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TITLE

The heterogeneity hidden in allergic rhinitis and its impact on coexisting asthma in adults: a population-based survey

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RUNNING TITLE: The heterogeneity of allergic rhinitis

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Abstract:

Background: It has been suggested that there is some overlap between allergic rhinitis (AR), sinusitis and polyposis but it has not been fully documented.

This study aimed to evaluate the prevalence of these coexisting diseases and their impact on bronchial asthma in the general population in Italy.

Methods: In 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 ARwith Sinusitis with Nasal Polyps (AR+SwNP) was administered. Random samples of subjects aged 20-44 years (n=5162) answered the postal questionnaire in 4 Italian centres (Pavia, Sassari, Torino, Verona). In allergic rhinitis 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). The self-reported diagnosis of AR+SsNP and AR+SwNPwas 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/year (RRR=2.30; 95%CI:1.19-4.46) and of having 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 allergic rhinitis in the epidemiological setting includes heterogeneous upper airway diseases that affect the clinical features of AR and its interactions with asthma.

Introduction

Allergic rhinitis (AR) is the most common immunologic disease and its prevalence is continuously on the increase, in particular in Western countries [1-3]. This not only affects the burden of the disease on patients [1-4], but it also has an impact on bronchial asthma and subsequently leads to an increased cost in health care use [1,6].

In epidemiology, validated questionnaires are used for the diagnosis of allergic rhinitis. An Italian study showed that the reliability of the question on allergic rhinitis seems adequate for epidemiological purposes and about 20% of the subjects who answered positively to the question on allergic rhinitis 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) 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 compared to 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 Nasal Polyps (AR+SsNP), AR with Sinusitis and with Nasal Polyps (AR+SwNP) and if the interaction between AR and bronchial asthma has been affected by concomitant upper airway diseases.

Materials and Methods

The study Gene Environment Interactions in Respiratory Diseases (GEIRD), is 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 3000 subjects from the general population aged 20 to 44 years old (male/female ratio=1) were selected from the registry of the local health authority in each of the four Italian centres: Pavia, Sassari, Torino, Verona [16].

A screening questionnaire on respiratory symptoms was administered to eligible subjects by mail up to three times in case of non response and once by phone for subjects who had not responded by mail.

The GEIRD screening questionnaire (available in www.geird.org), a modified version of questionnaires used in previous studies [17] included 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 questionnaire: “Do you have any nasal allergies including hay fever?”. Subjects who answered “yes” were classified as subjects with AR. If a subject answered “no” to the question he/she was classified as a subject without allergic rhinitis.

Subjects with allergic rhinitis subjects were further classified as follows:

- AR only: subjects with AR but without sinusitis (S) or Nasal Polyps (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 he/she answered “yes” to both of the following questions:” Have you ever had asthma?” and “ Was this confirmed by a doctor?”;
- current asthma if he/she had physician-diagnosed asthma and took any medicines for asthma and had had an attack of asthma or at least one among the following asthma-like symptoms: wheezing, chest tightness, shortness of breath, in the last 12 months.

As indicators of asthma severity/control we used:

- 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 medicines for asthma in the last 12 months (including inhalers, aerosols or tablets)?” and “Have you used any medicines 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 subjects used: “no medicines” if a subject answered “no” to both questions; “only asthma medicines” if a subjects took medicines for asthma and had not taken medicine for rhinitis in the last 12 months; “only rhinitis medicines” if a subjects took medicines for rhinitis and had not taken medicine for asthma in the last 12 months;

"both" if a subject had taken medicines for both rhinitis and for asthma in the last 12 months.

The presence of chronic cough and phlegm 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 has been to 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 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), season of response (spring, summer, autumn, winter). In addition, type of contact (mail, phone), percentile rank of cumulative response centre-specific and centre were included as design confounders in the analysis.

Statistical analysis

Categorical variables were summarized with percentages, and were compared across strata by the Pearson's Chi-squared test.

The associations among different allergic rhinitis overlapping diseases (AR only, AR+SnNP, 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 by 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 group with AR only 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, TX, USA).

Results

Prevalence of allergic rhinitis and demographic data

Overall 5162 subjects filled in the questionnaire in the 4 centres. The response rate was 53%, ranging from 37.1% (Pavia) to 67.7% (Verona). The overall prevalence of allergic rhinitis in the study was 25.4% (95%CI 24.2-26.6). The subjects who self-reported diagnosis of AR+SsNP and AR+SwNP were 5.7% and 1.2% respectively.

The subjects with AR were younger (table 2), fewer current smokers and they had a higher level of education than those without AR. The distribution of sex and 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 level of education 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 a 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 coexisting asthma varied significantly across the three different groups of AR subjects. In particular, the prevalence of current asthma increased from 15.8% in the group of AR only 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 hospitalized 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/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 at least one asthma attacks in the last year (RRR=2.30; 95%CI: 1.19-4.46) and of having 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 the drugs 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+S+P, whereas the use of medication for both rhinitis and asthma increased from 11% in the subjects with AR only to 28% in the subjects with AR+SwNP (p<0.001).

When we considered the distribution of the drugs used only by the subjects with current asthma, stratified by no asthma attacks and 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 (figure 2).

Discussion

The most important finding of the study was that AR coexisted with sinusitis, with and without nasal polyps, in 6.9% of the general population. In addition, subjects with AR+SwNP had a higher likelihood of having more severe asthma than those with AR only. We also discuss the reliability of a self-reported diagnosis of sinusitis and the identification of subjects with nasal polyps 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 nasal polyps and these prevalence were 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 center participating in this 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 nasal polyps, while the diagnosis of chronic rhino-sinusitis 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 questionnaire, we might suppose that the prevalence of AR+SsNP found in our survey is coherent 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 populations [22] and

found in a specific survey in France (2.1%) [23]. However other studies [24] found a higher prevalence of polyposis than our survey but this could be due to the fact that the 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 allergic rhinitis 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 their 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 one includes subjects with AR and with sinusitis, and the second one those with polyposis.

In the first group, the increase in the proportion of subjects who took drugs 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 the drug intake in the group of subjects with polyposis, it is evident that there is poor asthma control in this case.

We hypothesize that the positive answer to the question on the presence of nasal polyps made it possible to identify two different asthma phenotypes in the AR subjects.

In the first one, “early onset allergic asthma phenotype”, the disease could be determined by allergen-specific adaptative Th2 cells [27], and in the second one, “late onset eosinophilic asthma phenotype” could be driven by allergen independent innate lymphoid cells, and the responsiveness is characterized by refractory to steroids [28].

Although these two pathogenic mechanisms are not mutually exclusive, as confirmed by the detection of allergic sensitization in patients with nasal polyposis, 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 the poor adherence to the therapy [30].

Furthermore, the prevalence of poor control, even in subjects with the mildest asthma, seems to be consistent with the recent studies on the presence of mast cells at the alveolar level in subjects with allergic rhinitis and uncontrolled asthma [31-33].

Strengths and Limitations

The strength of this study is that we found the heterogeneity hidden in the diagnosis of allergic rhinitis obtained from the questionnaire. This is in contrast to the simple model used to compare allergic rhinitis and asthma (i.e. subjects with nasal polyp 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 [30] or any other clinical tests, which also influence the reliability of the self-reported diagnosis of the upper airways comorbidity, such as the diagnosis of chronic rhinosinusitis with and without polyps. Another important limitation is the lack of any information about type, duration and the adherence to the therapy for rhinitis and asthma. The only information available was if a subject had used or not used drugs for rhinitis and/or asthma in the last 12 months.

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Competing Interests

The authors confirm that Gabriele Nicolini is an employee of the ‘‘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.

Authors’ Contributions

Conceived and designed the experiments: Roberto de Marco. Pierpaolo Marchetti performed the data analysis. Leonardo Antonicelli, Pierpaolo Marchetti and Roberto de Marco wrote the paper. All the authors participated in the study design and in data collection and assembly, read and approved the final manuscripts.

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TABLES AND FIGURES

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

centers	n. of partecipating subjects (response rate (%))	prevalence (95%CI)			
		AR overall	AR only	AR+SsNP	AR+SwNP
Verona	1746 (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	1205 (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	1245 (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	**5162 (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)**

AR: Allergic Rhinits; SsNP:Sinusitis without Nasal Polyps; SwNP= Sinusitis with Nasal Polyps

CI: Confidence Interval

Table 2. characteristics of subjects stratified by presence of AR and different phenotypes for subjects with AR

variables	without AR	AR overall		subjects with AR			
				AR only	AR+Ss NP	AR+Sw NP	
	n= 3795	n= 1294	p	n= 945	n= 288	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	26.2	29.7		30.4	29.5	19.7	
30-39	43.8	42.6		42.0	43.4	49.2	
≥40	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	

AR: Allergic Rhinits; SsNP:Sinusitis without Nasal Polyps; SwNP= Sinusitis with Nasal Polyps

Table 3. crude prevalence (%) of different symptom or condition of asthma and drugs used in the last 12 months among subjects with allergic rhinitis, 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**

AR: Allergic Rhinits; SsNP:Sinusitis without Nasal Polyps; SwNP= Sinusitis with Nasal Polyps

ED: Emergency Department

534 Table 4. Association of different symptom or condition of asthma and among subjects with
535 allergic rhinitis, sinusitis and polyposis. (Relative Risk Ratio (RRR*) and 95%CI)

Conditions	**AR only**	**AR+SsNP**	**AR+SwNP**
		RRR (95%CI)	**RRR (95%CI)**
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)**

536 *adjusted for gender, age, smoking habits, level of education, season of response, centre,
537 type of contact and percentile rank of cumulative response.

538 AR: Allergic Rhinits; SsNP:Sinusitis without Nasal Polyps; SwNP= Sinusitis with Nasal
539 Polyps
540

541 ED: Emergency Department

542 RRR: Relative Risk Ratio

543 CI: Confidence Interval

544

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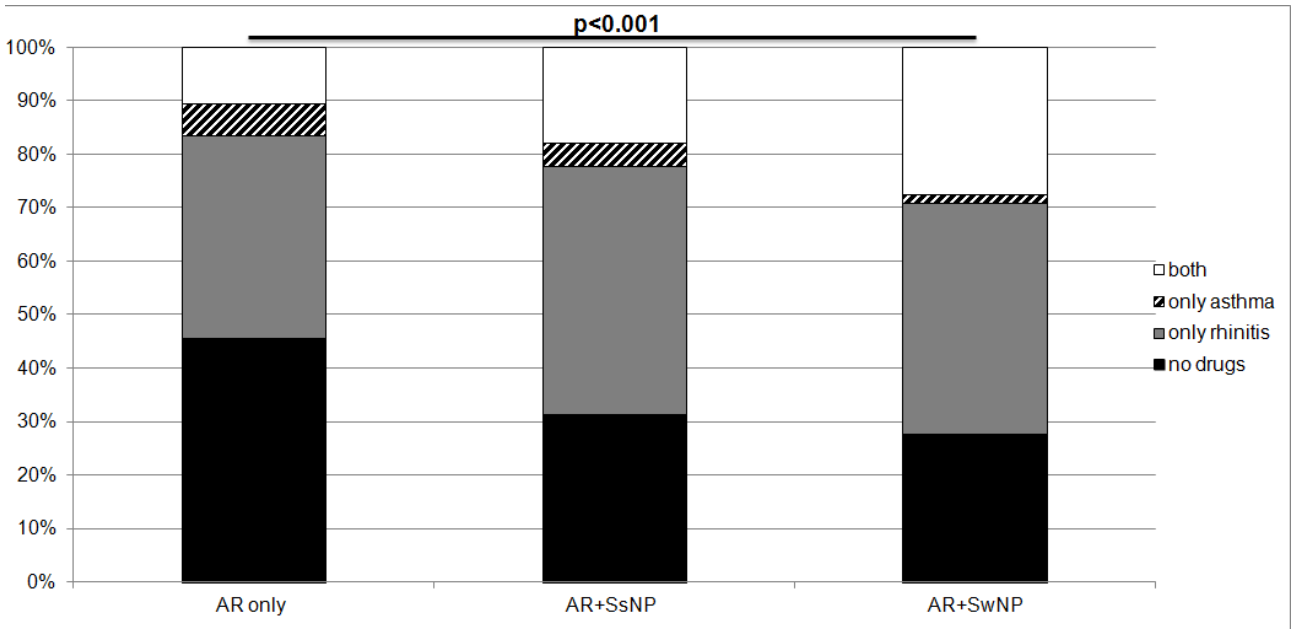
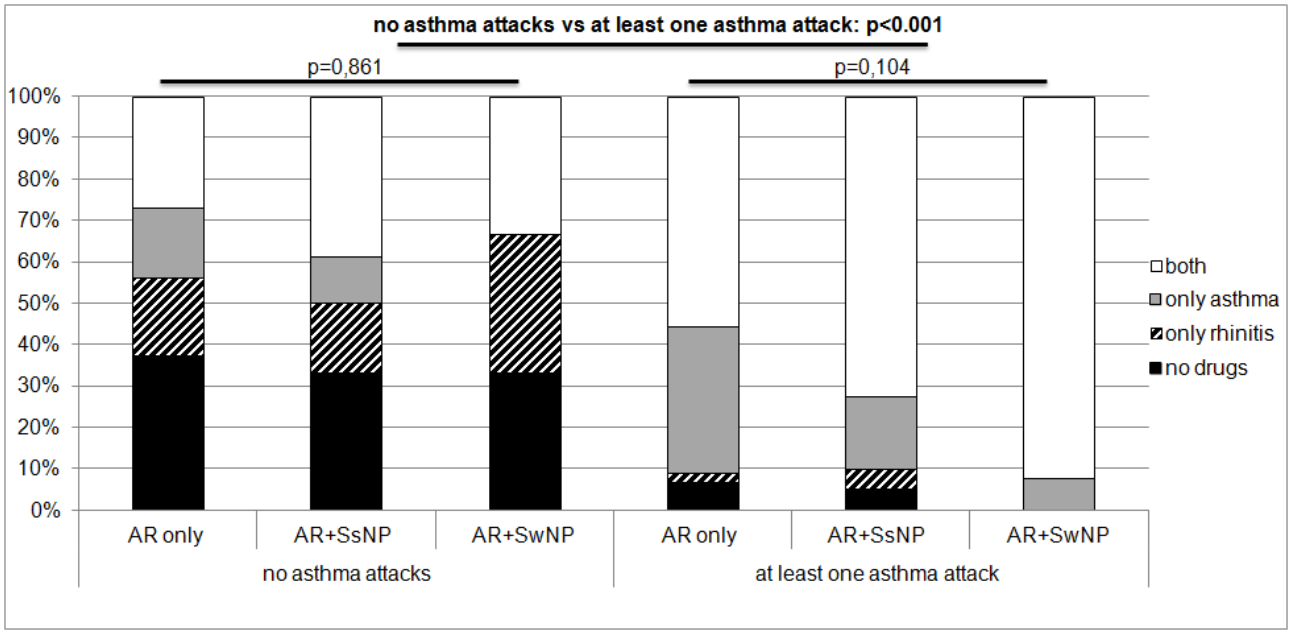
Figure 1. Distribution of subjects who used medication for rhinitis and asthma or both in the last12 months stratified by categories of rhinitis



AR: Allergic Rhinits; SsNP:Sinusitis without Nasal Polyps; SwNP= Sinusitis with Nasal Polyps

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



AR: Allergic Rhinits; SsNP:Sinusitis without Nasal Polyps; SwNP= Sinusitis with Nasal Polyps