

New evidence of increased risk of rhinitis in subjects with COPD: a longitudinal population study

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Background: The aim of this population-based study was to investigate the risk of developing noninfectious rhinitis (NIR) in subjects with chronic obstructive pulmonary disease (COPD).

Materials and methods: This is a longitudinal population-based study comprising 3,612 randomly selected subjects from Gothenburg, Sweden, aged 25–75 years. Lung function was measured at baseline with spirometry and the included subjects answered a questionnaire on respiratory symptoms. At follow-up, the subjects answered a questionnaire with a response rate of 87%. NIR was defined as symptoms of nasal obstruction, nasal secretion, and/or sneezing attacks without having a cold, during the last 5 years. COPD was defined as a spirometry ratio of forced expiratory volume in 1 second divided by forced vital capacity (FEV_1/FVC) <0.7 . Subjects who reported asthma and NIR at baseline were excluded from the study. The odds ratios for developing NIR (ie, new-onset NIR) in relation to age, gender, body mass index, COPD, smoking, and atopy were calculated.

Results: In subjects with COPD, the 5-year incidence of NIR was significantly increased (10.8% vs 7.4%, $P=0.005$) and was higher among subjects aged >40 years. Smoking, atopy, and occupational exposure to gas, fumes, or dust were also associated with new-onset NIR. COPD, smoking, and atopy remained individual risk factors for new-onset NIR in the logistic regression analysis.

Conclusions: This longitudinal population-based study of a large cohort showed that COPD is a risk factor for developing NIR. Smoking and atopy are also risk factors for NIR. The results indicate that there is a link present between upper and lower respiratory inflammation in NIR and COPD.

Keywords: COPD, rhinitis, smoking, epidemiology, spirometry

Introduction

Noninfectious rhinitis (NIR) affects 40% of the adult population, has a significant impact on health-related quality of life, and results in substantial health-economic costs to the society.^{1–3} NIR is characterized by symptoms of upper airway inflammation, such as nasal obstruction, secretion, itching and sneezing, and represents several pathological entities, including allergic rhinitis, vasomotor rhinitis, and chronic rhinosinusitis.⁴ The disease has previously been linked to asthma, smoking, occupational exposure to gas, fumes, or dust, and also to gastroesophageal reflux disease, but for many patients with NIR, the pathophysiology remains unknown.^{1,3,5,6} NIR has been reported in individuals with chronic obstructive pulmonary disease (COPD), but epidemiological evidence is lacking.⁷ COPD is an inflammatory, progressive airway disease with persistent airflow limitation. The airflow limitation in COPD is caused by a combination

of small airway disease (obstructive bronchiolitis) and the destruction of lung parenchyma (emphysema). Exposure to noxious particles and gases, particularly tobacco smoking, but also occupational exposure to gas, fumes, or dust, is related to the development of COPD.^{8,9} Interestingly, the same risk factors have also been associated with NIR.^{1,6} COPD occurs predominantly in patients aged >40 years as a direct result of the slow initial development of the disease.^{10–12} Furthermore, new research has shown paranasal sinus opacification to be associated with COPD and self-reported respiratory symptoms.¹³

The estimated prevalence of COPD in the Nordic countries, defined according to the Global Initiative for Chronic Obstructive Lung Disease stage I and higher, varies from 9.4% to 18.8%.^{14–18} To date, only a few studies have evaluated a possible link between NIR and COPD. This is surprising, as both NIR and COPD are common inflammatory conditions in the respiratory tract and could potentially be linked through a generalized airway inflammation in accordance with “the united airways” concept introduced to explain the link between upper and lower inflammatory airway disease in asthma and NIR, even though other inflammatory mechanisms are likely to be involved.⁷

The diagnosis and classification of COPD is based on a clinical assessment and spirometry is mandatory.⁸ To the authors’ knowledge, there are no large population-based studies of the relationship between rhinitis and COPD based on spirometry data. In the present study, data on spirometry and respiratory symptoms were combined from a large longitudinal population-based cohort, followed for 5 years. The main hypothesis of the study was that COPD is related to the development of NIR.

Material and methods

The adult onset asthma and nitric oxide cohort

This study is a part of the longitudinal population-based study called ADONIX (adult onset asthma and nitric oxide). ADONIX was approved by The Regional Ethical Review Board of Gothenburg (Dnr Ö 092-01) and has previously been described in detail.⁵ The ADONIX study was designed to evaluate risk factors for airway disease such as NIR, COPD, and asthma. A total of 6,665 subjects, randomly selected, aged 25–75 years, from the municipal register of Gothenburg, Sweden, were included at baseline between 2001 and 2003. Written informed consent was obtained from all participants. The subjects performed spirometry and answered a questionnaire with questions on upper

and lower respiratory symptoms and diseases. The subjects also underwent a measurement of fractional exhaled nitric oxide (FeNO) and a laboratory analysis of specific immunoglobulin E antibodies for atopy status. After 5 years, the included subjects were asked to answer a follow-up questionnaire. The response rate at follow-up was 87%.

Study design

This study evaluates the risk of developing new-onset NIR in relation to having COPD during a 5-year observation period. The questions used for new-onset NIR and associated risk factors, such as smoking, educational status, and occupational exposure to gas, fumes, or dust, are shown in Table 1. The questions on occupational exposure to gas, fumes, or dust, and educational status were added in 2005 and were therefore not answered by all the participants at baseline. For this reason, occupational exposure and educational status were analyzed separately in a sub-analysis.

The study population is shown in Figure 1. Subjects who reported NIR at baseline were excluded from the study population, along with subjects who did not answer the NIR question at follow-up. To avoid misclassification between asthma and COPD, all the subjects who reported asthma during the past 12 months at baseline were also excluded. As a result, 3,612 subjects were included in the analyses.

Table 1 Questionnaire items on new-onset NIR, gas, fumes, and dust, smoking, and educational status

Item	Question
New-onset NIR	During the last five years, have you ever been troubled by nasal symptoms, such as nasal obstruction, nasal secretion, and/or sneezing attacks without having a cold?
Gas, fumes, or dust	Have you been exposed to gas, fumes, or dust at work?
Smoking	Have you ever smoked daily for at least a month and, if you have stopped smoking, specify the age at which you stopped?
Current smoker	A positive answer to the first question and a negative answer to the second
Ex-smoker	A positive answer to the first question and a positive answer to the second
Education	Which courses/schools have you attended? (indicate the highest level of education). 1. Primary school. 2. Secondary school. 3. Vocational school. 4. High school. 5. University. 6. Another education
Low	Primary school
Middle	Secondary school or vocational school or high school
High	University
Other	Another education
Unknown	Unknown education

Abbreviation: NIR, noninfectious rhinitis.

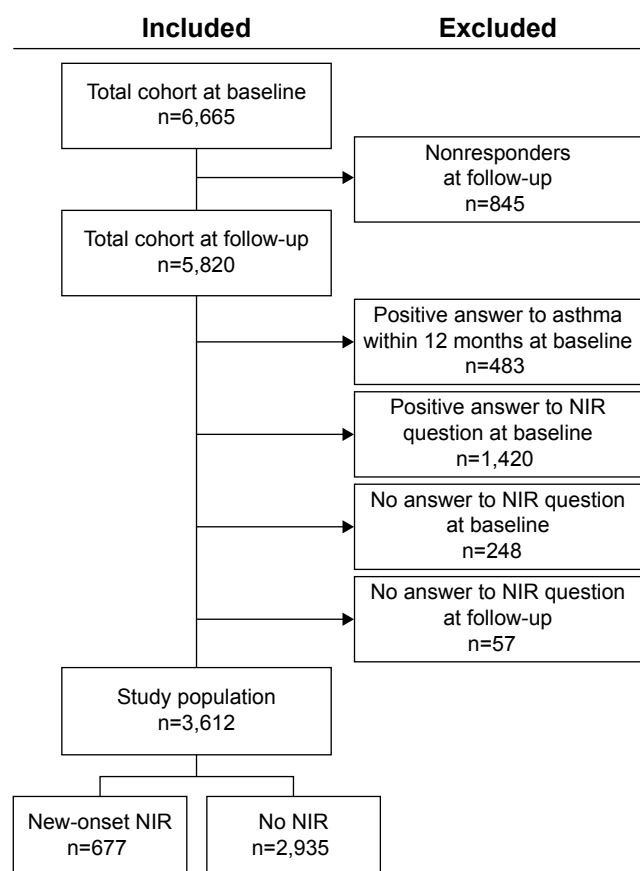


Figure 1 Flow chart of the study population and the subjects excluded.
Abbreviation: NIR, noninfectious rhinitis.

Spirometry was performed with a dry wedge spirometer (Vitalograph, Buckingham, UK). According to the guidelines available at the time of the study,¹⁹ the best of a minimum of three similar maneuvers was used. The ratio of the forced expiratory volume in 1 second (FEV₁) divided by forced vital capacity (FVC) was calculated and a cut-off value for the FEV₁/FVC ratio of <0.7 defined

COPD in accordance with the Global Initiative for Chronic Obstructive Lung Disease guidelines,⁸ apart from the fact that no reversibility test was performed. Spirometry data were available for 93% of the subjects at baseline (n=3,348). FeNO was measured before spirometry using a chemiluminescence analyzer and has been extensively described elsewhere.²⁰ A cut-off value of 50 ppb or more in the exhaled NO concentration was used to indicate a high likelihood of asthma in patients with COPD.²¹ Atopy was defined as a positive Phadiatop® test (Pharmacia, Uppsala, Sweden). Class 0 was regarded as negative and Class 1 as positive (atopic).²² Data on age, gender, and body mass index (BMI) were also collected (Table 2).

Statistics

Analyses were performed with the SAS statistical software version 9.4 (SAS Institute Inc., Cary, NC, USA). Univariate analyses included using *t*-tests and chi-square tests for continuous and categorical variables respectively. A multivariate logistic regression model was used to calculate odds ratios and 95% confidence intervals. *P*-values <0.05 were considered statistically significant.

Results

The comparison between subjects with new-onset NIR and no NIR at follow-up is presented in Table 2. As shown, there was no significant difference in mean age, gender, or BMI. The prevalence of COPD was 8% in the total study population and 9.2% for subjects aged over 40 years. New-onset NIR was significantly associated with COPD (10.8 vs 7.4 *P*=0.005). New-onset NIR was also related to smoking (*P*=0.004) and atopy (*P*<0.001) in the univariate analyses.

In the logistic regression analysis adjusted for age, gender, BMI, COPD, smoking, and atopy, COPD,

Table 2 New-onset of NIR in relation to age, gender, BMI, atopy, COPD, and smoking

Variables	New-onset NIR % (n) 18.7 (677)	No NIR % (n) 81.3 (2,935)	P-value	Total % (n) 100 (3,612)
Mean age, years (SD)	51.9 (11.7)	51.8 (11.5)	0.70	51.8 (11.5)
Female	52.4 (355)	52.5 (1,540)	1	52.5 (1,895)
BMI kg/m ² (SD)	26.1 (4.1)	25.9 (3.8)	0.52	26.0 (3.9)
Atopy	25.8 (170/660)	17.62 (507/2,877)	<0.001	19.1 (677/3,537)
COPD				
All	10.8 (67/620)	7.4 (202/2,728)	0.005	8.0 (269/3,348)
≥40 years	12.1 (63/521)	8.5 (196/2,297)	0.01	9.2 (259/2,818)
Smoking			0.004	
Current smoker	18.8 (127)	15.3 (448)		15.9 (575)
Ex-smoker	38.4 (260)	35.2 (1,032)		35.8 (1,292)
Never smoker	42.8 (290)	49.6 (1,455)		48.3 (1,745)

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; NIR, noninfectious rhinitis; SD, standard deviation.

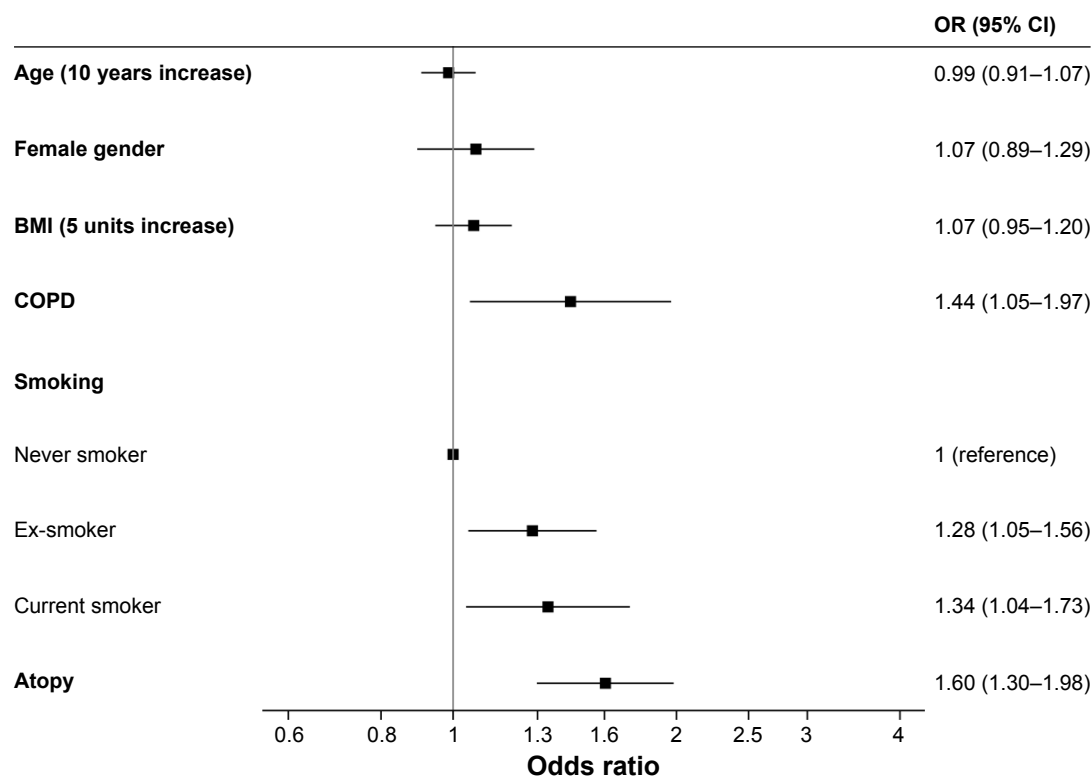


Figure 2 Odds ratios for new-onset NIR in relation to age, gender, BMI, COPD, smoking, and atopy.

Note: Never smoker was used as reference category among the smoking categories.

Abbreviations: BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; NIR, noninfectious rhinitis.

smoking, and atopy remained independently associated with new-onset NIR (Figure 2). The interaction between COPD and smoking in relation to new-onset NIR was calculated and was found to be nonsignificant (data not shown). There was no association between atopy and COPD, indicating a low risk of asthma misclassification (19.1% vs 19.2%, $P=1$). As shown in Figure 3, the vast majority of the subjects with COPD were aged >40 years,

as expected. Only 4.3% (11 of 257 subjects with COPD) displayed a FeNO value >50 ppb, ie, values that indicate the presence of atopy and asthma.

The sub-analysis of occupational exposure to gas, fumes, or dust ($n=2,257$), and educational status ($n=2,256$) introduced in 2005 revealed a significant association with new-onset NIR for gas, fumes, or dust ($P=0.006$) but not for educational status ($P=0.75$) (data not shown).

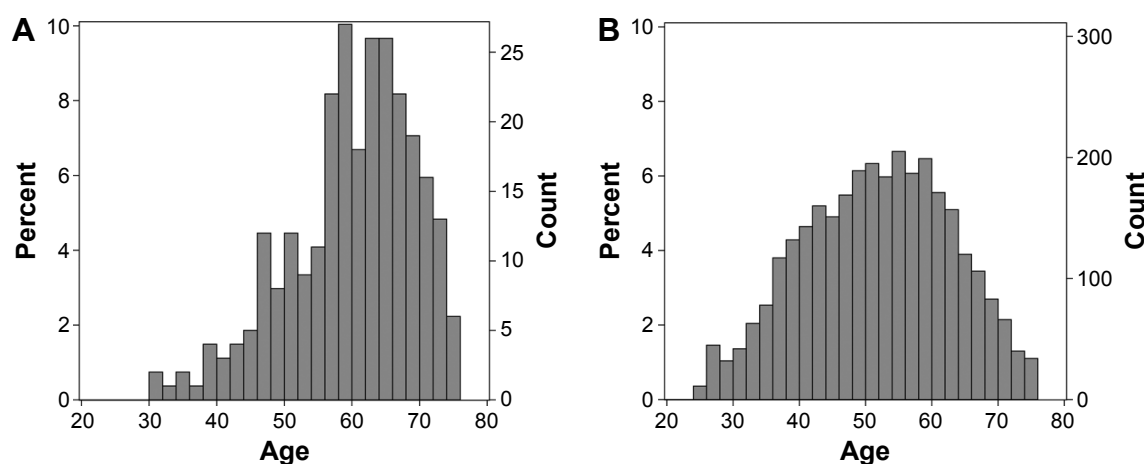


Figure 3 Age distribution when comparing the COPD group (A) and the general population (B).

Abbreviation: COPD, chronic obstructive pulmonary disease.

Discussion

In this longitudinal population-based study of a large cohort, the risk of developing NIR, over a 5-year period increased in individuals with COPD. Smoking and atopy were also risk factors for NIR. The results indicate that there is a link present between upper and lower respiratory inflammation in NIR and COPD, and it is therefore important to assess NIR in patients with COPD.

NIR is identified by the presence of nasal symptoms, but identifying individuals with COPD requires spirometry. The authors are not aware of any previous studies of NIR in COPD, including spirometry data from a large general population sample. In this study, spirometry was performed without bronchodilation according to the standard used at the time. This could have resulted in misclassification between COPD and asthma. In an attempt to minimize the risk of misclassification to eosinophilic inflammation and asthma, all subjects reporting asthma within 12 months at baseline were excluded from the analyses. Also, atopy in subjects with COPD was analyzed and no significant association with COPD was identified. Furthermore, only 4.3% of the subjects in the COPD group had FeNO >50 ppb, which indicates a low prevalence of eosinophilic inflammation in this group. Therefore, the subjects in this study with an FEV₁/FVC of <0.7 are believed to be a representative of COPD.

The prevalence of COPD in this general population sample was 8.8%, which is consistent with previous estimates ranging between 9.4% and 18.8%.^{14–18} The prevalence was also higher in subjects aged ≥40 and above, which is in accordance with other studies of COPD.¹¹

The main finding in this study was that the 5-year cumulative incidence of NIR was higher in the subjects with COPD, both in the univariate analyses and the logistic regression analyses. Smoking and atopy also remained independent risk factors for new-onset NIR in the logistic regression analyses. Although a previous study based on questionnaire data alone has indicated a relationship between rhinitis and COPD in a large population sample, this study adds vital information on lung function that is needed for a COPD diagnosis and confirms that there is a relationship between the two diseases.⁷

Although the study shows a link between upper and lower respiratory inflammation in COPD and NIR, it is important to note that the findings do not imply a causal relationship between COPD and NIR. In spite of this, both diseases share common features that could be of importance for disease development in the airway at different levels. A similar inflammatory response can be elicited in both the upper and

lower airways following exposure to inhaled irritants and sensitizers in the common airstream. Gas, fumes, or dust are regarded as risk factors for COPD,⁹ as well as for NIR.⁶ Individual vulnerability in the airway mucosa to irritants or deficits in systemic inflammatory responses could also explain why COPD and NIR can more commonly be found in the same subjects. The humoral spread of inflammatory mediators via the blood stream to both the upper and lower airways as seen in rhinitis and asthma is another possibility.²³

Tobacco smoke is an airborne irritant that is significantly associated not only with the development of COPD but also with NIR.^{1,11,12,24} In terms of the temporal relationship between the onset of COPD and NIR, it is important to recognize that the airway inflammation in COPD and NIR is likely to develop over time. In the absence of histological specimens from the airway, it is not possible to determine when and where inflammation starts and symptoms may begin later than signs of airway inflammation. Differences in the concentrations to which the upper and lower airways are exposed may also explain different patterns of symptom debut. Tobacco smoke is mainly inhaled through the mouth directly to the lungs and the tobacco load on the nasal mucosa is likely to be lower. To be able to establish plausible common pathophysiological mechanisms, there is therefore a need for clinical studies.

Two possible risk factors for new-onset NIR were analyzed separately, due to their late introduction in the questionnaire that missed a part of the study population, ie, educational status and occupational exposure to gas, fumes, or dust. Educational status was not associated with new-onset NIR, despite having previously been considered to be a risk factor for COPD.²⁵ Occupational exposure to gas, fumes, or dust was not included in the logistic regression due to missing data, but in the sub-analyses it showed an association with new-onset NIR. In developing countries, this is a major risk factor for COPD due to cooking over open fires and it may also be important for NIR, but the exposure in developed countries, such as Sweden, is expected to be low.

The main strength of the present study is its longitudinal population-based design with a large general population, including the availability of spirometry data for 93% of the subjects. It is, however, also important to consider the limitations of this study. NIR includes several phenotypes of rhinitis, both allergic and nonallergic, as well as chronic rhinosinusitis. As a result, the NIR question does not enable us to link COPD to a specific phenotype of rhinitis. The interval of 5 years in the follow-up questionnaire may have introduced recall bias when answering the NIR question.

Furthermore, this epidemiological study did not include a clinical assessment of COPD by a doctor and therefore have no information on the severity of the disease. The COPD definition that was used may also have introduced misclassification to other lower airway diseases showing a similar spirometry pattern, but, as previously discussed, the risk of including asthmatics in this study was minimized.

There is an established inflammatory link between asthma and rhinitis, which many regard as the concept of generalized airway inflammation – “the united airways”, helping to define and understand the disease.³ This study provides new evidence linking NIR to COPD, supported by the fact that both diseases involve inflammation of the airway mucosa and that they share common risk factors, such as exposure to tobacco smoke and cooking fumes. In contrast to the link between allergic rhinitis and asthma, the authors are aware of no common inflammatory pathway in COPD and NIR, such as the allergic inflammation that could explain the coexistence of the two diseases. To be able to confirm a pathophysiological relationship, further studies are needed, but the present study shows that COPD should be regarded as a co-factor in the development of NIR.

The link between NIR and COPD also suggest that the diagnosis and treatment of the two diseases in the same patient could be of importance for patient outcome in terms of early diagnosis, disease control, and patient satisfaction, which has to be addressed further.

Conclusion

This longitudinal population-based study of a large cohort shows that COPD is a risk factor for developing NIR. Smoking and atopy are also risk factors for NIR. The results indicate that there is a link present between upper and lower respiratory inflammation in NIR and COPD.

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Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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