

Original article

Rhinitis is an independent risk factor for developing cough apart from colds among adults

Background: In cross-sectional clinical studies, rhinitis has been shown to be strongly associated with co-existing chronic cough. However, to date, this association has been poorly delineated from a prospective and epidemiological standpoint.

Methods: We used data from the 'Pisa Prospective Study', a population-based longitudinal cohort study composed of a baseline and a follow-up survey taken approximately 5 years apart from each other. Information on cough, rhinitis, and other risk factors was collected by standardized questionnaire. Cough apart from colds was defined as either 'chronic' (most days for at least 3 months for at least two consecutive years) or 'occasional' (if the three above temporal conditions were not met). 'Any' cough was defined as the presence of either occasional or chronic cough.

Results: Complete information was available for 1670 subjects who were ≥ 15 years old and had no positive history of cough apart from colds at the baseline survey. Among them, 299 (18%) had rhinitis at baseline. By the follow-up survey, 16% of the subjects with rhinitis had developed any cough apart from colds, as compared with only 10% of the subjects without rhinitis (OR 1.7, 95% CI 1.2–2.5, $P < 0.005$). After adjustment for age, gender, asthma status, smoking, and occupational exposure, rhinitis remained significantly associated with an increased risk both for any cough (OR 1.8, 95% CI 1.2–2.6) and for occasional and chronic cough separately (OR 2.2, 95% CI 1.1–4.5, and OR 1.7, 95% CI 1.1–2.6, respectively).

Conclusions: Rhinitis is a significant and independent risk factor for developing cough among adults. Further research is needed to assess potential implications in terms of prevention.

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Cough is a common health complaint among children and adults. Figures on cough prevalence in the general population may vary considerably between studies not only for geographical and temporal reasons, but also because of different definitions of chronic or habitual cough. In the Tucson Epidemiological Study of Airways Obstructive Disease, about 17% of the participants (mean age: 45 years) reported the presence of chronic cough (i.e. cough present most days for at least 3 months in at least two consecutive years) (1). Most cases were found among smokers. European studies have reported somewhat lower figures for habitual cough. Recently, two reports from the European Community Respiratory Health Survey have estimated the prevalence of habitual productive and nonproductive cough to be between 8 and 11% in 20–44-year-old subjects (2, 3).

Chronic cough is part of the clinical definition of chronic bronchitis (4, 5) and, as such, is strongly associated with cigarette smoking. However, most

smokers readily recognize tobacco as the cause of their cough and only rarely seek medical advice for it (6). Consequently, the vast majority of cases presenting with long-term cough in the clinical setting recognize at least one of the three conditions included in the so-called 'pathogenic triad' (7): rhinitis, asthma, and gastro-oesophageal reflux. Among these causes, the association of cough with rhinitis is the most poorly delineated (8).

Most studies investigating the causes of chronic cough have used outpatient cohorts (7, 9–16). In these studies, patients who present with chronic cough to specialist clinics are investigated in relation to the presence of concomitant conditions, such as rhinitis, asthma, gastro-oesophageal reflux, and others. These studies hold particular interest from a clinical point of view, but they have severe limitations from an epidemiological standpoint. First, because the study populations are represented by patients reporting to clinics, their findings are hardly generalizable at the population level. For example,

if smokers are less likely than nonsmokers to go to the doctor for their cough, the magnitude of the association between cigarette smoking and cough is likely to be underestimated in such studies. Secondly, most clinical studies are cross-sectional in nature. Therefore, they cannot resolve the temporal relationship between the presence of cough and any of its potential causes. This limitation may have little impact on the therapeutic implications of these studies, but it affects significantly the conclusions that can be drawn in terms of risk factors and primary prevention of cough. Prospective data on cough-free subjects are required to determine whether related conditions, such as rhinitis, do precede temporally the onset of cough and to what extent they increase the risk of developing subsequent cough at the population level.

In the present study, using a large population-based prospective cohort, we sought (i) to identify a profile of risk factors for developing cough apart from colds in adults and (ii) to determine whether and to what extent rhinitis increases the risk for occasional and chronic cough, independent of other related factors.

Materials and methods

Study population

The study population comes from the Pisa Prospective Study, a large population-based longitudinal cohort study. Details of the study design and enrollment process have been reported elsewhere (17, 18). Briefly, in 1985–88, a sample of 5019 subjects from the general population were contacted for potential enrollment in the study. Among them, 3865 (77%) accepted to participate (baseline survey) and completed a standardized respiratory questionnaire. In 1991–93, participants were re-contacted for taking part in a follow-up survey. In addition to completing the questionnaire, during the follow-up survey subjects underwent skin-prick tests and spirometric tests with methacholine bronchial challenge. They also had a blood sample taken for IgE level measurements.

Questionnaire information

A modified National Heart, Blood, and Lung Institute (NHBLI) questionnaire was developed by the Consiglio Nazionale delle Ricerche (CNR) Special Project on chronic obstructive lung disease (CNR questionnaire). It contains more than 70 questions regarding respiratory symptoms, diseases and risk factors, described elsewhere (18). In the present study, rhinitis was coded as 'positive' if the subject reported hay fever or any other condition that made his/her nose runny or stuffy apart from colds. Rhinitis was coded as 'persistent' if it was positive in both the baseline and the follow-up survey. If rhinitis was positive at one of the surveys (either baseline or follow-up) but negative at the other survey, it was coded as 'inconsistent'. Asthma was defined as the positive report of a physician-confirmed diagnosis. Cough apart from colds was defined as either 'chronic' (most days for at least 3 months for at least two consecutive years) or 'occasional' (if the above three temporal conditions were not met). 'Any' cough was defined as the presence of either occasional or chronic cough. A positive history of occupational exposure was also assessed and was defined as the exposure in the workplace to any dust or gas or chemicals from a list of

potentially noxious substances for at least 5 years during the subject's lifetime (19).

Atopy and IgE levels

Skin-prick tests for the most common aeroallergens (house-dust mites – *Dermatophagoides pteronyssinus* and *D. farinae*; pollens – *Parietaria officinalis*, Graminaceae mix, *Olea europea*, and Compositae mix; moulds – *Alternaria tenuis* and *Aspergillus fumigatus*; animal danders – cat, dog, and horse) in the Pisa area were performed at the follow-up survey. Positive (histamine 10 mg/ml) and negative (saline solution) controls were included. Atopy was defined as having skin tests positive for at least one allergen (wheal maximal diameter at least 3 mm greater than that of the negative control). Blood was drawn at the time of the follow-up survey. Total serum IgE were measured with the Pharmacia Phadebas PRIST assay (Pharmacia Diagnostic Aktiebolag, Uppsala, Sweden).

Methacholine bronchial challenge test

The protocol used to perform the methacholine challenge test, which was the same as the one used in the other epidemiological survey conducted by our group in the Po Delta area (north Italy), has been described elsewhere in detail (20). Briefly, progressively increasing doses of methacholine were administered up to the maximal methacholine dose of 4.8 mg or when the % fall of forced expiratory volume in 1 s (FEV₁), compared with the postsaline value, was larger than 20%. Results of methacholine challenge test were expressed using the slope of the dose–response curve, as suggested by O'Connor et al. (21), in which the percent decrement in FEV₁ was divided by cumulative dose (mg). Given their skewed distribution, slope values were transformed in natural logarithm (ln SLOPE) and a constant (2.3) was added to allow ln transformation of negative and zero values.

Statistical analyses

Comparisons between groups were performed using *t*-test for continuous variables and chi-squared test for categorical variables. Values of IgE were log-transformed because of the right-skewness of their distribution. IgE levels and values of methacholine dose–response slope were also categorized as the highest tertile vs the other two tertiles combined. The association between potential risk factors and development of any, occasional and chronic cough was expressed as odds ratios (OR) with 95% confidence intervals (CI). Risk factors for any cough were tested for potential confounding using logistic regression models. Multinomial logistic regression models were used to compute the adjusted OR associated with each independent risk factor for predicting occasional and chronic cough, separately. In order to include individuals with missing data, in the multifactorial analysis a missing category was created for categorical variables. The adjusted OR for the association between rhinitis and any cough were also converted to corrected Relative Risks (RR), as described by Zhang and Yu (22), in order to provide a better estimate of the risk for development of cough associated with the presence of rhinitis at baseline.

Results

Among the 3865 participants in the baseline survey, 3435 (88.9%) were at least 15 years old at enrollment. Of these,

564 (16.4%) reported current or past episodes of cough apart from colds at baseline and were excluded from the analyses. We also excluded one subject with missing information on the presence of cough at baseline.

Among the remaining 2870 subjects, 1670 (58.2%) completed the follow-up survey. When compared with men, women were more likely to complete the follow-up survey (54.4% vs 61.0%; $P = 0.0004$). Moreover, mean age and prevalence rates of rhinitis at baseline were higher among subjects who attended the follow-up survey than among those lost to follow-up (47.8 vs 46.1 years, $P = 0.02$ and 17.9% vs 14.6%, $P = 0.02$, respectively). Approximately 19% of the subjects who attended both surveys had more than 8 years of formal education compared with 22% of the subjects lost to follow-up ($P = 0.05$). No significant differences between subjects lost to follow-up and those attending the follow-up survey were found in relation to smoking status, or history for physician-confirmed asthma.

Among the 1670 subjects who completed both the baseline and the follow-up survey, 299 (17.9%) had rhinitis at baseline. In Table 1, subjects with and without rhinitis at baseline are compared. When compared with subjects with no rhinitis, subjects with rhinitis were younger and tended to have more years of education. They were also more likely to have co-existing asthma, positive skin-prick tests, and higher methacholine Ln SLOPE at the follow-up survey. Although the distribution by smoking status was not significantly different between subjects with and without rhinitis, smokers with rhinitis tended to be less frequently current smokers and

had, on average, less pack-years than did smokers without rhinitis.

In Table 2, the proportion of subjects developing occasional and chronic cough by the follow-up survey is shown in relation to different demographic and clinical characteristics. Rhinitis and ever smoking at baseline were the only two risk factors significantly associated with both occasional and chronic cough.

More than 16% of subjects with rhinitis at baseline developed any cough apart from colds by the follow-up survey, when compared with 10% of subjects with no rhinitis. As expected, a positive history for occupational exposure and a physician-confirmed diagnosis of asthma at baseline were also significantly associated with the development of chronic cough. Subjects with cough showed a higher methacholine Ln SLOPE at the follow-up survey than those with no cough.

There appeared to be a dose-response relationship between persistence of rhinitis and the risk of developing cough. The proportion of subjects developing cough by the follow-up survey increased across the groups of subjects with no rhinitis, inconsistent rhinitis, and persistent rhinitis (9.7, 13.8 and 16.4%, respectively; test for trend: $P = 0.002$). When compared with subjects with no rhinitis, the corresponding OR for the association with cough were 1.49 (1.00–2.22) for subjects with inconsistent rhinitis, but up to 1.82 (1.18–2.82) for subjects with persistent rhinitis.

In Fig. 1, the crude ORs for the association between rhinitis at baseline and development of any cough during the follow-up period are shown stratified across different demographic and clinical variables. The association between rhinitis and cough appeared stronger among women than among men, but the test for homogeneity did not reach statistical significance ($P = 0.176$). In relation to the other strata, with the only exception of former smokers, the OR for the association between rhinitis and cough appeared quite homogeneous, although only borderline significance was reached in the groups with limited sample size, suggesting that rhinitis is a risk factor for developing cough among adults, regardless of age, smoking, atopy and asthma status.

Results of the multifactorial analyses are shown in Table 3. Because only 624 of the 1670 subjects (37%) underwent methacholine challenge test, bronchial responsiveness could not be tested in the multifactorial model for sample size reasons, although it was significantly associated with cough in the univariate analysis. Rhinitis and current smoking at baseline were independently associated with developing any, occasional and chronic cough by the follow-up survey. Age and asthma were significant predictors of any and chronic cough. Despite the nonsignificant ORs, gender was included in the models in order to control for potential confounding. Occupational exposure was borderline associated with any cough, although it did not reach statistical significance for predicting separately

Table 1. Comparison between subjects with and without rhinitis in the baseline survey

	With rhinitis (<i>n</i> = 299)	Without rhinitis (<i>n</i> = 1371)	<i>P</i> -value
Gender	37.1	40.7	0.253
(male) (%)			
Age in years (mean $\pm$ SEM)	45.6 $\pm$ 0.9	48.2 $\pm$ 0.5	0.019
Education (>8 years) (%)	23.1	18.3	0.058
Smoking (%)			
Never	54.5	53.0	0.108
Former	24.7	21.0	
Current	20.7	26.0	
Pack-years (<i>n</i> = 689)* (mean $\pm$ SEM)	14.2 $\pm$ 1.3	18.8 $\pm$ 0.7	0.009
Occupational exposure ($\geq$ 5 years) (%)	34.8	33.8	0.756
Physician-confirmed asthma (<i>n</i> = 1653) (%)	12.5	3.5	<0.0001
Positive Skin Prick tests (<i>n</i> = 1252)† (%)	48.8	26.5	<0.0001
IgE levels in IU/ml (<i>n</i> = 1126)† [geom. mean (95% CI)]	36.5 (30–44)	23.2 (21–25)	<0.0001
Ln SLOPE (<i>n</i> = 624)† (mean $\pm$ SEM)	2.56 $\pm$ 0.12	2.30 $\pm$ 0.04	0.016

n = 1670, unless indicated otherwise.

*Computed only among smokers.

†Measured at follow-up survey.

Table 2. Proportion of subjects developing occasional and chronic cough by the follow-up survey across groups with different demographic and clinical characteristics

	No cough at follow-up survey [% (n)]	Any cough at follow-up survey†	
		Occasional [% (n)]	Chronic [% (n)]
Rhinitis at baseline survey			
No	90.0 (1234)	2.0 (27)	8.0 (110)
Yes	83.9 (251)	4.0 (12)	12.0 (36)
OR (95% CI)		2.18 (1.09–4.37)*	1.61 (1.08–2.40)*
OR (95% CI) for any cough		1.72 (1.21–2.46)***	
Gender			
Female	89.2 (893)	2.5 (25)	8.3 (83)
Male	88.5 (592)	2.1 (14)	9.4 (63)
OR (95% CI)		0.84 (0.44–1.64)	1.14 (0.81–1.61)
OR (95% CI) for any cough		1.07 (0.79–1.47)	
Smoking at baseline survey			
Never	91.3 (812)	1.7 (15)	7.0 (62)
Ever	86.2 (673)	3.1 (24)	10.8 (84)
OR (95% CI)		1.93 (1.01–3.71)*	1.63 (1.16–2.30)***
OR (95% CI) for any cough		1.69 (1.24–2.31)****	
Occupational exposure at baseline survey			
No	90.4 (996)	2.2 (24)	7.4 (82)
Yes	86.1 (489)	2.6 (15)	11.3 (64)
OR (95% CI)		1.27 (0.66–2.45)	1.59 (1.13–2.24)**
OR (95% CI) for any cough		1.52 (1.11–2.07)**	
Physician-confirmed asthma at baseline survey			
No	89.5 (1405)	2.3 (36)	8.2 (128)
Yes	75.0 (63)	3.6 (3)	21.4 (18)
OR (95% CI)		1.86 (0.56–6.20)	3.14 (1.80–5.46)****
OR (95% CI) for any cough		2.86 (1.70–4.80)****	
Skin-prick tests at follow-up survey			
Negative	88.7 (769)	2.4 (21)	8.9 (77)
Positive	89.4 (344)	3.4 (13)	7.3 (28)
OR (95% CI)		1.38 (0.68–2.80)	0.81 (0.52–1.28)
OR (95% CI) for any cough		0.93 (0.64–1.38)	
IgE levels at follow-up survey			
Two lower tertiles	89.7 (674)	2.7 (19)	7.9 (58)
Highest tertile	89.3 (335)	3.5 (12)	7.7 (28)
OR (95% CI)		1.27 (0.61–2.65)	0.97 (0.61–1.55)
OR (95% CI) for any cough		1.04 (0.70–1.56)	
Methacholine dose–response slope at follow-up survey			
Two lower tertiles	93.5 (389)	2.5 (10)	4.2 (17)
Highest tertile	88.0 (183)	3.2 (6)	9.4 (19)
OR (95% CI)		1.27 (0.46–3.56)	2.38 (1.21–4.68)*
OR (95% CI) for any cough		1.97 (1.11–3.49)*	

Crude ORs are shown for occasional and chronic cough separately as well as for any cough.

†Any cough is occasional plus chronic cough combined.

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.005$; **** $P < 0.001$.

occasional and chronic cough in the multinomial logistic regression analysis. Of note, after selecting only subjects with no asthma at baseline, the adjusted ORs associated with rhinitis did not change relevantly for predicting any (OR 1.67, 95% CI 1.11–2.52), occasional (OR 2.16, 95% CI 1.01–4.59), and chronic (OR 1.57, 95% CI 0.98–2.49) cough. By converting the adjusted OR to corrected RR, we found subjects with rhinitis to have a 63% increased risk of developing cough in the total study population and a 57%

increased risk of developing cough in the study population with no asthma.

Discussion

In this study, using a large prospective population-based cohort, we provide evidence that rhinitis is an independent risk factor for developing cough apart from colds

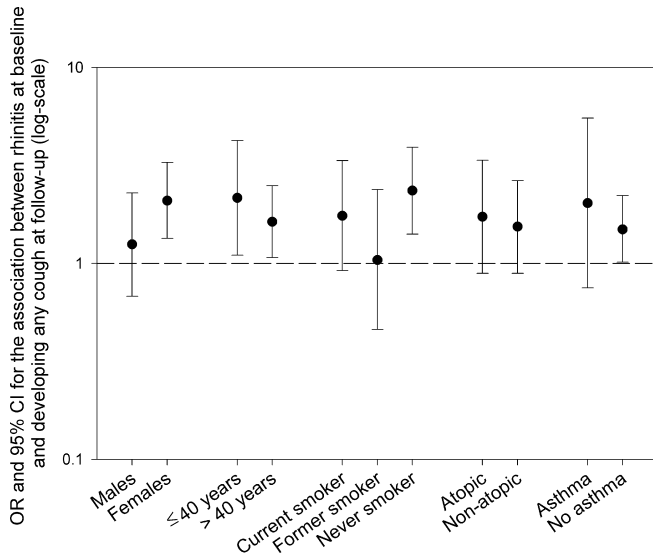


Figure 1. Crude OR and 95% CIs for the association between rhinitis at baseline and developing any cough by the follow-up survey stratified by different demographic and clinical variables. Cumulative OR and 95% CI: 1.72 (1.21–2.46).

among adults. The effect of rhinitis on subsequent cough was independent of gender, age, asthma, smoking and occupational exposure and it appeared to be present homogeneously both among nonsmokers and current smokers, asthmatics and nonasthmatics, atopic and nonatopic subjects.

Rhinitis increased the risk for developing both occasional and chronic cough. However, a word of caution should be spent about terminology. We defined 'chronic' cough based on the temporal requirements used for the clinical definition of chronic bronchitis (most days for at least 3 months for at least two consecutive years) (4, 5). Most clinical studies have used a less stringent criterion for defining chronic cough [i.e. cough lasting more than 3 weeks (23) or more than 8 weeks (24)]. This means that a significant proportion of our occasional cough cases

might have been classified as chronic cough if the latter temporal criteria were used.

A large number of previous studies have investigated the causes of chronic cough in the clinical setting (7, 9–16). Palombini et al. (7) studied 78 nonsmoking adults who complained of cough for more than 3 weeks and found that the vast majority of cases were due to postnasal drip, asthma, gastro-oesophageal reflux, or a combination of these three conditions. This 'pathogenic triad' has emerged from other clinical studies too. Irwin et al. (9), utilizing a systematic diagnostic protocol, were able to determine the causes of cough in 101 of 102 consecutive patients complaining of chronic cough. Postnasal drip syndrome was a cause 41% of the time, asthma 24%, gastro-oesophageal reflux (GER) 21%. These findings were mirrored in a study by Mello et al. (10), in which these three conditions accounted for 90% of chronic cough cases among 88 consecutive outpatients.

Previous epidemiological studies have measured the prevalence and determinants of cough in the general population. These findings are relatively insensitive to the selection bias that is intrinsically present in studies conducted on outpatient populations. In a recent report, using cross-sectional data from the multi-center European Community Respiratory Health Survey (ECRHS), Janson et al. (2) found a 10.2% median prevalence of productive and nonproductive cough. This study confirmed the association of cough with both rhinitis and asthma. Tobacco smoke and environmental tobacco smoke were also strongly associated with productive and nonproductive cough. In the study by Janson et al. (2) as well as in a previous report from the Swedish part of the ECRHS (3), nonproductive cough was also associated with female gender. We did not find gender to affect the risk for cough in our study, but findings are difficult to compare as we made no distinction between productive and nonproductive cough.

In the present study, by using prospective data, we were able to resolve the temporal relationship between risk factors and development of new cough and to estimate

Table 3. Results from multifactorial analysis ($n = 1653$)

	Logistic regression model	Multinomial logistic regression model	
	Any cough [OR (95% CI)]	Occasional cough [OR (95% CI)]	Chronic cough [OR (95% CI)]
Rhinitis at baseline survey	1.77 (1.22–2.58)	2.20 (1.07–4.50)	1.68 (1.10–2.56)
Gender (male)	0.87 (0.60–1.26)	0.73 (0.36–1.49)	1.03 (0.69–1.54)
Age at baseline (OR associated with 10-year increase)	1.26 (1.14–1.40)	1.00 (0.82–1.22)	1.36 (1.22–1.51)
Asthma at baseline survey	2.95 (1.71–5.09)	1.66 (0.48–5.73)	3.38 (1.89–6.06)
Smoking at baseline survey†			
Former	1.20 (0.76–1.91)	1.12 (0.41–3.07)	1.23 (0.74–2.04)
Current	2.67 (1.81–3.94)	3.22 (1.55–6.69)	2.55 (1.64–3.96)
Occupational exposure at baseline	1.33 (0.95–1.87)	*	*

*Variable was dropped, because it was not significant in the multinomial logistic regression model.

†Never smoker is the reference group.

Adjusted OR (with 95% CI) associated with potential predictors are shown for the development of any cough (logistic regression model) and occasional/chronic cough (multinomial logistic regression model). In addition to gender, variables were retained in the models at the $\alpha = 0.1$ level.

the increase in risk for cough associated with specific risk factors. We found that rhinitis was associated with a significant 63% increased risk of developing cough in the general population. Because rhinitis is a well-known independent risk factor for asthma (25–27), it is possible that the association between rhinitis and cough is at least partly due to the presence of subclinical asthma. We acknowledge that it is difficult to rule out this possibility based solely on epidemiological data, but our findings appear to argue against it. The ORs for the association between rhinitis and subsequent cough remained virtually unchanged after adjusting for potential confounders, including asthma. More importantly, rhinitis was homogeneously associated with an increased risk for cough among subjects with and without asthma and the same trend appeared to be present among subjects with and without the asthma-related phenotype of positive skin-prick tests.

However, it is possible that the same causal mechanisms that have been hypothesized for the link between rhinitis and asthma (28) are involved in the association between rhinitis and cough too. In this scenario, the co-existence of other environmental and genetic factors will then determine which subjects with rhinitis will go on to develop chronic cough, asthma, or both. Postnasal drip of inflammatory cells and mediators is probably the most likely mechanism to explain the link between rhinitis and cough (6), but the nasal-bronchial reflex might play an important role too (29). An indirect effect of nasal obstruction on lower airways is also possible, as mouth breathing might reduce filtration, humidification and warming of the inhaled air.

Regardless of the underlying mechanisms, there is convincing evidence that the treatment of co-existing rhinitis symptoms is beneficial to chronic cough (24). Our findings provide new longitudinal evidence for a strong effect of rhinitis on the risk of subsequent cough and might have implications in terms of primary prevention of chronic cough. It has already been hypothesized that the treatment of rhinitis can be beneficial against the onset of

asthma (25). These findings suggest that an integrated therapeutic approach of rhinitis in the long-term may be beneficial against other lower airway conditions, including chronic cough, and may have a significant impact in reducing the public health burden associated with both respiratory diseases. Randomized clinical trials will be required to test whether and to what extent this hypothesis is true.

Our study has several limitations. Information on atopy-related markers, including skin-prick tests and IgE levels, was not available at the baseline survey. Therefore, we could not investigate the temporal relationship between these factors and subsequent cough. Similarly, bronchial hyperresponsiveness was measured only at the follow-up survey in less than 38% of our study population and, therefore, we could not test it in the multifactorial analysis, despite its potential clinical interest. Finally, although we found an association between persistence of rhinitis symptoms and risk for new cough, we could not test a dose–response relationship based on severity of rhinitis, as no severity score was available from the questionnaire.

In conclusion, this study provides new epidemiological data on the association between rhinitis and incident cough by using a large prospective cohort. We found rhinitis to be a significant and independent risk factor for developing occasional and chronic cough among adults. This association satisfied several epidemiological criteria for causality, including a consistent temporal relationship between exposure and outcome, elevated magnitude of the association, and existence of a dose–response relationship. Furthermore, the effect of rhinitis on incident cough was independent of other known risk factors for cough, including age, smoking, asthma, and occupational exposure. These findings suggest that not only should the assessment of upper airway disease be included in diagnostic protocols for chronic cough, but also that a systematic therapeutic approach of rhinitis might have important implications in terms of prevention of lower airway diseases and symptoms.

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