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Original Research

Gastroesophageal reflux and snoring are related to asthma and respiratory symptoms: Results from a Nordic longitudinal population survey

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ABSTRACT

Aim: To study if individuals with nocturnal gastroesophageal reflux (nGER) and habitual snoring are more likely to develop asthma and respiratory symptoms (i.e. wheeze, cough, chest tightness, breathlessness) than those without these conditions, and if these associations are additive.

Methods: We used data from the population-based prospective questionnaire study Respiratory Health in Northern Europe (RHINE) (11,024 participants), with data from 1999 and 2011. Participants with heartburn or belching after going to bed, at least 1 night/week, were considered to have nGER. Participants reporting loud snoring at least 3 nights/week were considered to have habitual snoring. Participants were grouped into four groups by their nGER and snoring status: "never"; "former"; "incident"; "persistent". Incident respiratory symptoms were analyzed among participants without respective symptom at baseline.

Results: Snoring and nGER were independently associated with incident asthma and respiratory symptoms. The risk of incident wheeze was increased in subjects with incident or persistent snoring (adjusted odds ratio (95 % CI): 1.44 (1.21–1.72)), nGER (2.18 (1.60–2.98)) and in those with both snoring and nGER (2.59 (1.83–3.65)). The risk of developing asthma was increased in subjects with incident or persistent snoring (1.44 (1.15–1.82)), nGER (1.99 (1.35–2.93)) and in those with both snoring and nGER (1.72 (1.06–2.77)). No significant interaction was found between snoring and nGER. A similar pattern was found for the incidence of all other respiratory symptoms studied, with the highest risk among those with both incident or persistent nGER and snoring.

Conclusion: The risk of developing asthma and respiratory symptoms is increased among subjects with nGER and habitual snoring. These associations are independent of each other and confounding factors. Snoring and nGER together are additive on respiratory symptoms.

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1. Introduction

Nocturnal gastroesophageal reflux (nGER) is a common condition in modern society, with heartburn as the most common symptom [1]. An association between nGER and respiratory symptoms has been shown in several previous studies [2–4], and several clinical trials have shown that antireflux therapy leads to improvement of asthma symptoms, but with only minimal or no significant effect on lung function [5,6].

Habitual snoring is more prevalent in men than women [3,7]. The prevalence of habitual snoring among middle aged Swedish men has been estimated to be approximately 15,5% [8]. Snoring is a hallmark symptom of diseases such as obstructive sleep apnea (OSA), and individuals suffering from anatomical abnormalities such as large tongue, enlarged tonsils and large fat deposits around the neck area are at higher risk for snoring [9,10]. Snoring and nGER share several common risk factors, most importantly obesity [11,12], and snoring has similar to nGER been associated with asthma and respiratory symptoms [13,14]. A previous cross-sectional study showed that patients with both nGER and snoring had a positive association with respiratory symptoms compared to patients without nGER and snoring [15]. Otherwise, relatively little has been published on the association between these three conditions, snoring, nGER and respiratory symptoms, and especially longitudinal studies are lacking. Specifically, no previous study has looked at the incidence of respiratory symptoms by nGER and snoring combined, to evaluate potential causal association.

Recent studies have highlighted that respiratory symptoms by themselves, even in the absence of known respiratory disease, are associated with higher morbidity and mortality [16,17]. It is therefore of importance to study specifically risk factors for the development of respiratory symptoms, irrespective of concomitant respiratory disease.

The aim of this study is to investigate whether nGER and snoring are independent risk factors for developing asthma and respiratory symptoms (wheezing, productive cough, nocturnal chest tightness, nocturnal breathlessness and nocturnal cough). A secondary aim was to study whether subjects that have both nGER and snoring are more likely to develop asthma and respiratory symptoms than those who have neither or only one of these conditions.

2. Method and material

In 1999, a questionnaire was sent to randomly selected subjects in Uppsala, Umeå and Gothenburg (Sweden), Reykjavik (Iceland), Aarhus (Denmark), Bergen (Norway) and Tartu (Estonia), within the study Respiratory Health in Northern Europe (RHINE II) (15,760 responders, age 25–54 years), as previously described [18,19]. Twelve years later, a follow-up questionnaire (RHINE III) was sent to all participating subjects in RHINE II, whereof 12,878 answered (82 % response rate). The questionnaires included identical questions about airways symptoms, heartburn after going to bed, sleep and daytime symptoms, smoking, medication use and other health related issues, such as BMI (body mass index).

2.1. Nocturnal gastroesophageal reflux and snoring

The same definition of nGER and snoring was used at baseline and follow-up. The subjects were asked to estimate the frequency of nGER and snoring symptoms on the following 5-point scale: 1, never or almost never; 2, less than once a week; 3, once or twice a week; 4, 3–5 nights/days a week; and 5 almost every day or night.

Subjects were considered to have nGER if they reported having occurrence of heartburn or belching after going to bed, at least 1 night per week in the last months.

The definition of snoring was based on a positive reply to the question, “do you snore loudly and disturbingly”. Subjects responding at least 3 nights a week in the last months were considered to have habitual snoring.

Based on answers to these questions at baseline and follow-up, respondents were grouped into four groups by their nGER and snoring status: “never”; “former”; “incident” and “persistent”.

2.2. Asthma and respiratory symptoms

The participants were defined as having asthma if they had reported an asthma attack in the previous 12 months and/or currently using asthma medication. Respiratory symptoms included yes/no-questions for various symptoms during the previous 12 months, namely: wheezing or whistling in the chest, wheezing without having a cold, breathless with wheezing, productive cough, nocturnal chest tightness, nocturnal shortness of breath and nocturnal cough.

Participants that reported asthma or respiratory symptoms at follow-up but not at baseline were defined as having incident of asthma or respiratory symptoms, respectively. Incidence was analyzed among participants without asthma or respective symptom at baseline.

2.3. Definition of smoking

Respondents were grouped as never smokers, ex-smokers and current smokers, on the basis of their answers regarding to tobacco use at baseline.

2.4. Body mass index

Each subject reported weight in kilograms and height in meter at both baseline and follow-up questionnaires. Body mass index (kg/m^2) was calculated from these answers.

2.5. Statistical analysis

All statistics were calculated using STATA 14.1 software. To analyse differences between the study groups both at baseline and follow-up, the χ^2 test was used for categorical variables. When studying incident asthma or respiratory symptoms, participants reporting asthma or the respective respiratory symptom at baseline were excluded from each separate analysis.

Multilevel mixed-effects logistic regression models were used for adjusted analysis, with center as a random factor. A directed acyclic graph (DAG) was used to decide which variables to adjust for in the multivariate logistic regression analysis, which identified the factors age, sex, BMI, change in BMI from baseline to follow-up, smoking status, and center. We then evaluated if BMI and age were linearly or non-linearly associated with incident asthma or respiratory symptoms using splines, to inform further analysis steps (exemplified in Figs. S2 and S3 for incident asthma). Collectively, the analysis found evidence of a linear relationship.

First, we performed the regression analysis including both nGER and snoring as independent factors in the same model while adjusting for confounding factors. Second, we performed a regression analysis with a new group classification of four groups (1: Those without nGER or snoring at follow-up; 2: Those with incident or persistent snoring only; 3: Those with incident or persistent nGER only; 4: Those with incident or persistent snoring and nGER) and used as independent factor to analyse the additive associations of snoring and nGER combined. Lastly we performed interaction analyses using the same setup of regression models with an interaction between 1) snoring and nGER, 2) snoring/nGER status and BMI, 3) snoring/nGER status and age. As a sensitivity analysis, we performed the same multilevel mixed-effects logistic regression models as described above, stratified by BMI subgroups (BMI groups <20, 20–25, 25–30, 30+).

A p-value of <0.05 was considered statistically significant.

3. Results

3.1. Study population and baseline characteristics

Data on nGER and snoring at both time points was available for 10,424 subjects. Persistent snoring was most common among participants with persistent nGER (Fig. 1).

The baseline characteristics of the participants by their reflux and snoring status are presented in Table 1. Subjects with persistent nGER had a higher BMI, were more often smokers and were more likely to have hypertension, but no significant differences were found regarding sex and age. Subjects with persistent snoring were more often male, had higher BMI, were more often smokers and were more likely to have hypertension (Table 1).

3.2. Follow-up analysis

Regarding nGER, incident asthma was most common among subjects with incident of nGER, whereas incident of all respiratory symptoms were most common among those with persistent nGER (Table S1).

Regarding snoring, incident asthma was similarly common in previous, incident and persistent snorers, and in all groups more common than among never snorers. The incident of all studied respiratory symptoms was most common among those with incident and persistent snoring status (Table S1).

When analyzing both nGER and snoring combined, incident of a) chest tightness, b) wheeze, c) productive cough and d) nocturnal cough were highest in those that had both incident or persistent nGER and snoring (Fig. 2). A similar pattern was found for other respiratory symptoms (data not shown).

3.3. Multiple logistic regression analysis of incident asthma and respiratory symptoms

After adjusting for confounding factors, (sex, age, BMI and smoking) incident asthma was significantly more common among subjects with incident nGER and incident snoring, than subjects without nGER or snoring at both visits, respectively.

When nGER and snoring status were analyzed as separate traits in the same regression model, both incident and persistent nGER and snoring were found to be associated with incident asthma, and all studied respiratory symptoms, independently of each other (Table 2). Interaction analysis did not find a significant interaction between nGER and snoring in this context (data not shown).

Subjects with both incident or persistent nGER and snoring had the strongest association to onset of all studied respiratory symptoms, whereas for onset of asthma the group with incident or persistent nGER had the highest risk, followed by those with both incident or persistent nGER and snoring (Table 3, Supplementary Fig. S1). Interaction analyses were then performed to evaluate whether these associations differed by BMI or age groups, but did not find evidence of effect modification from BMI or age. A sensitivity analysis stratifying by different BMI levels did not show any pattern of differences by subgroups (data not shown).

4. Discussion

The main result of this longitudinal study is that incident and persistent nocturnal gastroesophageal reflux and snoring are independently associated with a higher incidence of asthma and respiratory symptoms (wheezing, productive cough, nocturnal chest tightness, nocturnal breathlessness and nocturnal cough). The present study also indicated that subjects with both nGER and snoring are at increased risk of developing respiratory symptoms.

Our results demonstrate that subjects with incident nGER were twice as likely to develop asthma compared to those without nGER. The reason why persistent nGER did not significantly associate with increased incident asthma is unclear and somewhat surprising. This contrasts the association of incident and persistent nGER with more respiratory symptoms, such as wheezing, nocturnal shortness of breath and cough, compared to participants without nGER. After adjusting for confounding factors, the results remained significant. Importantly, this association was not explained by concomitant snoring. The results of this study support previous studies that have reported an association of nGER with asthma and various respiratory symptoms [1,3,15].

Several studies have linked snoring to the development of asthma and respiratory symptoms [13,20,21]. In accordance with previous studies, we found that subjects with incident and persistent snoring had a higher risk of developing respiratory symptoms. After adjusting for confounding factors, incident asthma was associated with incident and persistent snoring, compared to those without snoring, with a slightly stronger association to new snoring.

The clinical implications of our results are first that individuals with both nGER and snoring need to be evaluated and monitored for respiratory symptoms, in light of their increased incidence of respiratory symptoms. Second, together with findings from other studies, our data support that both nGER and snoring may be independently associated with respiratory symptoms. Both nGER and snoring should therefore be evaluated among individuals with respiratory symptoms, and treated accordingly. Ultimately, further studies need to evaluate if treating nGER and snoring can decrease the risk of subsequent development of respiratory symptoms.

Different theories have been proposed to explain how nGER may cause respiratory symptoms. One is the reflux theory, which proposes that hyperresponsiveness, airway obstruction and tissue injury may appear due to recurrent microaspirations of gastric contents into the

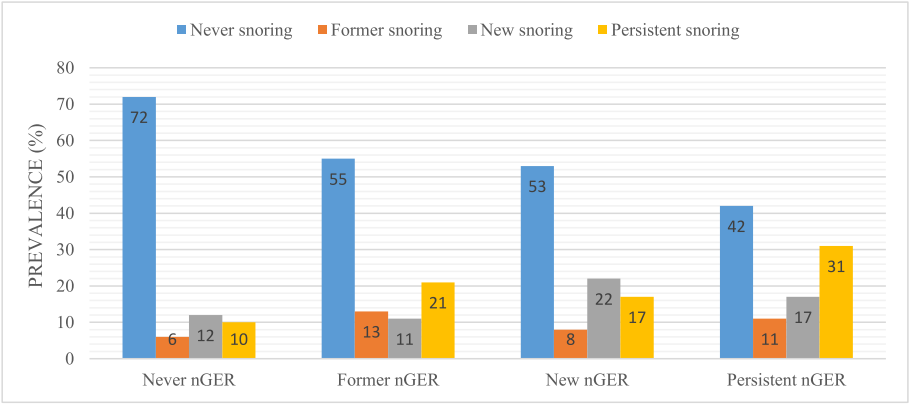

Fig. 1. Bar chart showing the prevalence between snoring and nGER in the study population.

Table 1
Characteristics of participants by reflux and snoring groups (RHINE II) by nGER or snoring status over 10 years.
Data are given as mean ± standard deviation (SD) or n (%). P-values calculated by chi-square test or anova as appropriate, for comparison between all groups. BMI, body mass index; nGER, nocturnal gastroesophageal reflux.

	Never nGER (n= 9701)	Former nGER (n= 528)	Incident nGER (n= 548)	Persistent nGER (n= 247)	P-value	Never snoring (n= 7321)	Former snoring (n= 703)	Incident snoring (n= 1359)	Persistent snoring (n= 1200)	P-value
Male	4409 (45.5)	265 (50.2)	252 (46.0)	117 (47.4)	0.19	2867 (39.2)	439 (62.5)	743 (54.7)	843 (70.3)	**<0.001**
Age (years)	39.9 ± 7.3	40.9 ± 7.2	40.7 ± 7.1	41.9 ± 7.0	0.83	39.3 ± 7.3	42.5 ± 7.2	40.2 ± 6.7	41.9 ± 6.9	**<0.001**
BMI (kg/m2)	24.5 ± 4	26.3 ± 4.4	25.2 ± 4.1	26.9 ± 4.5	**<0.001**	24.0 ± 3.7	26.7 ± 5.1	25.3 ± 3.9	26.9 ± 4.3	**<0.001**
Smoking:					**<0.001**					**<0.001**
Never	4652 (48.8)	198 (38.5)	236 (43.7)	94 (38.7)		3679 (51.2)	261 (38.2)	605 (45.3)	419 (35.3)	
Ex- smoker	2491 (26.1)	157 (30.5)	144 (26.3)	62 (25.5)		1854 (25.8)	199 (29.1)	342 (25.6)	349 (29.4)	
Current smoker	2393 (25.1)	160 (31.1)	160 (29.6)	87 (35.8)		1660 (23.1)	224 (32.8)	388 (29.1)	418 (35.2)	
Hypertension	580 (6.1)	67 (12.9)	41 (7.6)	39 (16.5)	**<0.001**	390 (5.4)	80 (11.6)	86 (6.4)	154 (13.1)	**<0.001**
Diabetes	129 (1.3)	6 (1.1)	10 (1.8)	4 (1.6)	0.73	83 (1.1)	16 (2.3)	22 (1.6)	25 (2.1)	**0.006**

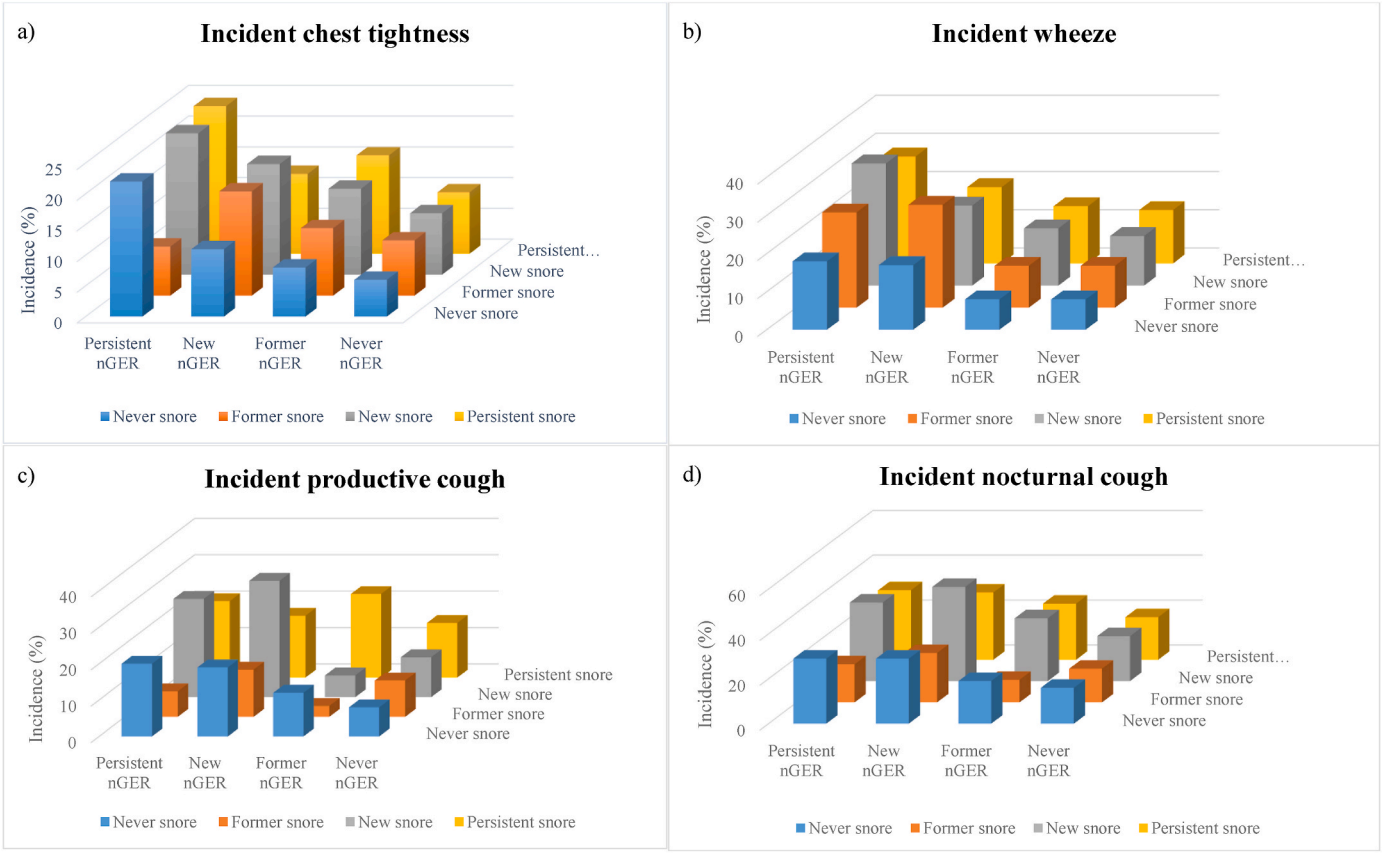

Fig. 2. 3D column chart showing incident of chest tightness, wheeze, productive cough and nocturnal cough by snoring and nGER status. Scales differ between graphs.

lungs. Another one, the vagal theory, proposes that airway obstruction may occur due to stimulation of the vagus nerve in the distal esophagus during reflux episodes [22–25]. On the other hand, some studies have suggested asthma as a causative factor for developing GERD. Asthma can lead to a pressure difference between intrathoracic and intra-abdominal space and cause regurgitation of acidic stomach contents through the lower esophageal sphincter. Furthermore, some groups of asthma medication lead to relaxation of the lower esophageal sphincter, allowing leakage of the acidic gastric contents into the esophagus which causes more reflux symptoms [26,27].

Snoring has been thought to cause respiratory symptoms in part through nGER and micro-aspirations. However, as we found a moderately strong association between snoring and respiratory symptoms, independent of nGER, there are likely other mechanisms implicated as well. Possible shared direct mechanistic links are low-grade inflammation, nerve reflex and intermittent hypoxia. Snoring is associated with local inflammation and chronic upper airway edema, which contribute to trigger or exacerbate asthma and respiratory symptoms [28,29]. In addition, there is evidence that when snoring is successfully treated, it may also lead to improvement of both respiratory symptoms and asthma

Table 2
Adjusted odds ratios (95 % CI) for incident asthma and respiratory symptoms by nGER and snoring status, as separate entities in the same model. Adjusted for age, sex, smoking status, body mass index (BMI, both at baseline and change until follow-up), and center. Never nGER and never snoring used as reference groups.

Incident:	Former nGER	Incident nGER	Persistent nGER	Former snoring	Incident snoring	Persistent snoring
	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)
Current asthma	**1.58 (1.05–2.38)**	**1.67 (1.15–2.43)**	1.16 (0.61–2.13)	1.33 (0.91–1.95)	**1.36 (1.03–1.81)**	1.20 (0.87–1.65)
Wheeze	0.92 (0.62–1.38)	**1.72 (1.28–2.31)**	**2.14 (1.40–3.26)**	1.09 (0.80–1.49)	1.23 (0.99–1.53)	**1.37 (1.08–1.74)**
Wheeze without a cold	**1.54 (1.06–2.24)**	**2.04 (1.49–2.79)**	**2.61 (1.67–4.06)**	1.36 (0.97–1.90)	**1.49 (1.17–1.90)**	**1.36 (1.04–1.78)**
Wheeze and breathlessness	1.39 (0.94–2.07)	**2.13 (1.55–2.92)**	**3.02 (2.00–4.57)**	1.14 (0.78–1.65)	**1.60 (1.26–2.05)**	**1.53 (1.17–2.01)**
Productive cough	**1.44 (1.00–2.06)**	**2.29 (1.74–3.03)**	**2.05 (1.30–3.23)**	0.95 (0.68–1.33)	**1.41 (1.14–1.76)**	**1.65 (1.31–2.09)**
Nocturnal chest tightness	**1.54 (1.07–2.21)**	**1.86 (1.37–2.54)**	**3.10 (2.02–4.76)**	**1.52 (1.11–2.10)**	**1.69 (1.35–2.12)**	**1.57 (1.22–2.03)**
Nocturnal breathlessness	1.23 (0.75–1.99)	**2.22 (1.54–3.20)**	**2.64 (1.57–4.45)**	**1.68 (1.12–2.51)**	**1.66 (1.24–2.23)**	**1.58 (1.13–2.21)**
Nocturnal cough	1.22 (0.89–1.69)	**2.13 (1.64–2.77)**	**1.75 (1.16–2.64)**	0.97 (0.73–1.29)	**1.39 (1.16–1.68)**	**1.35 (1.10–1.67)**

Table 3
Adjusted odds ratios (95 % CI) for incident asthma and respiratory symptoms by snoring and nGER status. Adjusted for age, sex, smoking status, body mass index (BMI, both at baseline and change until follow-up), and center. Without nGER and without snoring at follow-up used as a reference group.

Incident:	Incident or persistent snoring	Incident or persistent nGER	Both nGER and snoring, incident or persistent
	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)
Current asthma	1.30 (1.03–1.65)	1.79 (1.19–2.67)	1.57 (0.97–2.55)
Wheeze	1.26 (1.05–1.51)	1.90 (1.38–2.62)	2.23 (1.56–3.17)
Wheeze without a cold	1.43 (1.17–1.76)	2.40 (1.71–3.38)	2.65 (1.82–3.86)
Wheeze and breathlessness	1.64 (1.33–2.03)	2.74 (1.96–3.83)	3.07 (2.11–4.47)
Productive cough	1.52 (1.27–1.82)	2.16 (1.57–2.97)	3.30 (2.36–4.62)
Nocturnal chest tightness	1.61 (1.33–1.96)	2.65 (1.92–3.66)	3.07 (2.12–4.44)
Nocturnal breathlessness	1.53 (1.18–1.98)	2.45 (1.63–3.68)	3.65 (2.37–5.61)
Nocturnal cough	1.36 (1.16–1.59)	2.01 (1.50–2.69)	2.82 (2.04–3.89)

[21,30–32].

Snoring, nGER and respiratory symptoms are all associated with obesity, and therefore, special attention needed to be given to potential modifying effects of BMI. As we could not find evidence of any interaction between snoring/nGER status and BMI in their relation to incident respiratory symptoms or incident asthma, we interpret that the association of snoring/nGER status with incident respiratory symptoms or asthma is not explained by obesity. The same was true for age differences at baseline, which did not have any effect modification on these associations.

The major strength of our study is the large population size and the long follow up time. The present study also included participants from several different countries in Northern Europe. The major limitation of our study is that it is solely based on self-reported data which may cause measurement bias. Validation with studies using objective measures are therefore warranted. For example, BMI was calculated from self-reported height and weight and bias in self-reported information can cause measurement error. In the National Health and Nutrition Examination Survey (NHANES), overestimation of body height and underestimation of body weight was found to increase by increasing age (>60 years old) [33]. However, in our study, participants were 30–50 years, an interval where self-reported calculated BMI can be used, according to the NHANES study. Additionally, we assume that the potential misclassification should be non-differential between the study groups. Another limitation that should be addressed regarding this study, is the lack of more frequent measuring data. Although our study has an extensive follow up time, data was collected only at two occasion, baseline and follow-up. Further studies would benefit from more frequent measurements to better evaluate temporal associations. Also, as this cohort was relatively young at baseline and no spirometry was performed, we could not evaluate potential modifying effects from chronic obstructive pulmonary disease (COPD). However, adjusting for smoking status (as done in this analysis) arguably adjusts for COPD-related effects.

In conclusion, this study found that subjects with both nGER and habitual snoring had a higher risk of developing respiratory symptoms (wheezing, productive cough, nocturnal chest tightness, nocturnal breathlessness and nocturnal cough), than subjects with only nGER or habitual snoring. Having either nGER or habitual snoring was also independently associated with the development of respiratory symptoms. There is a need to better understand the impact and interactions of nGER and snoring in their association with respiratory symptoms. For the clinician, special consideration should be given to patients with both nGER and snoring, since prevalence and incidence of respiratory symptoms is higher in these patients.

CRediT authorship contribution statement

Rima Mir Fakhraei: Data curation, Formal analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Eva Lindberg:** Conceptualization, Funding acquisition, Methodology, Writing – review & editing. **Bryndís Benediktsdóttir:** Conceptualization, Methodology, Writing – review & editing. **Cecilie Svanes:** Conceptualization, Funding acquisition, Methodology, Writing – review & editing. **Ane Johannessen:** Conceptualization, Data curation, Funding acquisition, Methodology, Writing – review & editing. **Mathias Holm:** Conceptualization, Methodology, Writing – review & editing. **Lars Modig:** Conceptualization, Methodology, Writing – review & editing. **Karl A. Franklin:** Conceptualization, Methodology, Writing – review & editing. **Andrei Malinovschi:** Conceptualization, Funding acquisition, Methodology, Writing – review & editing. **Thorarinn Gislason:** Conceptualization, Funding acquisition, Methodology, Resources, Writing – review & editing. **Rain Jõgi:** Conceptualization, Funding acquisition, Methodology, Writing – review & editing. **Christine Cramer:** Conceptualization, Methodology, Writing – review & editing. **Christer Janson:** Conceptualization, Data curation, Funding acquisition, Methodology, Resources, Supervision, Writing – review & editing. **Össur Ingi Emilsson:** Conceptualization, Data curation, Formal analysis, Methodology, Resources, Supervision, Validation, Visualization, Writing – review & editing.

Declaration of competing interest

The authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2023.107495.

References

[1] Ö.I. Emilsson, A. Bengtsson, K.A. Franklin, K. Torén, B. Benediktsdóttir, A. Farkhooy, et al., Nocturnal gastro-oesophageal reflux, asthma and symptoms of OSA: a longitudinal, general population study, Eur. Respir. J. 41 (6) (2013 Jun) 1347–1354.
[2] T. Gislason, C. Janson, P. Vermeire, P. Plaschke, E. Björnsson, D. Gislason, et al., Respiratory symptoms and nocturnal gastroesophageal reflux: a population-based study of young adults in three European countries, Chest 121 (1) (2002 Jan) 158–163.
[3] M.I. Gunnbjörnsdóttir, E. Omenaas, T. Gíslason, E. Norrman, A.C. Olin, R. Jõgi, et al., Obesity and nocturnal gastro-oesophageal reflux are related to onset of asthma and respiratory symptoms, Eur. Respir. J. 24 (1) (2004 Jul) 116–121.
[4] S.M. Harding, Gastroesophageal reflux: a potential asthma trigger, Immunol. Allergy Clin. 25 (1) (2005 Feb) 131–148.
[5] T.R. Levin, R.M. Sperling, K.R. McQuaid, Omeprazole improves peak expiratory flow rate and quality of life in asthmatics with gastroesophageal reflux, Am. J. Gastroenterol. 93 (7) (1998 Jul) 1060–1063.
[6] S.K. Field, L.R. Sutherland, Does medical antireflux therapy improve asthma in asthmatics with gastroesophageal reflux?: a critical review of the literature, Chest 114 (1) (1998 Jul) 275–283.
[7] K.A. Franklin, T. Gíslason, E. Omenaas, R. Jõgi, E.J. Jensen, E. Lindberg, et al., The influence of active and passive smoking on habitual snoring, Am. J. Respir. Crit. Care Med. 170 (7) (2004 Oct 1) 799–803.
[8] T. Gislason, M. Almqvist, G. Eriksson, A. Taube, G. Boman, Prevalence of sleep apnea syndrome among Swedish men–an epidemiological study, J. Clin. Epidemiol. 41 (6) (1988) 571–576.
[9] B.A. Stuck, B. Hofauer, The diagnosis and treatment of snoring in adults, Dtsch Arztebl Int 116 (48) (2019 Nov 29) 817–824.
[10] M.S. Urschitz, A. Guenther, S. Eitner, P.M. Urschitz-Duprat, M. Schlaud, O. S. Ipsiroglu, et al., Risk factors and natural history of habitual snoring, Chest 126 (3) (2004 Sep) 790–800.
[11] B.C. Jacobson, S.C. Somers, C.S. Fuchs, C.P. Kelly, C.A. Camargo, Body-mass index and symptoms of gastroesophageal reflux in women, N. Engl. J. Med. 354 (22) (2006 Jun 1) 2340–2348.
[12] D. Teculescu, B. Hannhart, C. Aubry, B. Montaut-Verient, J.M. Virion, J. P. Michaely, et al., Who are the "occasional" snorers? Chest 122 (2) (2002 Aug) 562–568.
[13] L.G. Larsson, A. Lindberg, K.A. Franklin, B. Lundbäck, Symptoms related to obstructive sleep apnoea are common in subjects with asthma, chronic bronchitis and rhinitis in a general population, Respir. Med. 95 (5) (2001 May) 423–429.
[14] C. Janson, A. Johannessen, K. Franklin, C. Svanes, L. Schiöler, A. Malinovschi, et al., Change in the prevalence asthma, rhinitis and respiratory symptom over a 20 year period: association to year of birth, life style and sleep related symptoms, BMC Pulm. Med. 18 (1) (2018 Sep 12) 152.
[15] Ö.I. Emilsson, S.A. Hägg, E. Lindberg, K.A. Franklin, K. Toren, B. Benediktsdottir, et al., Snoring and nocturnal reflux: association with lung function decline and respiratory symptoms, ERJ Open Res 5 (2) (2019 May 28), 00010–2019.
[16] P.P. Balte, P.H.M. Chaves, D.J. Couper, P. Enright, D.R. Jacobs, R. Kalhan, et al., Association of nonobstructive chronic bronchitis with respiratory health outcomes in adults, JAMA Intern. Med. 180 (5) (2020 May) 676–686.
[17] Y. Çolak, B.G. Nordestgaard, J. Vestbo, P. Lange, S. Afzal, Prognostic significance of chronic respiratory symptoms in individuals with normal spirometry, Eur. Respir. J. 54 (3) (2019 Sep), 1900734.
[18] A. Johannessen, G. Verlato, B. Benediktsdottir, B. Forsberg, K. Franklin, T. Gislason, et al., Longterm follow-up in European respiratory health studies – patterns and implications, BMC Pulm. Med. 14 (1) (2014 Apr 16) 63.
[19] C. Janson, W. De Backer, T. Gislason, P. Plaschke, E. Björnsson, J. Hetta, et al., Increased prevalence of sleep disturbances and daytime sleepiness in subjects with bronchial asthma: a population study of young adults in three European countries, Eur. Respir. J. 9 (10) (1996 Oct) 2132–2138.
[20] M. Garden, M. O'Callaghan, S. Suresh, A.A. Mamum, J.M. Najman, Asthma and sleep disturbance in adolescents and young adults: a cohort study, J. Paediatr. Child Health 52 (11) (2016 Nov) 1019–1025.
[21] A. Ekici, M. Ekici, E. Kurtipek, H. Keles, T. Kara, M. Tunckol, et al., Association of asthma-related symptoms with snoring and apnea and effect on health-related quality of life, Chest 128 (5) (2005 Nov) 3358–3363.
[22] M.R. Stein, Possible mechanisms of influence of esophageal acid on airway hyperresponsiveness, Am. J. Med. 115 (Suppl 3A) (2003 Aug 18) 55S–59S.
[23] W.E. Berquist, G.S. Rachelefsky, M. Kadden, S.C. Siegel, R.M. Katz, E. W. Fonkalsrud, et al., Gastroesophageal reflux-associated recurrent pneumonia and chronic asthma in children, Pediatrics 68 (1) (1981 Jul) 29–35.
[24] L.E. Mansfield, H.H. Hameister, H.S. Spaulding, N.J. Smith, N. Glab, The role of the vague nerve in airway narrowing caused by intraesophageal hydrochloric acid provocation and esophageal distention, Ann. Allergy 47 (6) (1981 Dec) 431–434.
[25] S.M. Harding, Gastroesophageal reflux, asthma, and mechanisms of interaction, Am. J. Med. 111 (Suppl 8A) (2001 Dec 3) 8S–12S.
[26] K. Thakkar, R.O. Boatright, M.A. Gilger, H.B. El-Serag, Gastroesophageal reflux and asthma in children: a systematic review, Pediatrics 125 (4) (2010 Apr) e925–e930.
[27] F. Zerbib, O. Guisset, H. Lamouliatte, A. Quinton, J.P. Galmiche, J.M. Tunon-De-Lara, Effects of bronchial obstruction on lower esophageal sphincter motility and gastroesophageal reflux in patients with asthma, Am. J. Respir. Crit. Care Med. 166 (9) (2002 Nov 1) 1206–1211.
[28] M. Knuiman, A. James, M. Divitini, H. Bartholomew, Longitudinal study of risk factors for habitual snoring in a general adult population: the Busselton Health Study, Chest 130 (6) (2006 Dec) 1779–1783.
[29] D. Stănescu, S. Kostianev, A. Sanna, G. Liistro, C. Veriter, Expiratory flow limitation during sleep in heavy snorers and obstructive sleep apnoea patients, Eur. Respir. J. 9 (10) (1996 Oct) 2116–2121.
[30] C.S. Chan, A.J. Woolcock, C.E. Sullivan, Nocturnal asthma: role of snoring and obstructive sleep apnea, Am. Rev. Respir. Dis. 137 (6) (1988 Jun) 1502–1504.
[31] L. Li, Z. Xu, X. Jin, C. Yan, F. Jiang, S. Tong, et al., Sleep-disordered breathing and asthma: evidence from a large multicentric epidemiological study in China, Respir. Res. 16 (1) (2015) 56.
[32] S. Gunnlaugsson, M.H. Abul, L. Wright, C.R. Petty, P. Permaul, D.R. Gold, et al., Associations of snoring and asthma morbidity in the school inner-city asthma study, J. Allergy Clin. Immunol. Pract. 9 (10) (2021 Oct) 3679–3685, e1.
[33] M.F. Kuczmarski, R.J. Kuczmarski, M. Najjar, Effects of age on validity of self-reported height, weight, and body mass index: findings from the Third National Health and Nutrition Examination Survey, 1988-1994, J. Am. Diet Assoc. 101 (1) (2001 Jan) 28–34, quiz 35–6.