

The Heterogeneity Hidden in Allergic Rhinitis and Its Impact on Co-Existing Asthma in Adults: A Population-Based Survey

Leonardo Antonicelli^a Pierpaolo Marchetti^g Simone Accordini^g
Roberto Bono^b Aurelia Carosso^c Lucio Casali^d Lucia Cazzoletti^g
Angelo Corsico^j Marcello Ferrari^h Alessandro Fois^e Gabriele Nicolini^f
Mario Olivieriⁱ Pietro Pirina^e Giuseppe Verlato^g Simona Villani^k
Roberto de Marco^g

^aAllergy Unit, Department of Internal Medicine, Azienda Ospedaliero-Universitaria Ospedali Riuniti, Ancona,
^bDepartment of Public Health and Microbiology, University of Turin, and ^cUnit of Pneumology, National Local Health – ASL TO2, Turin, ^dUniversity of Perugia, Perugia, ^eInstitute of Respiratory Diseases, University of Sassari, Sassari, ^fGlobal Clinical Development, Chiesi Farmaceutici, Parma, ^gDepartment of Public Health and Community Medicine, Unit of Epidemiology and Medical Statistics, and ^hUnit of Internal Medicine, University of Verona, and ⁱUnit of Occupational Medicine, University Hospital of Verona, Verona, and Departments of ^jMolecular Medicine and ^kPublic Health, Experimental and Forensic Medicine, Unit of Biostatistics and Clinical Epidemiology, University of Pavia, Pavia, Italy

Key Words

Allergic rhinitis · Sinusitis · Polyposis · Asthma

Abstract

Background: It has been suggested that there is some overlap between allergic rhinitis (AR), sinusitis and polyposis, but this has not been fully documented. The present study aimed to evaluate the prevalence of these co-existing diseases and their impact on bronchial asthma in the general population of Italy. **Methods:** Within the frame of the multicentre Gene Environment Interactions in Respiratory Diseases (GEIRD) study, a postal screening questionnaire including questions about self-reported symptoms of asthma, AR, AR with sinusitis without nasal polyps (AR + SsNP) and AR with sinusitis with nasal polyps (AR + SwNP) was administered. Random samples of subjects aged between 20 and 44 years (n = 5,162) answered the postal questionnaire in 4 Italian

centres (Pavia, Sassari, Turin, Verona). In AR subjects, the association among AR only, AR + SsNP, AR + SwNP and bronchial asthma was estimated by the relative risk ratio (RRR) using multinomial regression models. **Results:** The prevalence of AR in the sample was 25.4% (95% CI 24.2–26.6). A self-reported diagnosis of AR + SsNP and AR + SwNP was reported by 5.7% (95% CI 5.0–6.3) and by 1.2% (95% CI 0.9–1.5) of the subjects, respectively. Current asthma was reported by 17.5% of the AR subjects. In the adjusted multivariate analysis, the risk of having current asthma (RRR = 2.31, 95% CI 1.29–4.15), of having at least 1 asthma attack per year (RRR = 2.30, 95% CI 1.19–4.46) and of having had an emergency department admission for respiratory diseases (RRR = 5.61, 95% CI 1.81–23.92) was higher for subjects with AR + SwNP than subjects with AR only. **Conclusions:** The diagnosis of AR in the epidemiological setting includes heterogeneous upper airway diseases that affect the clinical features of AR and its interactions with asthma. © 2016 S. Karger AG, Basel

Introduction

Allergic rhinitis (AR) is the most common immunological disease and its prevalence is continuously increasing, in particular in Western countries [1–3]. This not only affects the burden of the disease on patients [1–5], but also has an impact on bronchial asthma and subsequently leads to increased health care costs [1, 6].

In epidemiology, validated questionnaires are used for the diagnosis of AR. An Italian study showed that the reliability of the question regarding AR seems adequate for epidemiological purposes, but about 20% of the subjects who responded positively to this question had had a negative skin prick test or specific IgE levels [7]. Studies focusing on the non-allergic upper airway diseases (such as chronic rhinitis and rhinosinusitis, with and without nasal polyps, NP) showed the importance of the association between these diseases and severe/not controlled asthma, suggesting that these upper airway diseases have a greater impact on asthma than allergy [8–12].

The overlap between allergic and non-allergic upper airways diseases has been discussed in clinical studies, but its epidemiological results remain controversial and poorly defined [13–15]. This study aimed to evaluate the prevalence of AR, AR with sinusitis without NP (AR + SsNP) and AR with sinusitis with NP (AR + SwNP), and investigate whether the interaction between AR and bronchial asthma is affected by concomitant upper airway diseases.

Materials and Methods

The Gene Environment Interactions in Respiratory Diseases (GEIRD; see Appendix) study was a multicentre survey on respiratory health in the general adult population, carried out between 2007 and 2010. In the frame of this study, random samples of about 3,000 subjects from the general population aged 20–44 years (male:female ratio = 1:1) were selected from the registry of the local health authority in each of the four Italian centres of Pavia, Sassari, Turin and Verona [16].

A screening questionnaire on respiratory symptoms was administered to eligible subjects by mail, sent up to three times in cases of non-response, and once by phone for subjects who did not respond by mail. The GEIRD screening questionnaire (available at www.geird.org) is a modified version of questionnaires used in previous studies [17]. It includes self-reported information about respiratory symptoms (asthma, rhinitis and chronic bronchitis, cough and phlegm), environmental exposures (smoking habits) and education level as a proxy of socio-economic status.

Definitions and Conditions

The presence of AR was based on the answer to the question: 'Do you have any nasal allergies including hay fever?' Subjects

who answered 'yes' were classified as subjects with AR and those who answered 'no' were classified as a subject without AR.

AR subjects were further classified as follows:

- AR only: subjects with AR but without sinusitis or NP;
- AR + SsNP: subjects with AR and who also answered 'yes' to the question: 'Do you suffer from sinusitis?';
- AR + SwNP: subjects with AR and sinusitis and who also answered 'yes' to the question: 'Do you suffer from nasal polyps?'. The presence of asthma was defined as:
 - physician-diagnosed asthma if the subject answered 'yes' to both of the following questions: 'Have you ever had asthma?' and 'Was this confirmed by a doctor?';
 - current asthma if the subject had physician-diagnosed asthma and took any medicine for asthma and had had an attack of asthma or experienced at least one among the following asthma-like symptoms: wheezing, chest tightness or shortness of breath in the last 12 months.

We used the following as indicators of asthma severity/control:

- the number of asthma attacks reported by the subject in the last 12 months, classified as: 'at least 1 asthma attack' and '>3 asthma attacks';
- the presence of the asthma-chronic obstructive pulmonary disease (COPD) overlap syndrome, when a subject with current asthma answered 'yes' to the following question: 'Have you ever been told by a doctor that you have or had chronic bronchitis, COPD or emphysema?'
- the intake of drugs for rhinitis and asthma based on the answers to the following questions: 'Have you used any medicine for asthma in the last 12 months (including inhalers, aerosols or tablets)?' and 'Have you used any medicine for rhinitis in the last 12 months (including inhalers, aerosols or tablets)?' A four-level variable was computed to evaluate which type of drugs a subject used: 'no medicine' if a subject answered 'no' to both questions; 'only asthma medicine' if a subjects took medicine for asthma and had not taken medicine for rhinitis in the last 12 months; 'only rhinitis medicine' if a subjects took medicine for rhinitis and had not taken medicine for asthma in the last 12 months, and 'both' if a subject had taken medicine for both rhinitis and for asthma in the last 12 months.

The presence of chronic cough and phlegm was assessed by a positive answer to the question: 'Have you had coughing and phlegm on most days for a minimum of 3 months a year and for at least 2 successive years?' Also, a subject was recorded as having been to an Emergency Department (ED) for respiratory diseases if he/she answered 'yes' to both of the following questions: 'In the past 3 months have you been to an Emergency Department for any reason, excluding accidents and injuries?' and 'Was it due to respiratory problems?'

Confounders

The potential confounders considered in the analysis were: gender, age (<30, 30–39, ≥40 years), smoking habits (never smoker, ex-smoker, current smoker), level of education (primary and lower secondary school, upper secondary school, degree) and the season of response (spring, summer, autumn, winter). In addition, the type of contact (mail, phone), percentile rank of cumulative response and centre were included as design confounders in the analysis.

Table 1. Number of responders, response rate and prevalence of AR (with 95% CI) for each participating centre

Centres	Participating subjects ¹ , n	Prevalence (95% CI)			
		AR overall	AR only	AR + SsNP	AR + SwNP
Verona	1,746 (67.7)	24.4 (22.4–26.5)	17.8 (16.0–19.6)	5.5 (4.5–6.8)	1.1 (0.7–1.7)
Pavia	966 (37.1)	25.0 (22.2–27.8)	18.7 (16.3–21.3)	5.2 (3.9–6.8)	1.0 (0.5–8.3)
Turin	1,205 (54.6)	27.0 (24.4–29.6)	21.0 (18.7–23.5)	5.0 (3.8–6.4)	0.9 (0.5–1.7)
Sassari	1,245 (53.0)	25.7 (23.2–28.2)	17.2 (15.2–19.4)	6.7 (5.4–8.3)	1.7 (1.1–2.6)
Overall	5,162 (53.0)	25.4 (24.2–26.6)	18.6 (17.5–19.7)	5.7 (5.0–6.3)	1.2 (0.9–1.5)

¹ Response rate (%).**Table 2.** Characteristics of subjects stratified by presence of AR and different phenotypes for subjects with AR

Variables	Without AR (n = 3,795)	AR overall (n = 1,294)	p	Subjects with AR			
				AR only (n = 945)	AR + SsNP (n = 288)	AR + SwNP (n = 61)	p
Gender, %							
Female	53.5	53.6	0.93	51.8	63.5	36.1	<0.001
Age, %			0.041				0.516
<30 years	26.2	29.7		30.4	29.5	19.7	
30–39 years	43.8	42.6		42.0	43.4	49.2	
≥40 years	30.0	27.7		27.6	27.1	31.1	
Smoking habits, %			0.048				0.181
Never smoker	54.7	57.6		59.1	54.7	47.5	
Ex-smoker	18.0	18.6		17.2	22.1	23.0	
Current smoker	27.3	23.8		23.7	23.2	29.5	
Education, %			0.006				0.019
Primary and lower secondary school	23.4	19.2		18.4	18.8	32.8	
Upper secondary school	50.5	52.8		52.0	57.5	42.6	
Degree	26.1	28.1		29.6	23.7	24.6	
Season, %			0.052				0.237
Spring	46.1	46.0		47.3	42.0	44.3	
Summer	15.4	15.0		15.8	12.8	14.8	
Autumn	32.4	30.7		28.7	37.2	31.1	
Winter	6.1	8.3		8.2	8.0	9.8	

Statistical Analysis

Categorical variables were summarised with percentages and were compared across strata by Pearson's χ^2 test.

The associations among different AR overlapping diseases (AR only, AR + SsNP, AR + SwNP) and other outcomes (diagnosed and current asthma, number of asthma attacks, asthma-COPD overlap syndrome, cough and phlegm, and ED visits for respiratory diseases), were assessed using multinomial regression models adjusted for potential confounders (gender, age, smoking habits, level of education, season of response, type of contact, percentile rank of cumulative response and centre). The relative risk ratio (RRR) was estimated by choosing the AR-only group as the reference category. A p value <0.05 was considered statistically significant. Statistical analyses were performed with STATA 12.1 (Stata Corp LP, College Station, Tex., USA).

Results

Prevalence of AR and Demographic Data

Overall, 5,162 subjects completed the questionnaire in the 4 centres. The response rate was 53%, ranging from 37.1% (Pavia) to 67.7% (Verona). The overall prevalence of AR in the study was 25.4% (95% CI 24.2–26.6). The rates of self-reported diagnosis of AR + SsNP and AR + SwNP were 5.7 and 1.2%, respectively (table 1).

The subjects with AR were younger (table 2), fewer were current smokers and they had a higher level of education than those without AR. The distribution of sex and

Table 3. Crude prevalence (%) of different symptoms or asthma conditions and drugs used in the last 12 months among subjects with AR, sinusitis and polyposis

Conditions	AR overall	AR only	AR + SsNP	AR + SwNP	p
Physician-diagnosed asthma	23.8	23.0	24.8	31.7	0.28
Current asthma	17.5	15.8	20.1	31.2	<0.01
At least 1 asthma attack	11.5	10.2	13.9	21.3	0.01
>3 asthma attacks	3.2	3.0	3.9	3.3	0.76
Asthma-COPD overlap syndrome	3.0	2.6	3.2	8.6	0.03
Drugs for asthma used in the last 12 months	17.5	15.2	22.4	29.3	0.001
Cough and phlegm	22.7	17.9	34.9	40.7	<0.001
ED admissions for respiratory diseases	1.1	0.8	1.4	5.1	<0.01
Drugs for rhinitis used in the last 12 months	54.0	48.9	65.2	70.5	<0.001

Table 4. Association of different symptoms or asthma conditions among subjects with AR, sinusitis and polyposis

Conditions	AR only	AR + SsNP	AR + SwNP
Physician-diagnosed asthma	1	1.11 (0.81–1.52)	1.48 (0.83–2.64)
Current asthma	1	1.35 (0.95–1.91)	2.31 (1.29–4.15)
At least 1 asthma attack	1	1.39 (0.93–2.08)	2.30 (1.19–4.46)
>3 asthma attacks	1	1.26 (0.61–2.61)	1.03 (0.23–4.54)
Asthma-COPD overlap syndrome	1	1.08 (0.49–2.40)	2.71 (0.96–7.67)
Drugs for asthma used in the last 12 months	1	1.52 (1.08–2.15)	2.27 (1.23–4.19)
Cough and phlegm	1	2.59 (1.89–3.54)	2.91 (1.63–5.21)
ED admissions for respiratory diseases	1	1.91 (0.54–6.71)	5.61 (1.81–23.92)
Drugs for rhinitis used in the last 12 months	1	1.91 (1.43–2.54)	2.46 (1.38–4.40)

Values are RRR (95% CI), adjusted for gender, age, smoking habits, level of education, season of response, centre, type of contact and percentile rank of cumulative response.

education level among the three different groups of upper airway diseases (AR only, AR + SsNP and AR + SwNP) was statistically significant. The percentage of females was lower in subjects with AR + SwNP (36.1%) compared to the other two groups (51.8 and 63.5% for AR and AR + SsNP, respectively). The education level was significantly lower for subjects with AR + SwNP than for those of the other two groups ($p = 0.019$).

Overlapping Upper Airway Diseases and Asthma

Overall, 23.8% of the subjects with AR had physician-diagnosed asthma and 17.5% of the subjects reported current asthma at the time of the survey (table 3). The prevalence of current asthma and the distribution of the control/severity markers of co-existing asthma varied significantly across the three different groups of AR subjects. In particular, the prevalence of current asthma increased

from 15.8% in the AR-only group to 31.2% in the group AR + SwNP ($p < 0.001$). The same statistically significant trend was found when considering the proportion of subjects who had at least one asthma attack in the last 12 months ($p = 0.01$), of subjects with the asthma-COPD overlap syndrome ($p = 0.03$), of subjects with chronic cough and phlegm ($p < 0.001$), and of those who had been hospitalised for respiratory diseases ($p < 0.01$). The only exception to this general trend was the prevalence for subjects who had had more than three asthma attacks per year, which was similar in the three groups of upper airway diseases ($p = 0.76$).

In the multivariate analysis (table 4), after adjusting for potential confounders, the subjects with AR + SwNP had a statistically significant increased risk of having current asthma (RRR = 2.31, 95% CI 1.29–4.15), of having had at least one asthma attack in the last year (RRR = 2.30, 95%

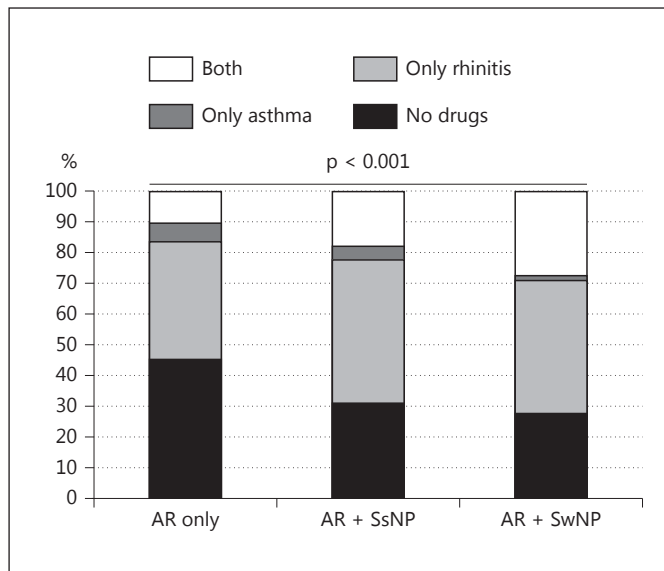


Fig. 1. Distribution of subjects who used medication for rhinitis and asthma, or both, in the last 12 months, stratified by categories of rhinitis.

CI 1.19–4.46) and of having had an ED admission for respiratory disease in the last 3 months (RRR = 5.61, 95% CI 1.81–23.92) than subjects with AR only.

Finally, the subjects with AR + SsNP and AR + SwNP had a statistically significant increased risk of having cough and phlegm (RRR = 2.59, 95% CI 1.89–3.54, and RRR = 2.91, 95% CI 1.63–5.21, respectively) than subjects with AR only, while the asthma-chronic bronchitis overlap syndrome did not show statistically significant variations among the AR groups.

Overlapping Upper Airway Diseases and Drug Intake for Rhinitis and Asthma

Overall, 54 and 17.5% of subjects with AR had used medication for rhinitis and asthma, respectively, in the last year. After adjusting for potential confounders, in the multivariate analysis we found an increased risk that the subjects with AR + SsNP and AR + SwNP took medications both for rhinitis (RRR = 1.91, 95% CI 1.43–2.54, and RRR = 2.46, 95% CI 1.38–4.40, respectively) and for asthma (RRR = 1.52, 95% CI 1.08–2.15, and RRR = 2.27, 95% CI 1.23–4.19, respectively) than subjects with AR only.

The overall distribution of drug intake for rhinitis and/or asthma across the three different groups of AR subjects is shown in the figure 1. The proportion of subjects who had not used medication in the last 12 months decreased

from 46% in subjects with AR only to 28% in those with AR + SwNP, whereas the use of medication for both rhinitis and asthma increased from 11% in AR-only subjects to 28% in subjects with AR + SwNP ($p < 0.001$).

When we considered the distribution of drugs used only by subjects with current asthma stratified by no asthma attacks and by at least one asthma attack, we found that the proportion who used drugs for asthma or for rhinitis was almost 65% in those who had not had an asthma attack and almost 95% in those who had had at least one asthma attack. The distribution of drugs used among the three groups of upper airway diseases was similar both for subjects with no asthma attack and at least one asthma attack (fig. 2).

Discussion

The most important finding of the study was that AR co-existed with sinusitis, with and without NP, in 6.9% of the general population. In particular, the coexistence of rhinosinusitis with and without polyps was reported by 4.7 and 22.5%, respectively, of young adults with AR. In addition, subjects with AR + SwNP had a higher likelihood of having more severe asthma than those with AR only. We will also discuss the reliability of a self-reported diagnosis of sinusitis and the identification of subjects with NP as a subgroup of those with AR.

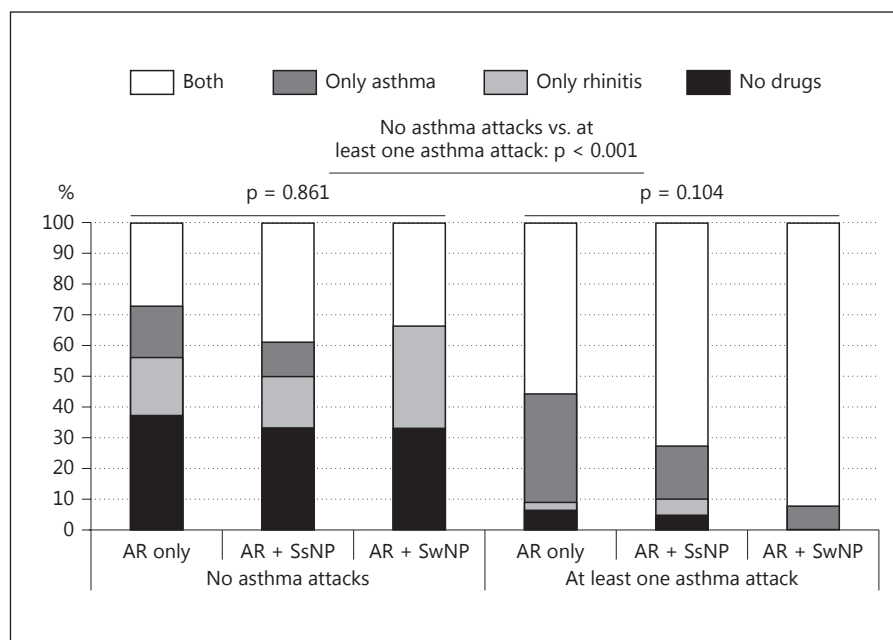
Prevalence of the Upper Airway Diseases

Overall, about 25% of the subjects reported AR; about 6% reported AR plus sinusitis with and without NP, and the prevalence of these was similar across the centres. Concerns about the self-reported diagnosis of chronic rhinosinusitis [18, 19] have led to the development of a specific questionnaire to diagnose chronic rhinosinusitis in the epidemiological setting [20].

A recent postal survey performed in Europe, using the EP3OS criteria questionnaire, found that the prevalence of chronic rhinosinusitis in the general population was 10.9%, with relevant variations of prevalence in the different geographical areas. In the only Italian centre participating in that survey (Palermo), the prevalence was 10.8% (6.9% self-reported doctor diagnosis) [21].

In the EP3OS study, the diagnosis of chronic rhinosinusitis includes patients with and without NP, while the diagnosis of chronic rhinosinusitis is limited only to the young adult subjects with AR in our survey. Although the diagnosis of sinusitis was only assessed in subjects with AR and consisted of a single question in the question-

Fig. 2. Distribution of subjects with AR who used medication for rhinitis and asthma in the last 12 months, stratified by categories of rhinitis and asthma attacks.



naire, we might suppose that the prevalence found in our survey is consistent with that found in Italy.

The prevalence of AR + SwNP found in our survey is in line with the estimated prevalence found both in Europe, which ranged from 2 to 4% of the general population [22], and that found in a specific survey in France (2.1%) [23]. However, other studies [24] found a higher prevalence of polyposis than our survey, which could be due to the fact that it was not in a population-based study. Overall, the reliability of the self-reported diagnosis of chronic rhinosinusitis and of AR + SwNP in our survey seems to be acceptable.

Impact of AR on Asthma

The increase in drug intake for rhinitis suggests an increase in severity from AR to AR + SwNP [25]. Moreover, the association between the severity of the upper airway diseases and the impact on asthma in the non-adjusted analysis seems to confirm the United Airways Diseases hypothesis [1, 26]. After adjusting for potential confounders, the results show the presence of two different subsets of subjects within the AR group. The first includes subjects with AR and sinusitis, and the second those with polyposis.

In the first group, the increase in the proportion of subjects who took medication for rhinitis and asthma suggests an increase in the severity of the upper airway diseases, which does not correspond to an increase in the

indicators of asthma severity (at least one asthma attack) and the ED visits for respiratory diseases. Despite the increase in drug intake in the group of subjects with polyposis, it is evident that there is poor asthma control in this case.

We hypothesise that the positive responses to the question on the presence of NP enables the identification of two different asthma phenotypes in the AR subjects: the first, 'early-onset allergic asthma phenotype', mainly determined by allergen-specific adaptive Th2 cells, is generally steroid sensitive [27], the second, 'late-onset eosinophilic asthma phenotype', is driven by allergen-independent innate lymphoid cells, with the responsiveness characterised by being refractory to steroids [28]. Although these two pathogenic mechanisms are not mutually exclusive, as confirmed by the detection of allergic sensitisation in patients with nasal polyposis [23], the role of the main pathogenic mechanism seems to be clear [29]. When the severity of the upper airway diseases increased, a similar prevalence of the most unstable subset of asthmatic subjects (about 3% of them) was unexpected. This may be due to poor adherence to the asthma therapy, which is very common in patients with AR only and mild asthma [30]. Furthermore, this seems to be consistent with recent studies on the presence of mast cells at the alveolar level in subjects with AR and uncontrolled asthma [31–33].

Strengths and Limitations

The strength of this study is that we found the heterogeneity hidden in the diagnosis of AR obtained from the questionnaire. This is in contrast to the simple model used to compare AR and asthma (i.e. subjects with NP within those with AR), and our finding suggests that their interaction should be considered with more caution.

The main limitation of our survey is that we could not determine the allergic pathogenesis of the upper airway diseases without cutaneous, serological [34] or any other clinical tests, which also influence the reliability of the self-reported diagnosis of upper airways comorbidities, such as the diagnosis of chronic rhinosinusitis with and without polyps. Another important limitation is the lack of any information about the type, duration and the adherence to therapy for rhinitis and asthma. The only information available for this was whether a subject had or had not used medication for rhinitis and/or asthma in the last 12 months.

Appendix

Members of the GEIRD study group: R. de Marco, G. Verlato, M.E. Zanolin, S. Accordini, O. Bortolami, M. Braggion, V. Cappa, L. Cazzoletti, P. Girardi, F. Locatelli, A. Marcon, E. Montoli, M. Rava, R. Vesentini, P. Marchetti, G. Pesce, L. Calciano, G. Nguyen (Unit of Epidemiology and Medical Statistics, University of Verona); M. Ferrari, L. Donatelli, C. Posenato, V. Lo Cascio (Section of Internal Medicine, University of Verona); L. Perbellini, M. Olivieri, J. D'Amato, E. Donatini, M. Martinelli (Unit of Occupational Medicine, Azienda Ospedaliera 'Istituti Ospitalieri di Verona'); P.F. Pignatti, C. Bombieri, M.D. Bettin, E. Trabetti (Unit of Biology and Genetics, University of Verona); A. Poli, M. Nicolis, S. Sembeni (Unit of Hygiene and Preventive, Environmental and Occupational Medicine, University of Verona); L. Antonicelli (Department of Internal Medicine, Ospedali Riuniti di Ancona); F. Attena, V. Galdo (Department of Public, Clinical and Preventive

Medicine, II University of Naples); V. Bellia, S. Battaglia (Department of Medicine, Pneumology, Physiology and Human Nutrition, University of Palermo); I. Cerveri, A.G. Corsico, F. Albicini, E. Gini, A. Grosso (Division of Respiratory Diseases, IRCCS Policlinico 'San Matteo', University of Pavia), A. Marinoni, S. Villani, V. Ferretti (Department of Health Sciences, University of Pavia); L. Casali, A. Miniucchi (Department of Internal Medicine, Section of Respiratory Diseases, University of Perugia); L. Briziarelli, M. Marcarelli (Department of Medical-Surgical Specialties and Public Health, University of Perugia); M.G. Panico (National Health Service, Epidemiology Unit, ASL 2, Salerno); P. Pirina, A.G. Fois, F. Becciu, A. Deledda, V. Spada (Institute of Respiratory Diseases, University of Sassari); M. Bugiani, A. Carosso, P. Piccioni, G. Castiglioni (National Health Service, CPA-ASL TO2, Unit of Respiratory Medicine and Allergology, Turin); R. Bono, R. Tassinari, G. Trucco (Department of Public Health and Microbiology, University of Turin); G. Rolla, E. Heffler (Department of Biomedical Sciences and Human Oncology, University of Turin); E. Migliore (Centre of Oncologic Prevention, Turin).

Acknowledgements

We are very grateful to Prof. Roberto de Marco, who tragically passed away on October 9, 2015, for his valuable contribution to this paper and for leading our research team with passion and tenacity until the end.

The GEIRD project was funded by: the Cariverona Foundation, the Italian Ministry of Health, Chiesi Farmaceutici, and the Italian Medicines Agency (AIFA). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Disclosure Statement

The authors confirm that Gabriele Nicolini is an employee of 'Chiesi Farmaceutici, Parma, Italy', one of the commercial funders of this research. There are no patents, products in development or marketed products to declare. All remaining authors declare that they have no competing interests.

References

- 1 Bousquet J, Khaltaev N, Cruz AA, et al: Allergic rhinitis and its impact on asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA²LEN and Allergen). *Allergy* 2008;63(suppl 86):8–160.
- 2 Bjerg A, Ekerljung L, Middelved R, Dahlén SE, Forsberg B, Franklin K, Larsson K, Lötvall J, Olafsdóttir IS, Torén K, Lundbäck B, Janson C: Increased prevalence of symptoms of rhinitis but not of asthma between 1990 and 2008 in Swedish adults: comparisons of the ECRHS and GA²LEN surveys. *PLoS One* 2011;17:e16082.
- 3 de Marco R, Cappa V, Accordini S, Rava M, Antonicelli L, Bortolami O, Braggion M, Bugiani M, Casali L, Cazzoletti L, Cerveri I, Fois AG, Girardi P, Locatelli F, Marcon A, Marinoni A, Panico MG, Pirina P, Villani S, Zanolin ME, Verlato G; GEIRD Study Group: Trends in the prevalence of asthma and allergic rhinitis in Italy between 1991 and 2010. *Eur Respir J* 2012;39:883–892.
- 4 Mösges R, Hellmich M, Su VY, Chou KT, Liu CJ: Increased mortality in AR patients? *Allergy* 2013;68:1209–1210.
- 5 Magnan A, Meunier JP, Saugnac C, Gasteau J, Neukirch F: Frequency and impact of allergic rhinitis in asthma patients in everyday general medical practice: a French observational cross-sectional study. *Allergy* 2008;63:292–298.
- 6 Price D, Zhang Q, Kocevar VS, Yin DD, Thomas M: Effect of a concomitant diagnosis of allergic rhinitis on asthma-related health care use by adults. *Clin Exp Allergy* 2005;35:282–287.

- ▶7 Olivieri M, Verlato G, Corsico A, Lo Cascio V, Bugiani M, Marinoni A, de Marco R; Italian European Community Respiratory Health Survey Group: Prevalence and features of allergic rhinitis in Italy. *Allergy* 2002;57:600–606.
- ▶8 Guerra S, Sherrill DL, Martinez FD, Barbee RA: Rhinitis as an independent risk factor for adult-onset asthma. *J Allergy Clin Immunol* 2002;109:419–425.
- ▶9 ten Brinke A, Sterk PJ, Masclee AA, Spinhoven P, Schmidt JT, Zwinderman AH, Rabe KF, Bel EH: Risk factors of frequent exacerbations in difficult-to-treat asthma. *Eur Respir J* 2005;26:812–818.
- ▶10 Ponte EV, Franco R and Nascimento HF, Souza-Machado A, Cunha S, Barreto ML, Nasipitz C, Cruz AA: Lack of control of severe asthma is associated with co-existence of moderate-to-severe rhinitis. *Allergy* 2008;63:564–569.
- ▶11 Lötval J, Ekerljung L, Lundbäck B: Multi-symptom asthma is closely related to nasal blockage, rhinorrhea and symptoms of chronic rhinosinusitis-evidence from the West Sweden Asthma Study. *Respir Res* 2010;11:163.
- ▶12 Jarvis D, Newson R, Lotvall J, Hastan D, Tomassen P, Keil T, Gjomarkaj M, Forsberg B, Gunnbjörnsdóttir M, Minov J, Brozek G, Dahlen SE, Toskala E, Kowalski ML, Olze H, Howarth P, Krämer U, Baelum J, Loureiro C, Kasper L, Bousquet PJ, Bousquet J, Bachert C, Fokkens W, Burney P: Asthma in adults and its association with chronic rhinosinusitis: the GA²LEN survey in Europe. *Allergy* 2012;67:91–98.
- ▶13 Bernstein JA: Allergic and mixed rhinitis: epidemiology and natural history. *Allergy Asthma Proc* 2010;31:365–369.
- ▶14 Wilson KF, McMains KC, Orlandi RR: The association between allergy and chronic rhinosinusitis with and without nasal polyps: an evidence-based review with recommendations. *Int Forum Allergy Rhinol* 2014;4:93–103.
- ▶15 Antonicelli L, Braschi MC, Bresciani M, Bonifazi M, Baldacci S, Angino A, Pala AP, Viegi G: The complex link between severity of asthma and rhinitis in mite allergic patients. *Respir Med* 2013;107:23–29.
- ▶16 de Marco R, Accordini S, Antonicelli L, Bellia V, Bettin MD, Bombieri C, Bonifazi F, Bugiani M, Carosso A, Casali L, Cazzoletti L, Cerveri I, Corsico AG, Ferrari M, Fois AG, Lo Cascio V, Marcon A, Marinoni A, Olivieri M, Perbellini L, Pignatti P, Pirina P, Poli A, Rolla G, Trabetti E, Verlato G, Villani S, Zanolin ME; GEIRD Study Group: The gene-Environment Interactions in Respiratory Diseases (GEIRD) project. *Int Arch Allergy Immunol* 2010;152:255–263.
- ▶17 de Marco R, Zanolin ME, Accordini S, Signorelli D, Marinoni A, Bugiani M, Lo Cascio V, Woods R, Burney P: A new questionnaire for the repeat of the first stage of the European Community Respiratory Health Survey: a pilot study. *Eur Respir J* 1999;14:1044–1048.
- ▶18 Tahamiler R, Canakcioglu S, Ogreden S, Acioglu E: The accuracy of symptom-based definition of chronic rhinosinusitis. *Allergy* 2007;62:1029–1032.
- ▶19 Raherison C, Montaudon M, Stoll D, Wallaert B, Darras J, Chanez P, Crampette L, Magnan A, Demessi P, Orlando JP, Didier A, Serrano E, Prud'homme A, Meurice JC, Klossek JM, Tunon-de-Lara JM; SPLF Working Group 'Nez-Bronches': How should nasal symptoms be investigated in asthma? A comparison of radiologic and endoscopic findings. *Allergy* 2004;59:821–826.
- ▶20 Tomassen P, Newson RB, Hoffmans R, Lötval J, Cardell LO, Gunnbjörnsdóttir M, Thilising T, Matricardi P, Krämer U, Makowska JS, Brozek G, Gjomarkaj M, Howarth P, Loureiro C, Toskala E, Fokkens W, Bachert C, Burney P, Jarvis D: Reliability of EP3OS symptom criteria and nasal endoscopy in the assessment of chronic rhinosinusitis: a GA²LEN study. *Allergy* 2011;66:556–561.
- ▶21 Hastan D, Fokkens WJ, Bachert C, Newson RB, Bislimovska J, Bockelbrink A, Bousquet PJ, Brozek G, Bruno A, Dahlén SE, Forsberg B, Gunnbjörnsdóttir M, Kasper L, Krämer U, Kowalski ML, Lange B, Lundbäck B, Salagean E, Todo-Bom A, Tomassen P, Toskala E, van Drunen CM, Bousquet J, Zuberbier T, Jarvis D, Burney P: Chronic rhinosinusitis in Europe – an underestimated disease. A GA²LEN study. *Allergy* 2011;66:1216–1223.
- ▶22 Wilson KF, McMains KC, Orlandi RR: The association between allergy and chronic rhinosinusitis with and without nasal polyps: an evidence-based review with recommendations. *Int Forum Allergy Rhinol* 2014;4:93–103.
- ▶23 Klossek JM, Neukirch F, Pribil C, Jankowski, Serrano E, Chanal I, El Hasnaoui A: Prevalence of nasal polyposis in France: a cross-sectional, case-control study. *Allergy* 2005;60:233–237.
- ▶24 Ahmadiashar A, Farjd HR, Moezzi F, Mousavinasab N: Nasal polyposis in patients with asthma and allergic rhinitis. *J Laryngol Otol* 2012;126:780–783.
- ▶25 Antonicelli L, Micucci C, Voltolini S, Senna GE, Di Blasi P, Visonà G, De Marco R, Bonifazi F: Relationship between ARIA classification and drug treatment in allergic rhinitis and asthma. *Allergy* 2007;62:1064–1070.
- ▶26 Licari A, Caimmi S, Bosa L, Marseglia A, Marseglia GL, Caimmi D: Rhinosinusitis and asthma: a very long engagement. *Int J Immunopathol Pharmacol* 2014;27:499–508.
- ▶27 Suojalehto H, Lindström I, Majuri ML, Mitts C, Karjalainen J, Wolff H, Alenius H: Altered microRNA expression of nasal mucosa in long-term asthma and allergic rhinitis. *Int Arch Allergy Immunol* 2014;163:168–178.
- ▶28 Hekking PP, Bel EH: Developing and emerging clinical asthma phenotypes. *J Allergy Clin Immunol Pract* 2014;2:671–680.
- ▶29 van Crombruggen K, Zhang N, Gevaert P, Tomassen P, Bachert C: Pathogenesis of chronic rhinosinusitis: inflammation. *J Allergy Clin Immunol* 2011;128:728–732.
- ▶30 Corsico AG, Cazzoletti L, de Marco R, Janson C, Jarvis D, Zoia MC, Bugiani M, Accordini S, Villani S, Marinoni A, Gislason D, Gulsvik A, Pin I, Vermeire P, Cerveri I: Factors affecting adherence to asthma treatment in an international cohort of young and middle-aged adults. *Respir Med* 2007;101:1363–1367.
- ▶31 Scichilone N, Battaglia S, Taormina S, Modica V, Pozzecco E, Bellia V: Alveolar nitric oxide and asthma control in mild untreated asthma. *J Allergy Clin Immunol* 2013;131:1513–1517.
- ▶32 Andersson CK, Tufvesson E, Aronsson D, Bergqvist A, Mori M, Bjerrmer L, Erjefält JS: Alveolar mast cells shift to an FcεRI-expressing phenotype in mild atopic asthma: a novel feature in allergic asthma pathology. *Allergy* 2011;66:1590–1597.
- ▶33 Andersson CK, Bergqvist A, Mori M, Mauad T, Bjerrmer L, Erjefält JS: Mast cell-associated alveolar inflammation in patients with atopic uncontrolled asthma. *J Allergy Clin Immunol* 2011;127:905–912.
- ▶34 Smith HE, Hogger C, Lallemand C, Crook D, Frew AJ: Is structured allergy history sufficient when assessing patients with asthma and rhinitis in general practice? *J Allergy Clin Immunol* 2009;123:646–650.