

Nocturnal GERD – a risk factor for rhinitis/rhinosinusitis: the RHINE study

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Abstract

Background: It has been suggested that gastroesophageal reflux disease (GERD) is a risk factor for developing rhinitis/rhinosinusitis, but data are lacking. This is a prospective 10-year follow-up study of a large multicenter cohort from Northern Europe, evaluating the relationship between nocturnal GERD and noninfectious rhinitis (NIR).

Methods: The study comprised 5417 subjects born between 1945 and 1973, who answered a questionnaire in 1999–2001 and again in 2010–2012. Noninfectious rhinitis was defined as having nasal obstruction, secretion, and/or sneezing without having the common cold. Odds ratios for developing NIR in relation to age, gender, BMI, smoking, asthma, and nocturnal GERD were calculated.

Results: During the 10-year observation period, 1034 subjects (19.1%) developed NIR. Subjects reporting nocturnal gastroesophageal reflux in both 1999 and 2010 had more NIR in 2010 (2.8% vs 1.2%, $P < 0.001$). There was a significant dose–response relationship between the number of reflux episodes/week in 1999 and the risk of having NIR in 2010, $P = 0.02$. In the multiple regression adjusted for age, gender, BMI, tobacco smoke, and asthma, those with nocturnal GERD in 1999 (≥ 3 episodes of nocturnal gastroesophageal reflux symptoms per week) had an OR of 1.6 (95% CI 1.0–2.5, $P = 0.03$) to develop NIR in 2010. Smoking was associated both with an increased risk of developing NIR (30.7% vs 24.0%, $P < 0.001$) and with the development of nocturnal GERD.

Conclusion: This large, population-based, 10-year study indicates that nocturnal GERD was a risk factor for noninfectious rhinitis/rhinosinusitis. GERD should therefore be considered in patients with rhinitis of known and unknown origin.

Noninfectious rhinitis (NIR) is a significant health problem that affects 40% of the population and includes both allergic and nonallergic disease. NIR is characterized by symptoms of nasal obstruction and secretion in the absence of common cold and is associated with a significant reduction in the

health-related quality of life, including impaired quality of sleep. NIR is also a significant risk factor for developing asthma (1, 2). The definition of NIR includes several rhinitic phenotypes such as allergic rhinitis, nonallergic rhinitis, and chronic rhinosinusitis with and without polyps, but it does not allow any distinction between them. Etiological factors are well understood in allergic rhinitis but less known in nonallergic rhinitis and in chronic rhinosinusitis with and without polyps where most of the etiology remains unknown (3). Specific therapy is therefore lacking. Gastroesophageal reflux

Abbreviations

GERD, gastroesophageal reflux disease; GER, gastroesophageal reflux; NIR, noninfectious rhinitis.

disease (GERD), especially nocturnal GERD, has been associated with airway inflammation in asthma, laryngitis, and reflux cough (4). An association has also been shown between GERD and chronic rhinosinusitis (CRS) suggesting a relationship with upper airway inflammation as well (4, 5). In a study of 74 untreated subjects complaining of heartburn and undergoing 24-h pH measurements, 69% reported nasal symptoms more than 5 days/month (6). CRS constitutes 11% of the European population (7), but a possible association between GERD and other forms of rhinitis/rhinosinusitis has also been suggested.

In a general population sample of 3307 subjects, aged 25–75 years, we have recently shown that symptoms of gastroesophageal reflux occurring >25 times/year were associated with an increased risk of developing NIR during a four-year follow-up, OR 2.5 (8). The reported frequency of reflux did not, however, allow us to analyze the impact of the timing or severity of the gastroesophageal reflux episodes, nor did it allow us to differentiate between physiologic reflux and disease. This study aims to study whether nocturnal gastroesophageal reflux, defined as symptoms of reflux occurring during the recumbent period, and specifically nocturnal GERD defined as ≥ 3 episodes of nocturnal reflux every week, is related to the development of noninfectious rhinitis in a large Northern European multicenter study where the subjects were followed for 10 years.

Materials and methods

Study population

This study is part of a longitudinal Northern European, population-based, multicenter study called RHINE that has been described previously (9). The study population in RHINE was randomly selected from the general population in seven geographic centers (Aarhus, Denmark; Reykjavik, Iceland; Bergen, Norway; Tartu, Estonia; and Gothenburg, Umeå, and Uppsala, Sweden). It was designed to evaluate airway inflammation, such as noninfectious rhinitis (NIR) and asthma, and associated risk factors, by questionnaire. The study population was born between 1945 and 1973 and participated in Stage I of the European Community Respiratory Health Survey (ECRHS I) in 1989–1992. Follow-up questionnaires were sent out in 1999–2001 and in 2010–2012.

Study design

In this study, we have analyzed new-onset NIR in relation to age, gender, BMI, asthma, tobacco smoke, and nocturnal gastroesophageal reflux based on data from the 1999 and 2010 questionnaires. A flow chart of the study population is presented in Fig. 1. A total of 12 605 subjects answered the questionnaire both in 1999 and in 2010. From this sample, subjects who reported NIR in 1999 and those who reported

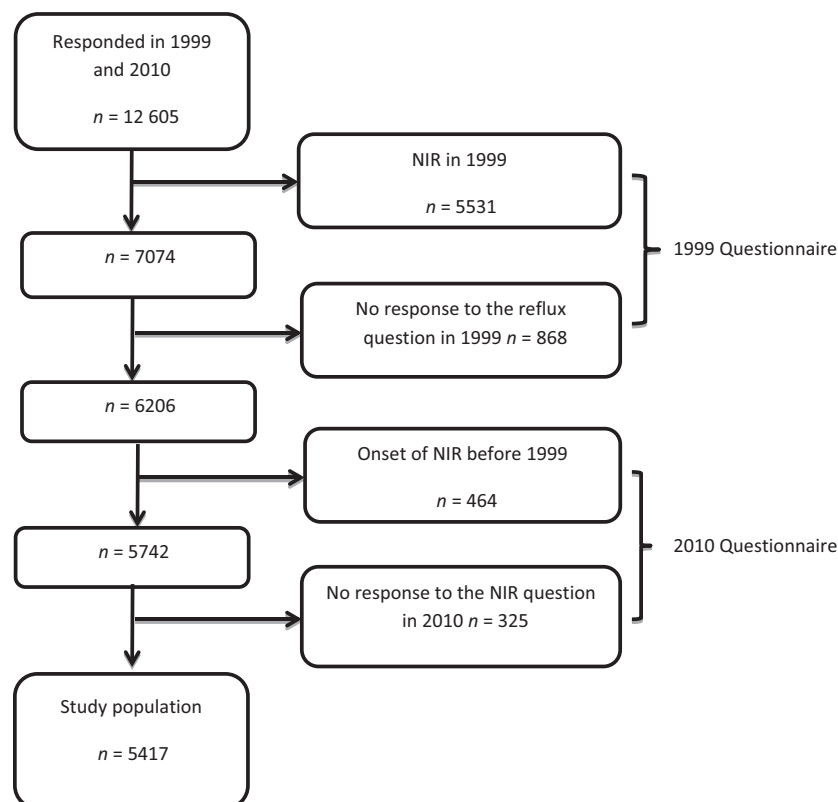


Figure 1 Flow chart of the subjects excluded and the study population.

NIR in 2010 with an onset before 1999 were excluded (5531 + 464). In addition, subjects who did not answer the reflux question in 1999 and those who did not answer the NIR question in 2010 were also excluded (868 + 325). This resulted in a study population of 5417 subjects. The 325 subjects who did not answer the NIR question in 2010 showed no significant difference with regard to reflux compared with the study population (Table 1).

Outcomes

Noninfectious rhinitis was defined as the affirmative answer to the question: *Have you ever been troubled by nasal symptoms such as nasal obstruction, nasal secretion, and/or sneezing attacks without having a cold? and When was this noticed the first time?* (10) The symptom-based definition of NIR includes both allergic and nonallergic rhinitis as well as chronic rhinosinusitis with and without nasal polyps.

Nocturnal gastroesophageal reflux was defined as the affirmative answer to the question: *How often during the last months have you experienced symptoms of heartburn or regurgitation when going to bed?* (11). The frequency of symptoms was rated on a five-point scale: never or seldom, less than once/week, 1–2 times/week, 3–5 times/week, or almost every day or night. Nocturnal GERD was defined as reporting nocturnal gastroesophageal reflux ≥ 3 –5 times/week, and nocturnal GER was defined as nocturnal gastroesophageal reflux 1–2 times/week. Nocturnal gastroesophageal reflux reported less than once/week was defined as nocturnal reflux.

The study was approved by the local ethics committee in Gothenburg.

Statistical analyses

Univariate analyses of NIR and the different variables, such as age, gender, BMI, asthma, tobacco smoke, and GER/GERD, were performed using t-tests, chi-square tests, and the Cochran–Armitage test for trend for continuous, nominal, and ordinal variables, respectively. Multivariate logistic regression was used to calculate odds ratios. All analyses were performed using SAS 9.4 (SAS Institute Inc, Cary, NC, USA).

All subjects who reported GER in both 1999 and 2010 in relation to their NIR status in 2010 were analyzed. We also

Table 1 Analyses of excluded subjects with no answer to the NIR question in 2010 (missing) compared with the study population stratified by reflux status in 1999. Nocturnal GER= reflux 1–2 times/week, nocturnal GERD= reflux ≥ 3 times/week. Difference in trend from nocturnal reflux to nocturnal GERD between ‘missing’ and ‘study population’, $P = 0.6$

	Missing <i>N</i> = 325	Study population <i>N</i> = 5417
Nocturnal Reflux <once/week <i>N</i> (%)	309 (95)	5146 (95)
Nocturnal GER <i>N</i> (%)	12 (4)	162 (3)
Nocturnal GERD <i>N</i> (%)	4 (1)	109 (2)

analyzed the subjects who reported GERD in 1999 in relation to NIR in 2010 and the trend for developing NIR in 2010, with increasing episodes of nocturnal reflux from no reflux to GER (1–2 episodes/week) and GERD (≥ 3 episodes per week) in 1999. In the regression model, age and BMI were used as continuous variables.

Results

During the observation period, 19.1% (1034/5417) developed NIR (Table 2). Age, female gender, tobacco smoke, asthma, and nocturnal GER in both 1999 and 2010 were significantly associated with NIR. In 1999, 109 (2.0%) subjects reported nocturnal GERD (symptoms of reflux ≥ 3 times/week), 162 (3.0%) reported nocturnal GER (symptoms of reflux 1–2 times/week), and 5146 (95%) reported reflux less than once/week. There was a significant trend between an increasing number of reflux episodes in 1999 and the risk of developing NIR by 2010 (Table 3).

In the multiple regression analyses including age, gender, BMI, tobacco smoke, asthma nocturnal GER and nocturnal GERD, nocturnal GERD, female gender, tobacco smoke, and asthma remained associated with an increased risk of developing NIR (Fig. 2). Current smoking was reported in

Table 2 New-onset noninfectious rhinitis (NIR) in 2010 in relation to age, gender, BMI, tobacco smoke, and asthma in 1999 and nocturnal GER reported by the same individuals both in 1999 and in 2010. Nocturnal GER= nocturnal gastroesophageal reflux 1–2 times/week

Total <i>N</i> = 5417 <i>N</i> (%)	NIR 2010 1034 (19.1)	No NIR 2010 4383 (80.9)	<i>P</i> -value
Mean age, mean (SD)	39.8 (7.5)	40.4 (7.2)	0.02
Female gender <i>N</i> (%)	604 (58.4)	2253 (51.4)	<0.001
BMI kg/m ² (SD)	24.6 (3.9)	24.7 (4.1)	0.4
Smoker <i>N</i> (%)	313 (30.7)	1036 (24)	<0.001
Asthma <i>N</i> (%)	52 (5.1)	104 (2.4)	<0.001
Nocturnal GER 1999 + 2010 <i>N</i> (%)	29 (2.8)	51 (1.2)	<0.001

Table 3 Trend for developing noninfectious rhinitis (NIR) during 1999–2010 in relation to the frequency of self-reported nocturnal gastroesophageal reflux in 1999. Difference in trend between NIR and no NIR in 2010, $P = 0.02$. Nocturnal GER= reflux 1–2 times/week, nocturnal GERD= reflux ≥ 3 times/week

	NIR 2010	No NIR 2010	Total <i>n</i> = 5417
Nocturnal reflux less than once/week <i>N</i> (%)	969 (18.8)	4177 (81.2)	5146
Nocturnal GER: reflux 1–2 times/week <i>N</i> (%)	35 (21.6)	127 (78.4)	162
Nocturnal GERD: reflux ≥ 3 –5 times/week <i>N</i> (%)	30 (27.5)	79 (72.5)	109

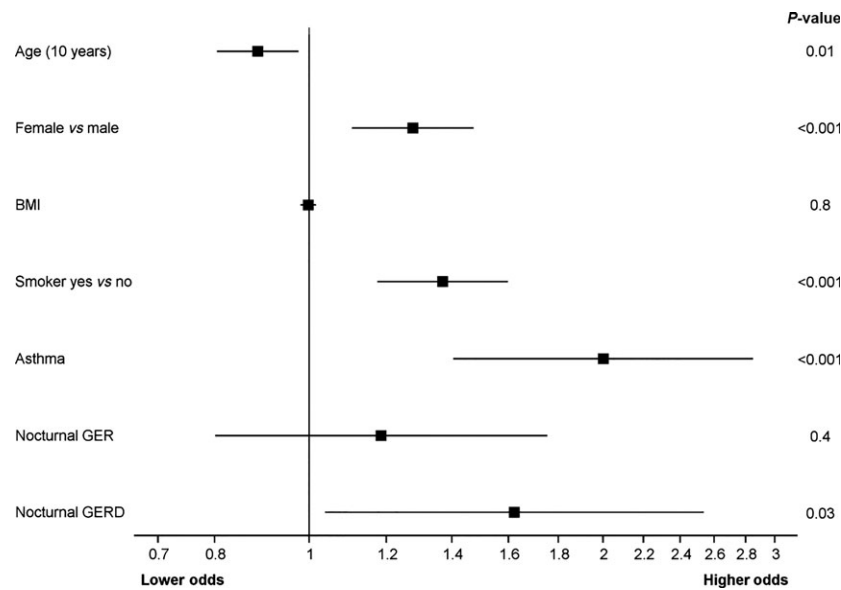


Figure 2 Odds ratios and *P*-values for noninfectious rhinitis (NIR) in 2010 in relation to age, gender, BMI, smoking, asthma, nocturnal GER, and nocturnal GERD in 1999. Nocturnal GER= reflux

1–2 times/week, nocturnal GERD = reflux ≥ 3 times/week. Age and BMI used as continuous variables.

1999 by 30.7% of subjects with NIR and by 24.0% of subjects without NIR, $P < 0.001$. Smoking was independently associated with the development of NIR. GERD as a risk factor for NIR was not affected by smoking status (smoker vs nonsmoker) (Table 4). Among the subjects who reported GERD in 1999 and developed NIR in 2010, 43% still suffered from GERD in 2010.

Discussion

This 10-year, multicenter, follow-up study of a large population sample showed that nocturnal GERD was associated with the development of noninfectious rhinitis (OR 1.6, 95% CI 1.0–2.5). This association increased with the frequency of nocturnal reflux episodes. The results suggest that nocturnal GERD should be evaluated in patients with noninfectious rhinitis/rhinosinusitis of known and unknown etiologies.

Nocturnal gastroesophageal reflux is of particular interest as it is present in 47–78% of patients with GERD (12). It has also been linked to more severe GERD, as demonstrated

by pH measurements and the occurrence of esophageal and extra-esophageal complications, including an impact on sleep and health-related QoL (13–15). The treatment of nocturnal GERD has been shown to improve insomnia and reduce early morning arousals, as well as awakenings during the night (14). It should be noted that there is a lack of consensus in the literature regarding the definition of nocturnal reflux, for example, whether to focus on the effects on sleep or the timing of the reported events (15). In the current study, nocturnal GERD was defined in line with the definition by Farup et al. in 2001 based on the frequency of reflux episodes (16). While the Montreal definition and classification of gastroesophageal reflux disease is patient-centered (based on whether symptoms are perceived as troublesome by the patient), clinical trials require a threshold measurement of severity to allow uniformity in the study population or comparison between trials (American Gastroenterological Association) (17). The cut-off criteria that are used, however, vary considerably between different studies. Taking account of the fact that two-thirds of subjects with heartburn at least three times a week reported sleep disturbances (13, 16), the present study therefore selected a cut-off of three or more reflux symptoms a week as the criterion in an attempt to differentiate between physiologic reflux and reflux disease.

In this study, nocturnal GERD in 1999 was significantly related to NIR in 2010, showing a dose–response relationship with an increasing number of reflux episodes. This was also consistent in the logistic regression (OR 1.6) adjusted for age, gender, BMI, asthma, and smoking. Similar results were also obtained in subjects experiencing one to two episodes/week (GER) in both 1999 and 2010. The frequency of reflux symptoms varies over time, however, in the study population;

Table 4 Odds ratios for noninfectious rhinitis (NIR) in 2010 in relation to nocturnal GER and nocturnal GERD in 1999 stratified by smoking in 1999. Nocturnal GER= reflux 1–2 times/week, nocturnal GERD= reflux ≥ 3 times/week

	Nonsmoker OR 95% CI	<i>P</i>	Smoker OR 95% CI	<i>P</i>
Nocturnal GER	1.3 (0.8–2.2)	0.2	0.9 (0.5–1.8)	0.6
Nocturnal GERD	1.7 (1.0–3.0)	0.05	1.4 (0.7–3.0)	0.4

43% of subjects reporting nocturnal GERD in 1999 still reported nocturnal GERD 10 years later among those who developed NIR compared with 19% of those who did not. It is likely that the subjects evaluated in the current study also suffered from daytime heartburn. As the prevalence of daytime and nocturnal reflux is likely to exceed the reported nocturnal reflux, the possibility cannot be ruled out that the results shown are also attributed to daytime reflux.

It is important to remember that the current observed association between the two conditions, nocturnal GERD and NIR, does not signify a causal relationship. As pointed out by the Montreal consensus group, it is rare that extra-esophageal syndromes occur in isolation, without concomitant manifestations of the typical esophageal syndrome, and these syndromes are usually multifactorial, with GERD as one of several aggravating cofactors (5). In fact, to establish a causal relationship, the criteria formulated by Hill would need to be fulfilled, that is, the presence of a biologic plausibility, a strength of the association, a temporal relationship, an observed dose–response relationship, and demonstrating that preventive measures were able to prevent the outcome in question (18). Such an undertaking would involve outcome studies with long-term PPI treatment, preferably using disease-specific questionnaires, such as the instrument for assessing nocturnal reflux recently developed by Spiegel et al. (19, 20).

The strength of the present study is that the subjects are part of a large multicenter cohort that has been followed since 1989 as part of the ECRHS study, with a follow-up time in this study of 10 years. Questionnaire data are, however, always subject to accuracy issues in defining a medical condition, as well as recall bias. Nocturnal GERD was assessed over the last months, which is often considered to be the maximum time with an acceptable balance between appropriate information and recall bias (21). In epidemiological studies of GERD, the intensity of symptoms has sometimes been addressed in addition to frequency as a measurement of disease load (22). This was not done in the present study. The fact that some subjects reported no NIR in 1999 and then reported NIR in 2010 with an onset before 1999 could be an expression of recall bias. The exclusion of these subjects did, however, not change the statistical relationships. Another potential limitation of this study is the

wide definition of NIR being used. The definition of NIR is symptom-based and includes both allergic and nonallergic rhinitis as well as chronic rhinosinusitis with and without polyps. The aim of the study was, however, to assess a possible relationship between symptoms of upper airway inflammation and GERD in a large population sample and not to target specific phenotypes of rhinitis and GERD. The result calls for the need to further study how GERD and rhinitis/rhinosinusitis interact in specific subpopulations.

Conclusion

This large population-based study indicates that nocturnal GERD was associated with a 1.6 times increase in the odds of developing adult-onset noninfectious rhinitis in a 10-year follow-up. Smoking, asthma, and female gender were also associated with developing NIR and, in addition to nocturnal GERD, should be considered when evaluating patients with rhinitis/rhinosinusitis.

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Author contributions

All the authors of this article have contributed to the design of the study, the collection and data processing, and data analyses, as well as providing input to the final manuscript. Statistical analyses were exclusively made by statistician Linus Schiöler.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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