Original Article

Nocturnal gastroesophageal reflux increases the risk of daytime sleepiness in women

Shadi Amid Hägg [a, *], Össur I. Emilsson [a, b], Karl Franklin [c], Christer Janson [a], Eva Lindberg [a]

[a] Department of Medical Sciences, Respiratory, Allergy and Sleep Research, Uppsala University, Uppsala, Sweden
[b] Faculty of Medicine, University of Iceland, Reykjavik, Iceland
[c] Department of Surgical and Perioperative Sciences, Surgery, Umea University, Sweden

ABSTRACT

Objective: Daytime sleepiness is common in women and has negative health effects. Nocturnal gastroesophageal reflux (nGER) and snoring are risk factors for daytime sleepiness, but the effect of their interaction remains unknown. The aim of this study was to examine how nGER and snoring combined affected daytime sleepiness and involuntary falling asleep in women.
Methods: A questionnaire was sent to randomly selected women in 2000 and 2010. Participants who answered questions regarding both nGER and snoring in both questionnaires were included (N = 4882). Daytime sleepiness was defined as severe or very severe problems with daytime sleepiness. Involuntary falling asleep was defined as sometimes, often or very often falling asleep involuntarily during the day. Respondents snoring loudly and disturbingly sometimes, often or very often were defined as snorers. Having nocturnal heartburn or acid reflux sometimes, often or very often was defined as having nGER.
Results: Daytime sleepiness was reported by 14% of the participants, involuntary falling asleep by 11%. After adjustment for age, smoking, physical activity, caffeine intake and alcohol dependency, increased odd ratios (ORs) for both daytime sleepiness (adjusted OR 4.2, 95% confidence interval (CI): 1.9—9.2) and involuntary falling asleep (adjusted OR 3.1, 95% CI: 1.5—6.4) were seen in women with the combination of nGER and snoring at both baseline and follow-up. The association with daytime sleepiness was also strong for those with only persistent nGER but not for those with only persistent snoring.
Conclusion: Women with nGER were at increased risk of developing daytime sleepiness and snoring augmented this association. In addition, women with both nGER and snoring were also at increased risk of developing involuntary falling asleep.

© 2018 Elsevier B.V. All rights reserved.

1. Introduction

Daytime sleepiness is a challenge in modern society, afflicting as many as 5—10% of adults [1—7]. It is more common in women than in men [8—11] and has a negative impact on various aspects of life, including an association with diabetes [12], hypertension [13], accidents [14—18], coronary heart disease, stroke [19] and cardiovascular mortality [20]. Daytime sleepiness is also associated with obesity, independent of sleep apnea [12,21,22]. Furthermore, there is an association with an increased risk of subsequent depression [23], cognitive decline and dementia [24,25] and poor performance in the workplace [26].

Of adults, 7—23% [27,28] are snorers and, although snoring is considered to be one of the cardinal symptoms of obstructive sleep apnea, the majority of snorers do not fulfill the diagnostic criteria for obstructive sleep apnea [29]. Moreover, snoring is a predictor of daytime sleepiness, independent of obstructive sleep apnea [30—32]. Gastroesophageal reflux, and nocturnal symptoms of reflux in particular, are associated with both poor quality of sleep [33—38] and daytime sleepiness [39,40]. Gastroesophageal reflux is reported by 10—20% [41] of the population and a significant proportion of them have nocturnal symptoms of gastroesophageal reflux [42,43].

Apart from daytime sleepiness, snoring and nocturnal gastroesophageal reflux (nGER) share common lifestyle factors as risk factors, which may explain some parts of the described interactions. For example, both are associated with obesity [44—46].

However, both snoring [30–32] and nGER are associated with daytime sleepiness after adjusting for obesity [47], indicating that obesity is not the only explanatory factor. Other lifestyle factors may also affect daytime sleepiness, gastroesophageal reflux and snoring. Alcohol exacerbates gastroesophageal reflux [48], snoring and daytime sleepiness [49], while moderate exercise protects from reflux [50] and lessens daytime sleepiness [51]. There is also a stronger association between symptoms of obstructive sleep apnea and nGER among women than men [47].

The combination of snoring and nGER is of special interest in the context of daytime sleepiness. Snoring is indicative of an increased upper-airway resistance and, to maintain ventilation, there is a compensatory increase in respiratory effort. The increased effort may lead to arousals and sleep fragmentation and daytime sleepiness. The repetitive increase in nocturnal respiratory effort [52] may provoke or exacerbate nGER. In turn, nGER is associated with airway irritation and micro-aspirations [53], which could cause impaired sleep quality. In theory, these micro-aspirations might be more pronounced among snorers due to subclinical abnormalities in swallowing [54] caused by vibration trauma to the pharyngeal tissues [55]. It is therefore possible that having nGER and snoring combined, leads to more severe daytime sleepiness.

Understanding the impact and interactions of these two conditions associated with daytime sleepiness may help guide physicians in the investigation and treatment of patients with daytime sleepiness, thereby decreasing its negative impact on everyday life and health. The aim of this study was to examine how the combination of nGER and snoring affects daytime sleepiness and involuntary falling asleep in women.

2. Methods

2.1. Population

The population-based, prospective Sleep and Health in Women (SHE study) was initiated in 2000, when a questionnaire was sent to randomly selected women over the age of 20 years in the Municipality of Uppsala, Sweden. The baseline questionnaire was completed by 7051 participants, yielding a response rate of 71.6% [1,28,56]. Ten years later, a follow-up questionnaire was sent to the 6455 women who were alive and still living in Sweden. The follow-up questionnaire was answered by 5193 women (response rate 80.5%). The study cohort consists of the participants who answered the questions regarding nGER and snoring at both baseline and follow-up. The informed consent of all participants was obtained, and the study was approved by the Ethics Committee at the Medical Faculty at Uppsala University (Dnr 2009/379).

2.2. Questionnaire

Both questionnaires included identical questions about snoring, nGER and all the other variables included in this study.

2.2.1. Snoring and nGER
Snoring was assessed by the question "How often do you snore loudly and disturbingly?". The response options were: never (1), rarely (2), sometimes (3), often (4) and very often (5). Participants scoring 3–5 were considered habitual snorers [56].

nGER was assessed by the question "How often do you have heartburn or acid reflux after going to bed?". The same five-point scale as for snoring was used (never–very often). Participants with a score of 3–5 on the nGER question were considered to have nGER.

Based on the responses to the questions on nGER and snoring, participants were further categorized into 'no nGER or snoring' (controls), 'nGER only,' 'snoring only' or 'nGER and snoring'. Subjects reporting nGER and/or snoring at both baseline and follow-up were categorized as 'persistent nGER,' 'persistent snoring' or 'persistent nGER and snoring,' respectively.

2.2.2. Sleepiness
The outcome variable of sleepiness was assessed by two different variables measuring problems with sleepiness during the daytime (daytime sleepiness) and an inability to stay awake (involuntary falling asleep), respectively. Regarding daytime sleepiness, the participants were asked "How severe are your problems with daytime sleepiness?" The severity of their problems was assessed using a five-point scale ranging from none (1), small (2), moderate (3) and severe (4) to very severe (5). Scores of 4 or 5 to the questions were defined as the participant having daytime sleepiness [57]. In the same manner, involuntary falling asleep was assessed by the question "How often do you involuntarily fall asleep during the day, for example, during a pause at work?". The corresponding responses were never (1), rarely (2), sometimes (3), often (4) and very often (5). Scores of 3–5 were defined as suffering from involuntary falling asleep [58].

Subjects that reported daytime sleepiness or involuntary falling asleep at follow-up but not at baseline were categorized as having 'new daytime sleepiness' and 'new involuntary falling asleep,' respectively.

2.2.3. Covariates
Self-reported weight and height were used to calculate body mass index (BMI) by dividing the weight in kg by the height in meters squared.

Depending on their physical activity during leisure time, participants were categorized into three groups; low, medium and high levels. A low level of physical activity was assigned to participants spending most of their leisure time in sedentary activities such as reading or watching television. The medium group was assigned if participants reported physical activity such as cycling or walking for at least 4 h a week. The group with a high level of physical activity comprised participants participating in activities such as swimming or running for at least 3 h a week or more vigorous activities on a weekly basis [56,59].

The question "How many cups of coffee or tea do you consume every day?" was used to estimate the participants' caffeine intake and they were subsequently categorized into the groups; 0 cups/day, 1–2 cups/day and ≥3 cups/day.

Participants were also categorized as 'never smokers,' 'former smokers' and 'smokers,' based on their answers regarding tobacco use at baseline. Moreover, they were categorized as alcohol dependent or non-alcohol dependent using the Cutting down, Annoyance by criticism, Guilty feeling, and Eye openers (CAGE) questionnaire. The CAGE questions from baseline were used: "Have you tried to cut down on your drinking?", "Have people annoyed you by criticizing your drinking?", "Have you ever felt guilty about your drinking?", "Have you ever had a drink first thing in the morning after drinking, as an eye-opener?". Two or more affirmative answers were defined as alcohol dependency [60,61].

Data on age, smoking, physical activity, caffeine intake, alcohol dependency and medication were retrieved from the baseline questionnaire. BMI was based on data from the baseline questionnaire, but the difference in BMI between 2000 and 2010 (ΔBMI) was also used in the calculations.

2.3. Statistical analysis

Statistical analyses were performed using Stata 12.1 (StataCorp LP, College Station, TX, USA). The results are presented as adjusted

odds ratios (ORs) with 95% confidence intervals (95% CI). *p*-Values of <0.05 were considered statistically significant.

The chi-squared test was used to analyze differences in categorical variables between the study groups at baseline, while the analysis of variance (ANOVA) test was used for comparisons of continuous values. Multiple logistic regression analyses were performed for both baseline and follow-up data and adjusted for the following baseline variables: age, smoking status, BMI, intake of beverages containing caffeine during the day, alcohol dependency and physical activity during leisure time, and also for ΔBMI.

3. Results

3.1. Study population and baseline characteristics

The total study population comprised 4882 women. At baseline, 1003 (20.5%) of the participants reported snoring only, 376 (7.7%) reported nGER only and 229 (4.7%) reported both snoring and nGER. Daytime sleepiness was reported by 677 (14%) of the participants and 534 (11%) reported involuntary falling asleep. There was some overlap between daytime sleepiness and involuntary falling asleep; 28.3% of those reporting daytime sleepiness also reported involuntary falling asleep and 40.0% of those reporting involuntary falling asleep also reported daytime sleepiness.

The women with both nGER and snoring at baseline were older, had a higher BMI, were more often smokers and had a lower level of physical activity than the other groups. They also reported most daytime sleepiness and involuntary falling asleep. The group with nGER only had the highest prevalence of alcohol dependency. At baseline, daytime sleepiness and involuntary falling asleep were more associated with nGER than snoring (Table 1).

3.2. Multiple logistic regression analysis at baseline

At baseline, after adjustment for age, BMI, smoking status, alcohol dependency, caffeine intake and physical activity, participants reporting nGER only had increased ORs for daytime sleepiness and involuntary falling asleep compared to subjects with no nGER or snoring. Those reporting snoring only had increased ORs for daytime sleepiness but not involuntary falling asleep compared to those with no nGER or snoring. The combination of nGER and snoring had the highest impact on the OR for daytime sleepiness (2.9; 95% CI 2.0—4.2) and involuntary falling asleep (2.1; 95% CI 1.4—3.1) (Table 2).

3.3. Follow-up characteristics and symptoms over time

Of those with no nGER or snoring at baseline, 76% did not report any of these problems at follow-up either. Altogether, 47% of participants with only snoring had persistent problems. Of those with only nGER, 31% had persistent problems and 32% of those with the combination of nGER and snoring reported still having both problems at follow-up.

Of the whole population, 2.2% reported nGER only at both baseline and follow-up and the corresponding prevalence for snoring only was 1.6%, while 1.8% reported the combination of nGER and snoring and 51.2% had no symptoms of nGER or snoring, either at baseline or at follow-up.

Among the 3796 participants without daytime sleepiness and involuntary falling asleep at baseline, 2960 women answered questions regarding daytime sleepiness and falling asleep at

Table 2
Results from multiple logistic regression at baseline for associations with daytime sleepiness and involuntary falling asleep.

	Daytime sleepiness			Involuntary falling asleep		
	OR	95% CI	*p*	OR	95% CI	*p*
No nGER or snoring	1.0			1.0		
nGER only	1.9	1.4—2.6	<0.001	1.4	1.0—1.9	0.012
Snoring only	1.3	1.1—1.7	0.014	1.2	1.0—1.6	0.084
nGER and snoring	2.9	2.0—4.2	<0.001	2.1	1.4—3.1	<0.001
Age (baseline)	0.7	0.7—0.8	<0.001	1.0	1.0—1.1	0.883
BMI (baseline)	1.0	1.0—1.0	0.356	1.0	1.0—1.0	0.145
Smoking status	1.1	1.0—1.2	0.011	0.9	0.8—1.0	0.005
Never smoker	1.0			1.0		
Former smoker	1.1	0.8—1.3	0.591	0.8	0.6—0.8	0.046
Current smoker	1.4	1.1—1.8	0.005	0.9	0.7—1.2	0.474
Alcohol dependency	1.5	1.1—2.1	0.005	1.4	1.0—1.9	0.09
Caffeine						
0	1.0			1.0		
1—2 cups	0.8	0.5—1.1	0.198	0.9	0.6—1.3	0.453
3 or more cups	0.8	0.5—1.1	0.172	0.7	0.5—1.1	0.131
Physical activity						
High	1.0			1.0		
Medium	1.5	1.2—1.8	0.002	0.9	0.7—1.2	0.423
Low	2.0	1.5—2.6	<0.001	0.9	0.7—1.3	0.607

The results are presented as odds ratio (OR) and 95% confidence interval (CI) after adjusting for age, body mass index (BMI), smoking, alcohol dependency, caffeine intake and level of physical activity. nGER, nocturnal gastroesophageal reflux. For age, OR is calculated for an increase of 10 years.

Table 1
Baseline characteristics of the cohort.

	All subjects N = 4882	No nGER, no snoring N = 3253	nGER only N = 376	Snoring only N = 1003	nGER and snoring N = 229	*p*
Age	42.4 ± 14.9	39.7 ± 14.5	42.6 ± 15.9	49.1 ± 13.3	50.4 ± 12.9	<0.001
BMI	23.9 ± 3.9	23.1 ± 3.5	24.6 ± 4.1	25.5 ± 4.3	27.1 ± 4.7	<0.001
Smoking status						
Never smoker	2995 (61.6%)	2157 (66.2%)	210 (55.9%)	519 (52.0%)	109 (48.0%)	
Former smoker	1098 (22.6%)	687 (21.1.2%)	84 (22.3%)	264 (26.5%)	63 (27.8%)	<0.001
Smoker	767 (15.8%)	415 (12.7%)	82 (21.9%)	215 (21.2%)	55 (24.2%)	
Alcohol dependency	300 (6.0%)	190 (6.0%)	43 (11.9%)	49 (5.0%)	18 (8.3%)	<0.001
Caffeine intake						
0 cups	238 (4.9%)	181 (5.6%)	25 (6.7%)	25 (2.5%)	7 (3.1%)	
1—2 cups	1342 (27.7%)	972 (30.0%)	107 (28.5%)	212 (21.2%)	51 (22.6%)	<0.001
≥3 cups	3258 (67.3%)	2084 (64%)	244 (64.9%)	762 (76.3%)	168 (74.3%)	
Physical activity						
Low	757 (15.4%)	419 (12.9%)	84 (22.7%)	176 (17.6%)	68 (30.4%)	
Medium	3047 (62.8%)	2019 (62.0%)	232 (62.7%)	660 (66.1%)	136 (60.1%)	<0.001
High	1056 (21.8%)	819 (25.2%)	54 (14.6%)	163 (16.3%)	20 (8.9%)	
Daytime sleepiness	680 (14.1%)	403 (12.5%)	83 (23.3%)	134 (13.5%)	60 (26.4%)	<0.001
Involuntary falling asleep	538 (11.0%)	319 (9.8%)	51 (13.7%)	123 (12.3%)	45 (19.7%)	<0.001

Data presented as the mean ± standard deviation (SD) or N (%). BMI, body mass index; nGER, nocturnal gastroesophageal reflux. p-Value calculated with the analysis of variance (ANOVA) test.

follow-up. Of those women, 210 (7.0%) reported new daytime sleepiness and 127 (4.0%) new involuntary falling asleep. A combination of both new daytime sleepiness and new involuntary falling asleep was reported by 48 (2.0%).

Regarding nGER, participants reporting persistent symptoms had the highest incidence of both daytime sleepiness and involuntary falling asleep [Fig. 1(A) and (B)]. New daytime sleepiness was most common in those with new snoring while new involuntary falling asleep was almost equally prevalent in both persistent snoring and former snoring [Fig. 1 (C) and (d)].

3.4. Multiple logistic regression analysis at follow-up

The group with persistent nGER and snoring had the highest risk of new daytime sleepiness (OR 3.4, 95% CI 1.4–5.3) and involuntary falling asleep (OR 5.6, 95% CI 2.9–10.7). Moreover, the group with persistent nGER was associated with an increased risk of both daytime sleepiness (OR 2.7, CI 1.4–5.3) and involuntary falling asleep (OR 2.6, 1.2–5.6), while persistent snoring was only associated with involuntary falling asleep (OR 2.1, 95% CI 1.4–3.2).

After adjustment for possible confounders, women with persistent nGER displayed increased odds for new daytime sleepiness, with an adjusted OR of 3.0 (95% CI 1.7–5.9). Snoring attenuated this association and women with the combination of persistent nGER and persistent snoring seem to have an even higher risk of new daytime sleepiness (adjusted OR 4.2, 95% CI 1.9–9.2). In addition, the participants with combined persistent nGER and snoring were at increased risk of involuntary falling asleep (adjusted OR 3.1, 95% CI 1.5–6.4) (Table 3).

4. Discussion

This study showed that women with persistent nGER were at increased risk of developing daytime sleepiness and that snoring augmented this association. Women with both nGER and snoring were also at a risk of involuntary falling asleep during the day. The effect was strong and snoring women with nGER had a four-times greater risk of developing daytime sleepiness and an almost three-times greater risk of developing involuntary falling asleep during the day.

To the best of our knowledge, no previous study comparing the combination of snoring and nGER and their association with daytime sleepiness has been conducted.

In our study population, the prevalence of snoring was 25.6%, which is slightly higher than a Hungarian survey, where 21.0% of the women reported habitual snoring [27]. Of the women in our population, 14% reported nGER, which is higher than the corresponding prevalence (7.7%) in the study by Emilsson et al., [47]. Differences in prevalence might be due to differences in mean age and/or BMI between study populations. However, as neither of the cited studies presented age or BMI for the whole population, it is not possible to compare this further.

Our finding of an additive effect of nGER and snoring on the development of daytime sleepiness is of clinical interest. A study has found that nGER might be exacerbated by the repetitive increased nocturnal respiratory effort [52] that occurs in patients with obstructive sleep apnea syndrome. Correspondingly, non-apneic respiratory events are also associated with increased airway resistance and respiratory effort [62]. We therefore hypothesize that, among snorers, nGER may indicate a significant
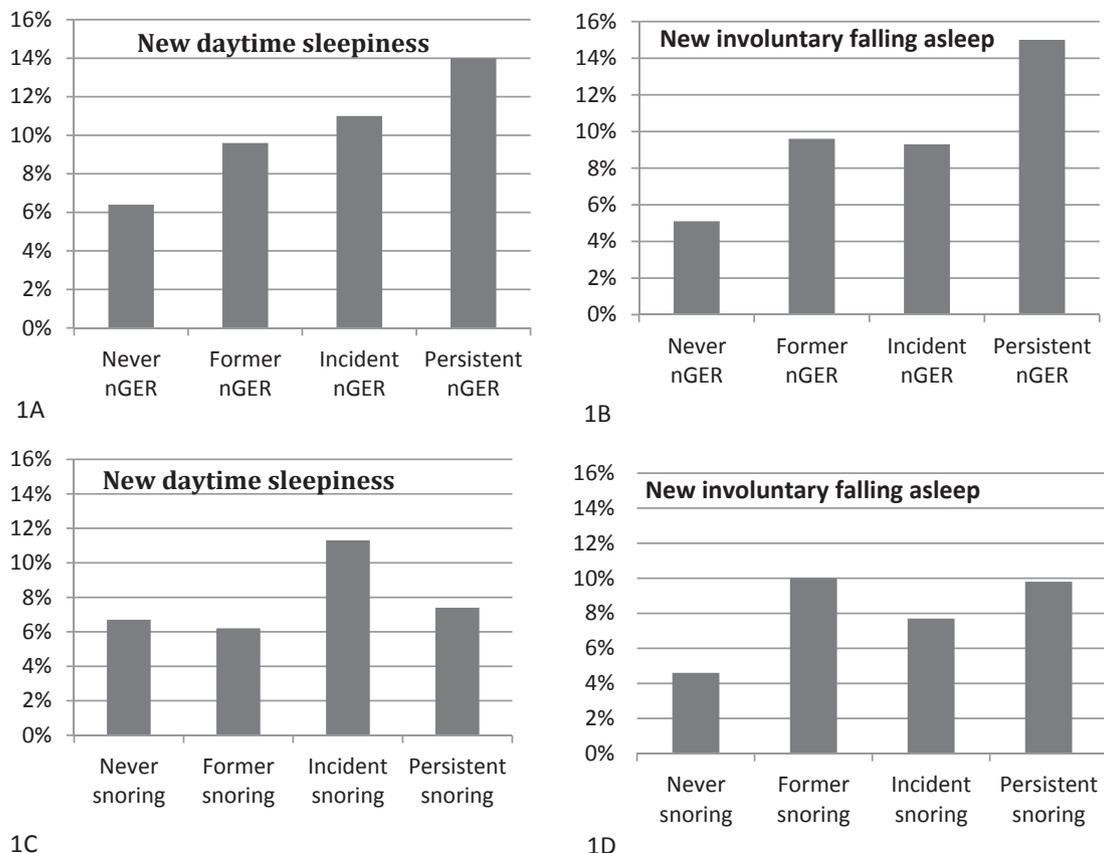

Fig. 1. Bar charts depicting the prevalence of new daytime sleepiness and new involuntary falling asleep in relation to nocturnal gastroesophageal reflux (nGER) and snoring.

Table 3
Risk factors for new daytime sleepiness and involuntary falling asleep.

	New daytime sleepiness			New involuntary falling asleep		
	OR	95% CI	p	OR	95% CI	p
No nGER or snoring	1.0			1.0		
nGER and/or snoring only at baseline or follow-up	1.8	1.3–2.4	<0.001	1.7	1.2–2.4	0.004
Persistent nGER only	3.0	1.5–5.9	0.002	1.7	0.7–4.0	0.213
Persistent snoring only	1.2	0.7–1.9	0.513	1.4	0.9–2.2	0.174
Persistent nGER and snoring	4.2	1.9–9.2	<0.001	3.1	1.5–6.4	0.003
Age (baseline)	0.7	0.7–0.8	<0.001	1.5	1.3–1.7	<0.001
BMI (baseline)	1.0	1.0–1.0	0.146	1.0	1.0–1.1	0.111
Δ-BMI	1.1	1.0–1.1	0.018	1.0	1.0–1.1	0.242
Smoking status (baseline)						
Never smoker	1.0					
Former smoker	1.4	1.0–1.9	0.039	0.9	0.6–1.3	0.608
Current smoker	1.3	0.9–1.9	0.157	1.2	0.8–1.8	0.434
Alcohol dependency (baseline)	2.1	1.4–3.2	<0.001	1.1	0.6–2.1	0.664
Caffeine (baseline)						
0	1.0			1.0		
1–2 cups	1.2	0.7–2.3	0.504	0.6	0.3–1.2	0.137
3 or more cups	1.0	0.6–1.9	0.916	0.5	0.3–1.0	0.068
Physical activity (baseline)						
High	1.0			1.0		
Medium	1.2	0.8–1.6	0.329	1.4	0.9–2.2	0.141
Low	1.3	0.8–2.0	0.227	1.4	0.8–2.5	0.186

The results are presented as odds ratio (OR) and 95% confidence interval (CI) adjusted for age, body mass index (BMI), smoking, alcohol dependency, caffeine intake and level of physical activity at baseline and Δ-BMI during the follow-up period. For age, OR is calculated for an increase of 10 years. nGER, nocturnal gastroesophageal reflux.

increase in respiratory effort, such as in patients with obstructive sleep apnea.

In recent years, progress has been made in determining the underlying mechanisms of the link between nGER and poor sleep quality. One study found that the vast majority of acid reflux events during the night (90%) were associated with short arousals [63]. In contrast, in other studies, the majority of reflux events followed arousals or conscious awakening periods, suggesting that reflux was not the primary cause of the events but was secondary to arousals/awakenings from other causes, ie, snoring [64,65]. It is more probable that a combination of arousals and conscious awakenings lead to sleep fragmentation, resulting in poor sleep quality and daytime sleepiness [66]. Conversely, poor sleep enhances the oesophageal hypersensitivity exacerbating gastroesophageal reflux, which in turn leads to more sleep disruptions in a vicious cycle. A factor that might be of importance is that of nocturnal swallowing. In a recent study with the primary aim to analyze nocturnal swallowing in patients with spinal cord injury, it was noticed that both in patients and in the healthy controls, nocturnal swallowing was associated with arousals [67]. Patients with gastroesophageal reflux disease have a higher frequency of nocturnal swallowing compared with healthy subjects [68,69] which therefore may lead to worsening of sleep fragmentation.

Daytime sleepiness is a common complaint in the general population and investigating its underlying causes poses a challenge for clinicians. If questions relating to snoring and nGER are incorporated in the basic interview, the clinician may potentially find treatable causes of daytime sleepiness in complaints of nGER and/or snoring. The efficiency of proton pump inhibitors in the treatment of nGER is well documented [70,71] and it also reduces the gastroesophageal-reflux-related sleep complaints [66,71–73] and daytime sleepiness [74]. Refractory gastroesophageal reflux is associated with nGER [75], indicating that patients with the most difficult gastroesophageal reflux can be found by screening for nGER.

This large-scale population-based study had a high response rate both at baseline and at follow-up. The inclusion of lifestyle factors – smoking, physical activity, alcohol dependency and caffeine intake – is another strength of the study. The most important limitation is that all data were self-reported with no objective measurement, which can lead to bias and misclassification. When it comes to symptoms of nGER in a study of this size, the use of a measure such as 24-h pH probe or upper endoscopy would not be feasible. There is no gold standard for measuring gastroesophageal reflux and many investigators note the validity of establishing gastroesophageal reflux based on symptoms [76,77]. Furthermore, global guidelines for gastroesophageal reflux recommend establishing a diagnosis on the basis of patients' self-reported symptoms [78]. Regarding EDS, instead of a more common measure, such as the Epworth Sleepiness scale (ESS), EDS was assessed using a five-point scale. The scale has been compared to ESS and has been found to correlate relatively well to the ESS [79]. Self-reported snoring is not the ideal measurement of snoring frequency but previous validation against sleep monitoring has suggested it to be a reliable measure [80]. Furthermore, as polysomnography was not performed, we have no information on sleep time, a variable that could interfere with daytime sleepiness. As the study was conducted only in women, the results cannot be generalized to apply to men, and the goal of the study was not to examine gender differences.

In conclusion, we found that women with nGER were at an increased risk of developing daytime sleepiness and that snoring augmented this association. In addition, women with both nGER and snoring were at increased risk of developing involuntary falling asleep during the day.

Author contributions

All authors provided substantive contributions to the study, design, data collection and interpretation of results. S.A.H. performed the data analysis and wrote the first draft of the manuscript. All authors contributed substantially to revising the article critically for important intellectual content, and for final approval of the version to be published.

Acknowledgments

Conflict of interest

All of the authors declare that the submitted article is not related to any financial interest/relationship.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2018.08.036.

References

[1] Theorell-Haglow J, Lindberg E, Janson C. What are the important risk factors for daytime sleepiness and fatigue in women? Sleep 2006;29(6):751–7.

[2] Gislason T, Almqvist M, Eriksson G, et al. Prevalence of sleep apnea syndrome among Swedish men–an epidemiological study. J Clin Epidemiol 1988;41(6):571–6.

[3] Whitney CW, Enright PL, Newman AB, et al. Correlates of daytime sleepiness in 4578 elderly persons: the cardiovascular health study. Sleep 1998;21(1):27–36.

[4] Ohayon MM. Determining the level of sleepiness in the American population and its correlates. J Psychiatr Res 2012;46(4):422–7.

[5] Fernandez-Mendoza J, Vgontzas AN, Kritikou I, et al. Natural history of excessive daytime sleepiness: role of obesity, weight loss, depression, and sleep propensity. Sleep 2015;38(3):351–60.

[6] Swanson LM, Arnedt JT, Rosekind MR, et al. Sleep disorders and work performance: findings from the 2008 National Sleep Foundation Sleep in America poll. J Sleep Res 2011;20(3):487–94.

[7] Walsleben JA, Kapur VK, Newman AB, et al. Sleep and reported daytime sleepiness in normal subjects: the Sleep Heart Health Study. Sleep 2004;27(2):293–8.

[8] Hayley AC, Williams LJ, Kennedy GA, et al. Prevalence of excessive daytime sleepiness in a sample of the Australian adult population. Sleep Med 2014;15(3):348–54.

[9] Tsuno N, Jaussent I, Dauvilliers Y, et al. Determinants of excessive daytime sleepiness in a French community-dwelling elderly population. J Sleep Res 2007;16(4):364–71.

[10] Janson C, Gislason T, De Backer W, et al. Daytime sleepiness, snoring and gastro-oesophageal reflux amongst young adults in three European countries. J Intern Med 1995;237(3):277–85.

[11] Hara C, Lopes Rocha F, Lima-Costa MF. Prevalence of excessive daytime sleepiness and associated factors in a Brazilian community: the Bambui study. Sleep Med 2004;5(1):31–6.

[12] Bixler EO, Vgontzas AN, Lin HM, et al. Excessive daytime sleepiness in a general population sample: the role of sleep apnea, age, obesity, diabetes, and depression. J Clin Endocrinol Metab 2005;90(8):4510–5.

[13] Goldstein IB, Ancoli-Israel S, Shapiro D. Relationship between daytime sleepiness and blood pressure in healthy older adults. Am J Hypertens 2004;17(9):787–92.

[14] Hayley AC, Williams LJ, Kennedy GA, et al. Excessive daytime sleepiness and falls among older men and women: cross-sectional examination of a population-based sample. BMC Geriatr 2015;15:74.

[15] Ward KL, Hillman DR, James A, et al. Excessive daytime sleepiness increases the risk of motor vehicle crash in obstructive sleep apnea. J Clin Sleep Med 2013;9(10):1013–21.

[16] Vennelle M, Engleman HM, Douglas NJ. Sleepiness and sleep-related accidents in commercial bus drivers. Sleep Breath 2010;14(1):39–42.

[17] Drake C, Roehrs T, Breslau N, et al. The 10-year risk of verified motor vehicle crashes in relation to physiologic sleepiness. Sleep 2010;33(6):745–52.

[18] Teo JS, Briffa NK, Devine A, et al. Do sleep problems or urinary incontinence predict falls in elderly women? Aust J Physiother 2006;52(1):19–24.

[19] Jaussent I, Empana JP, Ancelin ML, et al. Insomnia, daytime sleepiness and cardio-cerebrovascular diseases in the elderly: a 6-year prospective study. PloS One 2013;8(2):e56048.

[20] Empana JP, Dauvilliers Y, Dartigues JF, et al. Excessive daytime sleepiness is an independent risk indicator for cardiovascular mortality in community-dwelling elderly: the three city study. Stroke 2009;40(4):1219–24.

[21] Vgontzas AN, Bixler EO, Tan TL, et al. Obesity without sleep apnea is associated with daytime sleepiness. Arch Intern Med 1998;158(12):1333–7.

[22] Resta O, Foschino Barbaro MP, Bonfitto P, et al. Low sleep quality and daytime sleepiness in obese patients without obstructive sleep apnoea syndrome. J Intern Med 2003;253(5):536–43.

[23] Jaussent I, Bouyer J, Ancelin ML, et al. Insomnia and daytime sleepiness are risk factors for depressive symptoms in the elderly. Sleep 2011;34(8):1103–10.

[24] Jaussent I, Bouyer J, Ancelin ML, et al. Excessive sleepiness is predictive of cognitive decline in the elderly. Sleep 2012;35(9):1201–7.

[25] Ohayon MM, Vecchierini MF. Daytime sleepiness and cognitive impairment in the elderly population. Arch Intern Med 2002;162(2):201–8.

[26] Haavisto ML, Porkka-Heiskanen T, Hublin C, et al. Sleep restriction for the duration of a work week impairs multitasking performance. J Sleep Res 2010;19(3):444–54.

[27] Torzsa P, Keszei A, Kalabay L, et al. Socio-demographic characteristics, health behaviour, co-morbidity and accidents in snorers: a population survey. Sleep Breath 2011;15(4):809–18.

[28] Svensson M, Lindberg E, Naessen T, et al. Risk factors associated with snoring in women with special emphasis on body mass index: a population-based study. Chest 2006;129(4):933–41.

[29] Lindberg E, Gislason T. Epidemiology of sleep-related obstructive breathing. Sleep Med Rev 2000;4(5):411–33.

[30] Svensson M, Franklin KA, Theorell-Haglow J, et al. Daytime sleepiness relates to snoring independent of the apnea-hypopnea index in women from the general population. Chest 2008;134(5):919–24.

[31] Hunsaker DH, Riffenburgh RH. Snoring significance in patients undergoing home sleep studies. Otolaryngol Head Neck Surg 2006;134(5):756–60.

[32] Janson C, Hillerdal G, Larsson L, et al. Excessive daytime sleepiness and fatigue in nonapnoeic snorers: improvement after UPPP. Eur Respir J 1994;7(5):845–9.

[33] Jansson C, Nordenstedt H, Wallander MA, et al. A population-based study showing an association between gastroesophageal reflux disease and sleep problems. Clin Gastroenterol Hepatol 2009;7(9):960–5.

[34] Kusano M, Kouzu T, Kawano T, et al. Nationwide epidemiological study on gastroesophageal reflux disease and sleep disorders in the Japanese population. J Gastroenterol 2008;43(11):833–41.

[35] Fujiwara Y, Kohata Y, Kaji M, et al. Sleep dysfunction in Japanese patients with gastroesophageal reflux disease: prevalence, risk factors, and efficacy of rabeprazole. Digestion 2010;81(3):135–41.

[36] Chen CL, Robert JJ, Orr WC. Sleep symptoms and gastroesophageal reflux. J Clin Gastroenterol 2008;42(1):13–7.

[37] Mody R, Bolge SC, Kannan H, et al. Effects of gastroesophageal reflux disease on sleep and outcomes. Clin Gastroenterol Hepatol 2009;7(9):953–9.

[38] Orr WC, Goodrich S, Estep ME, et al. The relationship between complaints of night-time heartburn and sleep-related gastroesophageal reflux. Dis Esophagus 2014;27(4):303–10.

[39] Emilsson OI, Bengtsson A, Franklin KA, et al. Nocturnal gastro-oesophageal reflux, asthma and symptoms of OSA: a longitudinal, general population study. Eur Respir J 2013;41(6):1347–54.

[40] Shaker R. Nighttime GERD: clinical implications and therapeutic challenges. Best Pract Res Clin Gastroenterol 2004;(Suppl. 18):31–8.

[41] Dent J, El-Serag HB, Wallander MA, et al. Epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut 2005;54(5):710–7.

[42] Bruley des Varannes S, Errieau G, Tessier C. Two thirds of patients with gastroesophageal reflux have nocturnal symptoms: survey by 562 general practitioners of 36,663 patients. Presse Med 2007;36(4 Pt 1):591–7.

[43] Farup C, Kleinman L, Sloan S, et al. The impact of nocturnal symptoms associated with gastroesophageal reflux disease on health-related quality of life. Arch Intern Med 2001;161(1):45–52.

[44] Teculescu D, Hannhart B, Aubry C, et al. Who are the "occasional" snorers? Chest 2002;122(2):562–8.

[45] Lindberg E, Taube A, Janson C, et al. A 10-year follow-up of snoring in men. Chest 1998;114(4):1048–55.

[46] Dixon JB, Dixon ME, Anderson ML, et al. Daytime sleepiness in the obese: not as simple as obstructive sleep apnea. Obesity (Silver Spring) 2007;15(10):2504–11.

[47] Emilsson ÖI, Janson C, Benediktsdóttir B, et al. Nocturnal gastroesophageal reflux, lung function and symptoms of obstructive sleep apnea: results from an epidemiological survey. Respir Med 2011;106(3):459–66.

[48] Rubenstein JH, Chen JW. Epidemiology of gastroesophageal reflux disease. Gastroenterol Clin North Am 2014;43(1):1–14.

[49] Wilsmore BR, Grunstein RR, Fransen M, et al. Sleep habits, insomnia, and daytime sleepiness in a large and healthy community-based sample of New Zealanders. J Clin Sleep Med 2013;9(6):559–66.

[50] Nilsson M, Johnsen R, Ye W, et al. Lifestyle related risk factors in the aetiology of gastro-oesophageal reflux. Gut 2004;53(12):1730–5.

[51] Kwon AM, Shin C. Structural equation modelling for the effect of physical exercise on excessive daytime sleepiness. Publ Health 2016;141:95–9.

[52] Shepherd K, Hillman D, Holloway R, et al. Mechanisms of nocturnal gastroesophageal reflux events in obstructive sleep apnea. Sleep Breath 2011;15(3):561–70.

[53] Emilsson OI, Benediktsdottir B, Olafsson I, et al. Respiratory symptoms, sleep-disordered breathing and biomarkers in nocturnal gastroesophageal reflux. Respir Res 2016;17(1):115.

[54] Jaghagen EL, Berggren D, Isberg A. Swallowing dysfunction related to snoring: a videoradiographic study. Acta Otolaryngol 2000;120(3):438–43.

[55] Kimoff RJ, Sforza E, Champagne V, et al. Upper airway sensation in snoring and obstructive sleep apnea. Am J Resp Crit Care Med 2001;164(2):250–5.

[56] Lindberg E, Berne C, Franklin KA, et al. Snoring and daytime sleepiness as risk factors for hypertension and diabetes in women—a population-based study. Respir Med 2007;101(6):1283–90.

[57] Theorell-Haglow J, Akerstedt T, Schwarz J, et al. Predictors for development of excessive daytime sleepiness in women: a population-based 10-year follow-up. Sleep 2015;38(12):1995–2003.

[58] Svensson M, Franklin KA, Theorell-Haglow J, et al. Daytime sleepiness relates to snoring independent of the apnea—hypopnea index in women from the general population. Chest 2008;134(5):919–24.

[59] Lissner L, Bengtsson C, Bjorkelund C, et al. Physical activity levels and changes in relation to longevity. A prospective study of Swedish women. Am J Epidemiol 1996;143(1):54—62.
[60] Ewing JA. Detecting alcoholism. The CAGE questionnaire. J Am Med Assoc 1984;252(14):1905—7.
[61] Mayfield D, McLeod G, Hall P. The CAGE questionnaire: validation of a new alcoholism screening instrument. Am J Psychiatry 1974;131(10):1121—3.
[62] Sankari A, Pranathiageswaran S, Maresh S, et al. Characteristics and consequences of non-apneic respiratory events during sleep. Sleep 2017;40(1).
[63] Dickman R, Green C, Fass SS, et al. Relationships between sleep quality and pH monitoring findings in persons with gastroesophageal reflux disease. J Clin Sleep Med 2007;3(5):505—13.
[64] Freidin N, Fisher MJ, Taylor W, et al. Sleep and nocturnal acid reflux in normal subjects and patients with reflux oesophagitis. Gut 1991;32(11):1275—9.
[65] Poh CH, Allen L, Gasiorowska A, et al. Conscious awakenings are commonly associated with acid reflux events in patients with gastroesophageal reflux disease. Clin Gastroenterol Hepatol 2010;8(10):851—7.
[66] Dimarino Jr AJ, Banwait KS, Eschinger E, et al. The effect of gastro-oesophageal reflux and omeprazole on key sleep parameters. Aliment Pharmacol Ther 2005;22(4):325—9.
[67] Rizwan A, Sankari A, Bascom AT, et al. Nocturnal swallowing and arousal threshold in individuals with chronic spinal cord injury. J Appl Physiol 2018;125(2):445—52.
[68] Pohl D, Arevalo F, Singh E, et al. Swallowing activity assessed by ambulatory impedance-pH monitoring predicts awake and asleep periods at night. Dig Dis Sci 2013;58(4):1049—53.
[69] Sato K, Umeno H, Chitose S, et al. Deglutition and respiratory patterns during sleep in younger adults. Acta Otolaryngol 2011;131(2):190—6.
[70] Sachs G, Shin JM, Howden CW. Review article: the clinical pharmacology of proton pump inhibitors. Aliment Pharmacol Ther 2006;23(Suppl. 2):2—8.
[71] Fass R, Johnson DA, Orr WC, et al. The effect of dexlansoprazole MR on nocturnal heartburn and GERD-related sleep disturbances in patients with symptomatic GERD. Am J Gastroenterol 2011;106(3):421—31.
[72] Johnson DA, Orr WC, Crawley JA, et al. Effect of esomeprazole on nighttime heartburn and sleep quality in patients with GERD: a randomized, placebo-controlled trial. Am J Gastroenterol 2005;100(9):1914—22.
[73] Johnson D, Crawley JA, Hwang C, et al. Clinical trial: esomeprazole for moderate-to-severe nighttime heartburn and gastro-oesophageal reflux disease-related sleep disturbances. Aliment Pharmacol Ther 2010;32(2):182—90.
[74] Hiramoto K, Fujiwara Y, Ochi M, et al. Effects of esomeprazole on sleep in patients with gastroesophageal reflux disease as assessed on actigraphy. Intern Med 2015;54(6):559—65.
[75] Fujiwara Y, Habu Y, Ashida K, et al. Sleep disturbances and refractory gastroesophageal reflux disease symptoms in patients receiving once-daily proton pump inhibitors and efficacy of twice-daily rabeprazole treatment. Digestion 2013;88(3):145—52.
[76] Coyne KS, Wiklund I, Schmier J, et al. Development and validation of a disease-specific treatment satisfaction questionnaire for gastro-oesophageal reflux disease. Aliment Pharmacol Ther 2003;18(9):907—15.
[77] Pare P, Meyer F, Armstrong D, et al. Validation of the GSFQ, a self-administered symptom frequency questionnaire for patients with gastro-esophageal reflux disease. Can J Gastroenterol 2003;17(5):307—12.
[78] Hunt R, Armstrong D, Katelaris P, et al. World gastroenterology organisation global guidelines: GERD global perspective on gastroesophageal reflux disease. J Clin Gastroenterol 2017;51(6):467—78.
[79] Theorell-Haglow J. Assessing daytime sleepiness in women: a comparison of different methods. Lungforum 2005;15(Suppl. 22):13.
[80] Telakivi T, Partinen M, Koskenvuo M, et al. Periodic breathing and hypoxia in snorers and controls: validation of snoring history and association with blood pressure and obesity. Acta Neurol Scand 1987;76(1):69—75.