nocturia and assessed for differences between those with and without missing data according to proxy reporting.

Results

Of the 10,512 adults aged ≥ 20 who completed the survey, 9,148 (87%) had complete nocturia and FOSQ-gp data. The US population adjusted prevalence of clinically relevant nocturia occurring at least twice per night was 21.1% among men and 26.6% among women ($p < 0.001$) and increased across age categories for both genders. Nearly half of the men and women in the oldest age category (66 years of age and older) reported nocturia at least twice nightly, compared to less than 15 percent of men and 20 percent of women in the youngest age category. Those men and women reporting their ethnic/racial background as non-Hispanic black were more likely to report nocturia (Table 1). Up to 25% of men and more than 30% of women with clinically relevant nocturia reported at least three of the chronic conditions queried in NHANES, compared to less than 15% of men and less than 20% of women without clinically relevant nocturia. Depression as determined by a positive screen on the PHQ-9 questionnaire occurred frequently in both men and women with clinically relevant nocturia. As expected, sleep apnea and a BMI greater than 30 kg/m² were also associated with clinically relevant nocturia.

Older age was associated with worse FOSQ-gp scores in both men and women even in the absence of nocturia. Specifically, among men with no nocturia, the mean FOSQ-gp score was 3.75 (95% CI 3.71 – 3.79) in those aged 20-45 years, 3.65 (95% CI 3.55 – 3.75) in those aged 46-65 years, and 3.19 (95% CI 2.89 – 3.49) in men aged 66 years and older. Among women with no nocturia, the mean FOSQ-gp score was 3.67 (95% CI 3.62 - 3.73) in those aged 20-45 years, 3.56 (95% CI 3.44 - 3.67) in those aged 45-65 years, and 2.84 (95% CI 2.62 – 3.05) among women aged 66 years and older.

As a group, both men and women with clinically relevant nocturia (2 or more episodes per night) reported lower FOSQ-gp scores than those with minimal nocturia (0-1 episodes per night). Men with minimal nocturia (0-1 episodes per night) reported a mean FOSQ-gp score of 3.65 (95% CI 3.61 - 3.69) compared to men experiencing clinically relevant nocturia who reported a mean score of 3.19 (95% CI 3.09 – 3.31, $p < 0.001$). Women with minimal nocturia reported a mean FOSQ-gp score of 3.52 (95% CI 3.48 – 3.56) compared to women with clinical relevant nocturia who reported a mean score of 3.09 (95% CI 3.02 – 3.16, $p < 0.001$).

In multivariable models adjusting for BMI, race/ethnicity, number of chronic conditions and depression, an association between older age category and worse FOSQ-gp scores was observed with increasing nocturia frequency among men (Figure 1) and women (Figure 2) (p -value for age category of < 0.0001 for both genders). Effect modification by age category

was only present among men (p-value for interaction term 0.01 among men). Adjustment for sleep apnea did not change the association between frequent nocturia and functional outcomes related to sleep and, thus, was not included in the final models (final models included in Supplementary file).

Overall, there were no differences with regard to age category (p=0.31), gender (p=0.98), and race/ethnicity (p=0.48) for NHANES participants with complete FOSQ-gp and nocturia data compared to participants excluded from the analysis for incomplete data. A total of 99.6% of the participants did not have a proxy complete the initial interview questions and 99.5% of the participants did not have a proxy complete the interview in the mobile examination center where the assessments of nocturia and FOSQ-gp were completed. We did not find any differences for those with and without missing data according to proxy reporting (p=0.81).

Discussion

These analyses from a population-based sample of men and women demonstrate that the association of nocturia and functional outcomes of sleep is greater among adults older than 65 years compared to younger adults. The association between increasing nocturia frequency and poor functional outcomes of sleep was most dramatic among older men; however, older women with more frequent nocturia also consistently reported worse functional outcomes of sleep as reflected by lower FOSQ-gp scores.

While previous studies have documented the negative impact of frequent nocturia with regard to sleep disruption among predominantly older adult populations^{3,6-8,18}, less is known about the relative impact of frequent nocturia among older adults compared to young and middle-aged adults^{5,9}. In one study among community-dwelling adults, the authors found that disrupted sleep had the greatest impact on younger adults who make up a larger part of the working population⁹. Our results suggest that older adult populations are both more burdened by frequent nocturia and report more negative functional outcomes that result from sleep disruption. Thus, optimization of existing nocturia treatments and the development of new treatments should target older adults.

Nocturia has been described as one of the most bothersome lower urinary tract symptoms and is known to occur more frequently as adults age^{19,20}. Our results are consistent with previous studies suggesting the prevalence of nocturia increases dramatically as men age²¹. Our results also confirm previous reports that frequent nocturia (at least twice per night) is common among older women, although the increase in prevalence with increasing age in women is not as dramatic because a significant number of younger women (up to a third) in our sample also experienced nocturia^{5,21}. Finally, results from our study, which used a nation-wide sample, confirm reports from the Boston Area Community Health study indicating that nocturia is associated with worse quality of life and interference with daily activities⁹.

For this assessment, we focused on conditions associated with nocturia that might confound the relationship with sleep dysfunction. Frequent nocturia occurred more commonly among

non-Hispanic black men and women. Similar to previous studies of factors associated with nocturia, we found that among both men and women, those with nocturia were more likely to have multiple chronic conditions, an obese BMI, and report a history of depression^{7,16,18,22,23}. As expected, sleep apnea was more common among those with nocturia; however, the presence of self-reported sleep apnea did not confound the association between nocturia and functional outcomes related to sleep in men or women. While directionality cannot be assumed in this cross-sectional evaluation, these results suggest sleep apnea is not directly involved in the causal pathway between nocturia and disrupted sleep.

Nocturia remains a challenging urinary symptom to treat, largely because multiple contributing conditions often coexist within a single individual experiencing nocturia²⁴. Current treatment strategies are typically focused exclusively on the lower urinary tract²⁵⁻²⁷, even though several reports suggest that older adults with nocturia are more likely to find nocturia to be clinically bothersome if it is complicated by poor sleep quality^{28,29}. Widespread usage of available drug treatments for nocturia that target the lower urinary tract such as bladder relaxants, alpha blockers, or desmopressin are more often limited in older adults because of their potential for higher side effects¹⁰. Less is known about the impact of multicomponent therapies such as strategies that simultaneously combine treatments for sleep and lower urinary tract dysfunction^{23,30,31}. Our results suggest sleep dysfunction is common and frequently affects daily activities, predominantly among older adults with nocturia. Additional research is needed to determine effective treatment strategies for nocturia, particularly among older adults who are more vulnerable to the side effects of many drugs.

There are limitations to our evaluation. While the presence of nocturia was assessed using a validated question, the response depends upon self-report and does not include information that might be gained from a patient-completed frequency-volume chart that would allow insight into the etiology of nocturia. As with most prevalence studies, NHANES sampled only the non-institutionalized population, whereas nocturia may be even more frequent among adults in long-term care facilities. However, large sample sizes can be achieved by merging data sets containing validated nocturia and sleep items from several waves of the NHANES, thereby providing sufficient power to assess the impact of nocturia across different subgroups of community-dwelling adults. The analysis of associated conditions may be limited as data regarding the presence of other conditions which could be related to nocturia were not obtained during these waves of the NHANES. Lastly, these cross-sectional data do not allow for an assessment of causality or evaluation of changes in the strength of relationships between nocturia and sleep outcomes over time.

Conclusions

These results demonstrate that not only is nocturia more common among older versus younger men and women, but also that the association between nocturia and worsened functional outcomes of sleep is greater among adults over the age of 65 years and strongest among older men. Because older adults with nocturia often have multiple contributing conditions and are more vulnerable to the side effects of drug therapy, the treatment of

nocturia is particularly challenging among this age group. Multicomponent treatment approaches for nocturia that simultaneously address the combined effects of lower urinary tract and sleep dysfunction require further investigation. The development and optimization of treatment strategies for nocturia that are well tolerated in older adults should remain a priority.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

C.V. is supported by a Department of Veterans Affairs Career Development Award from Rehabilitation R&D (1 IK2 RX000747). C.F. is supported by the Beeson Career Development in Aging Research Award Program (supported by National Institute On Aging, American Federation for Aging Research, The John A. Hartford Foundation, and The Atlantic Philanthropies [K23AG045937]). A.M. is supported by NIH funding through the National Institute on Diabetes and Digestive and Kidney Disease (1R21DK096201-01).

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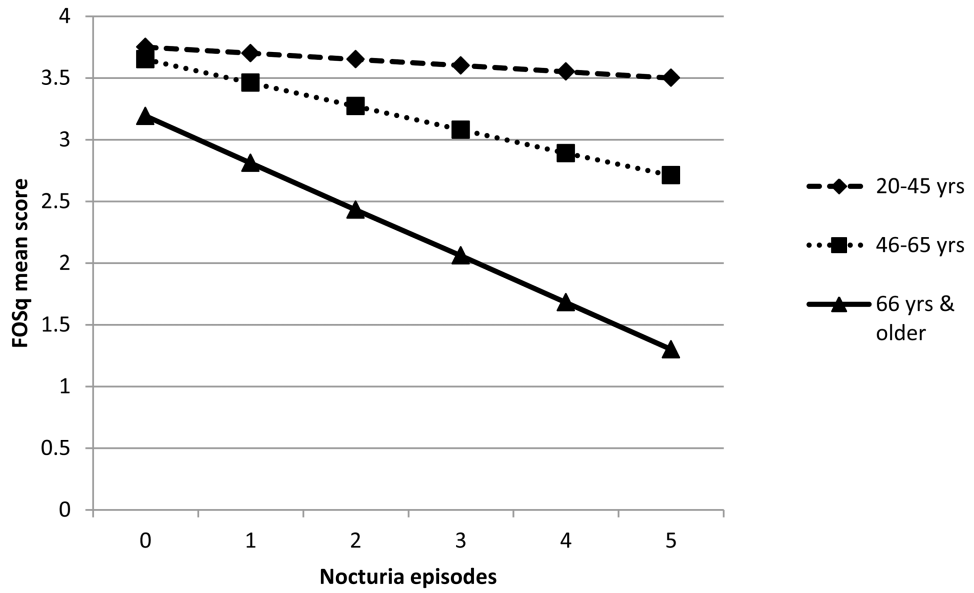


Figure 1. Association of nocturia and functional outcomes of sleep among men*
*Stratified by age and adjusted for BMI, race/ethnicity, number of comorbid conditions, depression and effect modification by workforce-related age category (p=0.01 for interaction term of age category & nocturia)

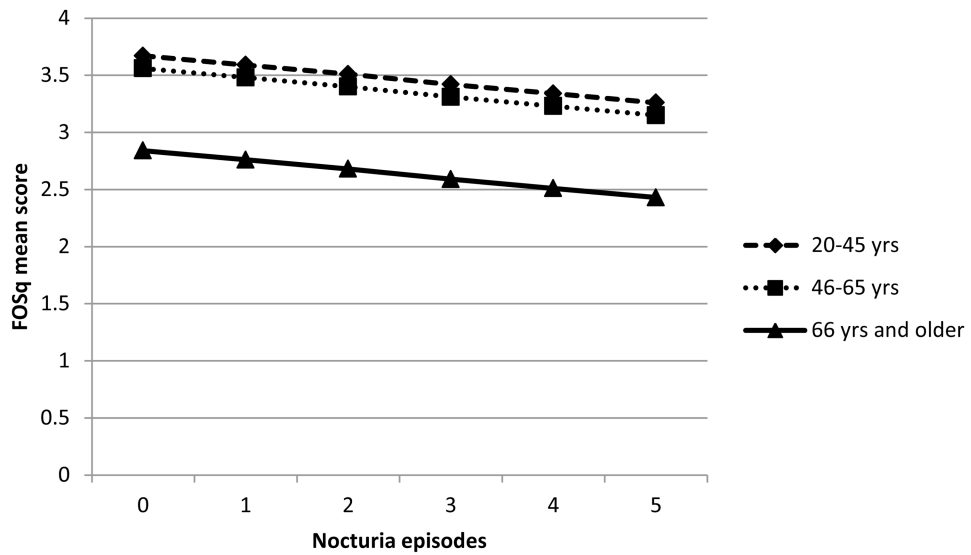


Figure 2. Association of nocturia and functional outcomes of sleep among women*
*Stratified by age and adjusted for BMI, race/ethnicity, number of comorbid conditions, depression; no effect modification by work-force related age category ($p=0.07$ for interaction term of age category & nocturia)

Table 1

Baseline characteristics of men and women by nocturia status

Characteristic*	Men		p-value	Women		p-value
	Nocturia 0-1 episodes per night (n=3,316)	Nocturia 2 episodes per night (n=1,333)		Nocturia 0-1 episodes per night (n=3,023)	Nocturia 2 episodes per night (n=1,476)	
Age Category			<0.001			<0.001
20-45 yrs	88.9 (87.1-90.6)	11.1 (9.4-13.0)		82.2 (79.7-84.4)	17.8 (15.6-20.3)	
46-65 yrs	76.0 (72.6-79.1)	24.0 (20.9-27.4)		70.0 (66.4-73.3)	30.0 (26.7-33.6)	
66 yrs and older	52.0 (48.7-55.2)	48.0 (44.8-51.3)		57.0 (53.0-61.0)	43.0 (39.1-47.0)	
Race/Ethnicity			0.001			<0.001
Hispanic-Mexican American	79.9 (76.2-83.1)	20.1 (16.9-23.7)		73.5 (69.7-77.0)	26.5 (23.0-30.3)	
Hispanic – other	77.8 (71.7-82.9)	22.2 (17.1-28.3)		67.6 (59.7-74.7)	32.4 (25.3-40.3)	
Non-Hispanic white	79.9 (77.7-82.0)	20.1 (18.0-22.3)		75.3 (72.2-78.3)	24.6 (21.7-27.8)	
Non-Hispanic black	69.7 (65.9-73.3)	30.3 (26.7-34.1)		60.3 (56.7-63.8)	39.7 (36.2-43.3)	
Other – including multi-racial	82.6 (73.8-88.9)	17.4 (11.1-26.2)		80.1 (71.3-86.7)	19.9 (36.2-43.3)	
Body Mass Index			0.009			<0.001
< 25.0	81.7 (78.3-84.7)	18.3 (15.3-21.8)		81.1 (79.0-83.1)	18.9 (16.9-21.0)	
25.0-29.9	80.2 (77.2-82.9)	19.8 (17.1-22.9)		72.1 (67.8-76.0)	27.9 (24.0-32.2)	
> 30.0	75.2 (72.1-78.0)	24.8 (22.0-27.9)		66.6 (63.6-69.5)	33.4 (30.5-36.4)	
Number of Chronic conditions †			<0.001			<0.001
None	87.3 (85.5-90.0)	12.7 (11.0-14.5)		81.3 (79.4-83.0)	18.7 (17.0-20.6)	
1	72.2 (68.9-75.3)	27.8 (24.7-31.1)		72.2 (68.4-75.7)	27.8 (24.3-31.6)	
2	56.7 (49.5-63.6)	43.3 (36.3-50.5)		59.4 (53.6-64.9)	40.6 (35.1-46.4)	
3 or more	47.6 (40.5-54.7)	52.4 (45.3-59.4)		47.2 (41.3-53.2)	52.8 (46.8-58.7)	
Depression ** (Moderate-Severe)			0.005			<0.001
No	79.4 (77.4-81.2)	20.7 (18.8-22.6)		74.3 (72.3-76.2)	25.7 (23.8-27.7)	
Yes	58.5 (41.4-73.8)	41.5 (26.3-58.6)		52.2 (40.6-63.5)	47.8 (36.5-59.4)	
Sleep Apnea ‡			0.006			0.0009
No	79.8 (77.8-81.7)	20.2 (18.3-22.2)		74.5 (72.5-76.4)	25.5 (23.6-27.5)	

Characteristic*	Men		Women		p-value
	Nocturia 0-1 episodes per night (n=3,316)	Nocturia 2 episodes per night (n=1,333)	Nocturia 0-1 episodes per night (n=3,023)	Nocturia 2 episodes per night (n=1,476)	
Yes	71.2 (64.7-77.0)	28.7 (23.0-35.3)	59.2 (29.3-68.4)	40.8 (31.6-50.7)	
FOSQ-gp score					
Mean (95% CI)	3.65 (3.61-3.69)	3.19 (3.09-3.31)	3.52 (3.48-3.56)	3.09 (3.02-3.16)	<0.001
Prostate Enlargement [‡]	N=1,929	N=1,139	N/A	N/A	<0.001
No	74.9 (71.8-77.7)	25.1 (22.3-28.2)			
Yes	58.0 (53.3-62.6)	42.0 (37.4-46.6)			

* Proportion (95% CI) unless noted, estimates weighted to be nationally representative

** Based upon a PHQ-9 score of 10 or greater

[‡] Self-reported

[‡] Self-reported and queried only among men 40 yrs and older