



# UNIVERSITÀ DEGLI STUDI DI TORINO

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

11

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14

15 **TITLE**

16 **The heterogeneity hidden in allergic rhinitis and its impact on coexisting asthma in**  
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18

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41 **RUNNING TITLE: The heterogeneity of allergic rhinitis**

42

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49

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52

53

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63 **Abstract:**

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

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

68 **Methods:** In the frame of the multicentre Gene Environment Interactions in Respiratory  
69 Diseases (GEIRD) study, a postal screening questionnaire including questions about self  
70 reported symptoms of asthma, AR, AR with Sinusitis without Nasal Polyps (AR+SsNP)  
71 and ARwith Sinusitis with Nasal Polyps (AR+SwNP) was administered. Random samples  
72 of subjects aged 20-44 years (n=5162) answered the postal questionnaire in 4 Italian  
73 centres (Pavia, Sassari, Torino, Verona). In allergic rhinitis subjects, the association  
74 among AR only, AR+SsNP, AR+SwNP, and bronchial asthma was estimated by the  
75 Relative Risk Ratio (RRR) using multinomial regression models.

76 **Results:** The prevalence of AR in the sample was 25.4% (95%CI:24.2-26.6). The self-  
77 reported diagnosis of AR+SsNP and AR+SwNPwas reported by 5.7% (95%CI:5.0-6.3) and  
78 by 1.2% (95%CI:0.9-1.5) of the subjects respectively. Current asthma was reported by  
79 17.5% of the AR subjects. In the adjusted multivariate analysis, the risk of having current  
80 asthma (RRR=2.31; 95%CI:1.29-4.15), of having at least 1 asthma attack/year  
81 (RRR=2.30; 95%CI:1.19-4.46) and of having an emergency department admission for  
82 respiratory diseases (RRR=5.61; 95%CI:1.81-23.92) was higher for subjects with  
83 AR+SwNP , than subjects with AR only.

84 **Conclusions:** The diagnosis of allergic rhinitis in the epidemiological setting includes  
85 heterogeneous upper airway diseases that affect the clinical features of AR and its  
86 interactions with asthma.

87

88

89 **Introduction**

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

94 In epidemiology, validated questionnaires are used for the diagnosis of allergic rhinitis. An  
95 Italian study showed that the reliability of the question on allergic rhinitis seems adequate  
96 for epidemiological purposes and about 20% of the subjects who answered positively to  
97 the question on allergic rhinitis had had a negative skin prick test or specific IgE levels [7].

98 Studies focusing on the non-allergic upper airway diseases (such as chronic rhinitis and  
99 rhinosinusitis, with and without nasal polyps) showed the importance of the association  
100 between these diseases and severe/not controlled asthma suggesting that these upper  
101 airway diseases have a greater impact on asthma compared to allergy [8-12].

102 The overlap between allergic and non allergic upper airways diseases has been discussed  
103 in clinical studies, but its epidemiological results remain controversial and poorly defined  
104 [13-15].

105 This study aimed to evaluate the prevalence of AR, AR with Sinusitis without Nasal Polyps  
106 (AR+SsNP), AR with Sinusitis and with Nasal Polyps (AR+SwNP) and if the interaction  
107 between AR and bronchial asthma has been affected by concomitant upper airway  
108 diseases.

109

## 110 **Materials and Methods**

111 The study Gene Environment Interactions in Respiratory Diseases (GEIRD), is a  
112 multicentre survey on respiratory health in the general adult population, carried out  
113 between 2007 and 2010. In the frame of this study, random samples of about 3000  
114 subjects from the general population aged 20 to 44 years old (male/female ratio=1) were  
115 selected from the registry of the local health authority in each of the four Italian centres:  
116 Pavia, Sassari, Torino, Verona [16].

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

120 The GEIRD screening questionnaire (available in [www.geird.org](http://www.geird.org)), a modified version of  
121 questionnaires used in previous studies [17] included self reported information about  
122 respiratory symptoms (asthma, rhinitis and chronic bronchitis, cough and phlegm),  
123 environmental exposures (smoking habits) and education level as a proxy of socio-  
124 economic status.

125

### 126 *Definitions and conditions*

127 The presence of AR was based on the answer to the questionnaire: “Do you have any  
128 nasal allergies including hay fever?”. Subjects who answered “yes” were classified as  
129 subjects with AR. If a subject answered “no” to the question he/she was classified as a  
130 subject without allergic rhinitis.

131 Subjects with allergic rhinitis subjects were further classified as follows:

- 132 • AR only: subjects with AR but without sinusitis (S) or Nasal Polyps (NP);
- 133 • AR+SsNP: subjects with AR and who also answered “yes” to the question: “Do  
134 you suffer from sinusitis?”;

- 135           • AR+SwNP: subjects with AR and Sinusitis and who also answered “yes” to the  
136           question: “Do you suffer from nasal polyps?”.

137 The presence of asthma was defined as :

- 138           • physician-diagnosed asthma if he/she answered “yes” to both of the following  
139           questions:” Have you ever had asthma?” and “ Was this confirmed by a doctor?”;  
140           • current asthma if he/she had physician-diagnosed asthma and took any  
141           medicines for asthma and had had an attack of asthma or at least one among  
142           the following asthma-like symptoms: wheezing, chest tightness, shortness of  
143           breath, in the last 12 months.

144 As indicators of asthma severity/control we used:

- 145           • the number of asthma attacks reported by the subject in the last 12 months  
146           classified as: “at least 1 asthma attack” and “>3 asthma attacks” ;  
147           • the presence of the *asthma-chronic obstructive pulmonary disease (COPD)* overlap  
148           syndrome, when a subject with current asthma answered “yes” to the following  
149           question: “Have you ever been told by a doctor that you have or had chronic  
150           bronchitis, COPD or emphysema?”  
151           • the intake of drugs for rhinitis and asthma based on the answers to the following  
152           questions: “Have you used any medicines for asthma in the last 12 months  
153           (including inhalers, aerosols or tablets)?” and “Have you used any medicines for  
154           rhinitis in the last 12 months (including inhalers, aerosols or tablets)?”.

155 A four level variable was computed to evaluate which type of drugs a subjects used:  
156 “no medicines” if a subject answered “no” to both questions; “only asthma  
157 medicines” if a subjects took medicines for asthma and had not taken medicine for  
158 rhinitis in the last 12 months; “only rhinitis medicines” if a subjects took  
159 medicines for rhinitis and had not taken medicine for asthma in the last 12 months;



160 “both” if a subject had taken medicines for both rhinitis and for asthma in the last 12  
161 months.

162 The presence of chronic cough and phlegm assessed by a positive answer to the question  
163 “Have you had coughing and phlegm on most days for a minimum of 3 months a year and  
164 for at least 2 successive years?”

165 Also, a subject has been to Emergency Department (ED) for respiratory diseases if he/she  
166 answered “yes” to both of the following questions: “In the past 3 months have you been to  
167 Emergency Department for any reason, excluding accidents and injuries?” and “Was it due  
168 to respiratory problems?”.

169

#### 170 *Confounders*

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

177

#### 178 *Statistical analysis*

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

181 The associations among different allergic rhinitis overlapping diseases (AR only,  
182 AR+SnNP, AR+SwNP), and other outcomes (diagnosed and current asthma, number of  
183 asthma attacks, asthma-COPD overlap syndrome, cough and phlegm and ED visits for  
184 respiratory diseases), were assessed by using multinomial regression models adjusted for  
185 potential confounders (gender, age, smoking habits, level of education, season of

186 response, type of contact, percentile rank of cumulative response and centre). The  
187 Relative Risk Ratio (RRR) was estimated by choosing the group with AR only as the  
188 reference category. A p-value  $<0.05$  was considered statistically significant. Statistical  
189 analyses were performed with STATA 12.1 (Stata Corp LP, College Station, TX, USA).  
190

191 **Results**

192 *Prevalence of allergic rhinitis and demographic data*

193 Overall 5162 subjects filled in the questionnaire in the 4 centres. The response rate was  
194 53%, ranging from 37.1% (Pavia) to 67.7% (Verona). The overall prevalence of allergic  
195 rhinitis in the study was 25.4% (95%CI 24.2-26.6). The subjects who self-reported  
196 diagnosis of AR+SsNP and AR+SwNP were 5.7% and 1.2% respectively.

197 The subjects with AR were younger (table 2), fewer current smokers and they had a higher  
198 level of education than those without AR. The distribution of sex and education level  
199 among the three different groups of upper airway diseases (AR only, AR+SsNP and  
200 AR+SwNP) was statistically significant. The percentage of females was lower in subjects  
201 with AR+SwNP (36.1%) compared to the other two groups (51.8% and 63.5% for AR and  
202 AR+SsNP respectively). The level of education was significantly lower for subjects with  
203 AR+SwNP than for those of the other two groups ( $p=0.019$ ).

204

205 *Overlapping upper airway diseases and asthma*

206 Overall, 23.8% of the subjects with AR had a physician diagnosed asthma and 17.5% of  
207 the subjects reported current asthma at the time of the survey (table 3). The prevalence of  
208 current asthma and the distribution of the control/severity markers of coexisting asthma  
209 varied significantly across the three different groups of AR subjects. In particular, the  
210 prevalence of current asthma increased from 15.8% in the group of AR only to 31.2% in  
211 the group AR+SwNP ( $p<0.001$ ). The same statistically significant trend was found when  
212 considering the proportion of subjects who had at least one asthma attack in the last 12  
213 months ( $p=0.01$ ), of subjects with the asthma-COPD overlap syndrome ( $p=0.03$ ), of  
214 subjects with chronic cough and phlegm ( $p<0.001$ ) and of those who had been  
215 hospitalized for respiratory diseases ( $p<0.01$ ).

216 The only exception to this general trend was the prevalence for subjects who had had  
217 more than three asthma attacks/year which, was similar in the three groups of upper  
218 airway diseases ( $p=0.76$ ).

219 In the multivariate analysis (table 4), after adjusting for potential confounders, the subjects  
220 with AR+SwNP, had a statistically significant increased risk of having current asthma  
221 (RRR=2.31; 95%CI:1.29-4.15), of having at least one asthma attacks in the last year  
222 (RRR=2.30; 95%CI: 1.19-4.46) and of having an ED admission for respiratory disease in  
223 the last 3 months (RRR= 5.61; 95%CI: 1.81-23.92) than subjects with AR only.

224 Finally, the subjects with AR+SsNP and AR+SwNP had a statistically significant increased  
225 risk of having cough and phlegm (RRR=2.59; 95%CI: 1.89-3.54 and RRR=2.91; 95%CI:  
226 1.63-5.21 respectively) than subjects with AR only, while the asthma-chronic bronchitis  
227 overlap syndrome did not show statistically significant variations among the AR groups.

228

229 *Overlapping upper airway diseases and drug intake for rhinitis and asthma.*

230 Overall, 54% and 17.5% of subjects with AR had used medication for rhinitis and asthma  
231 respectively in the last year. After adjusting for potential confounders, in the multivariate  
232 analysis we found an increased risk that the subjects with AR+SsNP and AR+SwNP took  
233 medications both for rhinitis (RRR=1.91; 95%CI: 1.43-2.54 and RRR=2.46; 95%CI: 1.38-  
234 4.40 respectively) and for asthma (RRR=1.52; 95%CI: 1.08-2.15 and RRR=2.27; 95%CI:  
235 1.23-4.19 respectively) than subjects with AR only.

236 The overall distribution of the drugs intake for rhinitis and/or asthma across the three  
237 different groups of AR subjects is shown in the figure 1. The proportion of subjects who  
238 had not used medication in the last 12 months decreased from 46% in subjects with AR  
239 only to 28% in those with AR+S+P, whereas the use of medication for both rhinitis and  
240 asthma increased from 11% in the subjects with AR only to 28% in the subjects with  
241 AR+SwNP ( $p<0.001$ ).

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

248

249

250

251 **Discussion**

252 The most important finding of the study was that AR coexisted with sinusitis, with and  
253 without nasal polyps, in 6.9% of the general population. In addition, subjects with  
254 AR+SwNP had a higher likelihood of having more severe asthma than those with AR only.  
255 We also discuss the reliability of a self-reported diagnosis of sinusitis and the identification  
256 of subjects with nasal polyps as a subgroup of those with AR.

257

258 *Prevalence of the upper airway diseases.*

259 Overall, about 25% of the subjects reported AR, about 6% reported AR plus sinusitis with  
260 and without nasal polyps and these prevalence were similar across the centres.

261 Concerns about the self-reported diagnosis of chronic rhinosinusitis [18,19] have led to the  
262 development of a specific questionnaire, to diagnose chronic rhinosinusitis in the  
263 epidemiological setting [20].

264 A recent postal survey performed in Europe, using the EP3OS criteria questionnaire, found  
265 that the prevalence of chronic rhinosinusitis in the general population was 10.9%, with  
266 relevant variations of prevalence in the different geographical areas. In the only Italian  
267 center participating in this survey (Palermo) the prevalence was 10.8% (6,9% self-reported  
268 doctor-diagnosis) [21].

269 In the EP3OS study, the diagnosis of chronic rhinosinusitis includes patients with and  
270 without nasal polyps, while the diagnosis of chronic rhino-sinusitis is limited only to the  
271 young adult subjects with AR in our survey. Although the diagnosis of sinusitis was only  
272 assessed in subjects with AR and consisted of a single question in the questionnaire, we  
273 might suppose that the prevalence of AR+SsNP found in our survey is coherent with that  
274 found in Italy.

275 The prevalence of AR+SwNP found in our survey is in line with the estimated prevalence  
276 found both in Europe, which ranged from 2 to 4% of the general populations [22] and

277 found in a specific survey in France (2.1%) [23]. However other studies [24] found a higher  
278 prevalence of polyposis than our survey but this could be due to the fact that the it was not  
279 in a population-based study.

280 Overall, the reliability of the self-reported diagnosis of chronic rhinosinusitis and of  
281 AR+SwNP in our survey seems to be acceptable.

282

### 283 *Impact of allergic rhinitis on asthma*

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

291 In the first group, the increase in the proportion of subjects who took drugs for rhinitis and  
292 asthma suggests an increase in the severity of the upper airway diseases, which, does not  
293 correspond to an increase in the indicators of asthma severity (at least one asthma attack)  
294 and the ED visits for respiratory diseases.

295 Despite the increase in the drug intake in the group of subjects with polyposis, it is evident  
296 that there is poor asthma control in this case.

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

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

303 Although these two pathogenic mechanisms are not mutually exclusive, as confirmed by  
304 the detection of allergic sensitization in patients with nasal polyposis, the role of the main  
305 pathogenic mechanism seems to be clear [29].

306 When the severity of the upper airway diseases increased, a similar prevalence of the  
307 most unstable subset of asthmatic subjects (about 3% of them) was unexpected. This may  
308 be due to the poor adherence to the therapy [30].

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

312

### 313 **Strengths and Limitations**

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

319 The main limitation of our survey is that we could not determine the allergic pathogenesis  
320 of the upper airway diseases without cutaneous, serological [30] or any other clinical tests,  
321 which also influence the reliability of the self-reported diagnosis of the upper airways  
322 comorbidity, such as the diagnosis of chronic rhinosinusitis with and without polyps.  
323 Another important limitation is the lack of any information about type, duration and the  
324 adherence to the therapy for rhinitis and asthma. The only information available was if a  
325 subject had used or not used drugs for rhinitis and/or asthma in the last 12 months.

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357

### 358 **Competing Interests**

359 The authors confirm that Gabriele Nicolini is an employee of the “Chiesi Farmaceutici,  
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361 products in development or marketed products to declare. All remaining authors declare  
362 that they have no competing interests.

363

### 364 **Authors' Contributions**

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

369

370

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506 **TABLES AND FIGURES**

507

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

centers	n. of participating 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)
<b>overall</b>	<b>5162 (53,0)</b>	<b>25.4 (24.2-26.6)</b>	<b>18.6 (17.5-19.7)</b>	<b>5.7 (5.0-6.3)</b>	<b>1.2 (0.9-1.5)</b>

510 AR: Allergic Rhinitis; SsNP: Sinusitis without Nasal Polyps; SwNP= Sinusitis with Nasal  
 511 Polyps

512 CI: Confidence Interval

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

variables	without AR n= 3795	AR overall n= 1294	p	subjects with AR			p
				AR only n= 945	AR+Ss NP n= 288	AR+Sw NP n= 61	
<b>gender (%)</b>							
<i>female</i>	53.5	53.6	0.93	51.8	63.5	36.1	<b>&lt;0.001</b>
<b>age (%)</b>			<b>0.041</b>				0.516
<i>&lt;30</i>	26.2	29.7		30.4	29.5	19.7	
<i>30-39</i>	43.8	42.6		42.0	43.4	49.2	
<i>≥40</i>	30.0	27.7		27.6	27.1	31.1	
<b>smoking habits (%)</b>			0.048				0.181
<i>never smoker</i>	54.7	57.6		59.1	54.7	47.5	
<i>ex-smoker</i>	18.0	18.6		17.2	22.1	23.0	
<i>current smoker</i>	27.3	23.8		23.7	23.2	29.5	
<b>education (%)</b>			<b>0.006</b>				<b>0.019</b>
<i>primary and lower secondary school</i>	23.4	19.2		18.4	18.8	32.8	
<i>upper secondary school</i>	50.5	52.8		52.0	57.5	42.6	
<i>degree</i>	26.1	28.1		29.6	23.7	24.6	
<b>season (%)</b>			0.052				0.237
<i>spring</i>	46.1	46.0		47.3	42.0	44.3	
<i>summer</i>	15.4	15.0		15.8	12.8	14.8	
<i>autumn</i>	32.4	30.7		28.7	37.2	31.1	
<i>winter</i>	6.1	8.3		8.2	8.0	9.8	

519 AR: Allergic Rhinitis; SsNP: Sinusitis without Nasal Polyps; SwNP= Sinusitis with Nasal  
 520 Polyps

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

527

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	<b>&lt;0.01</b>
At least 1 asthma attack	11.5	10.2	13.9	21.3	<b>0.01</b>
>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	<b>0.03</b>
Drugs for asthma used in the last 12 months	17.5	15.2	22.4	29.3	<b>0.001</b>
Cough and phlegm	22.7	17.9	34.9	40.7	<b>&lt;0.001</b>
ED admissions for respiratory diseases	1.1	0.8	1.4	5.1	<b>&lt;0.01</b>
Drugs for rhinitis used in the last 12 months	54.0	48.9	65.2	70.5	<b>&lt;0.001</b>

528 AR: Allergic Rhinitis; SsNP: Sinusitis without Nasal Polyps; SwNP= Sinusitis with Nasal  
529 Polyps

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531 ED: Emergency Department

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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)	<b>2.31 (1.29-4.15)</b>
At least 1 asthma attack	1	1.39 (0.93-2.08)	<b>2.30 (1.19-4.46)</b>
>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	<b>1.52 (1.08-2.15)</b>	<b>2.27 (1.23-4.19)</b>
Cough and phlegm	1	<b>2.59 (1.89-3.54)</b>	<b>2.91 (1.63-5.21)</b>
ED admissions for respiratory diseases	1	1.91 (0.54-6.71)	<b>5.61 (1.81-23.92)</b>
Drugs for rhinitis used in the last 12 months	1	<b>1.91 (1.43-2.54)</b>	<b>2.46 (1.38-4.40)</b>

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 Rhinitis; SsNP: Sinusitis without Nasal Polyps; SwNP= Sinusitis with Nasal  
 539 Polyps

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541 ED: Emergency Department

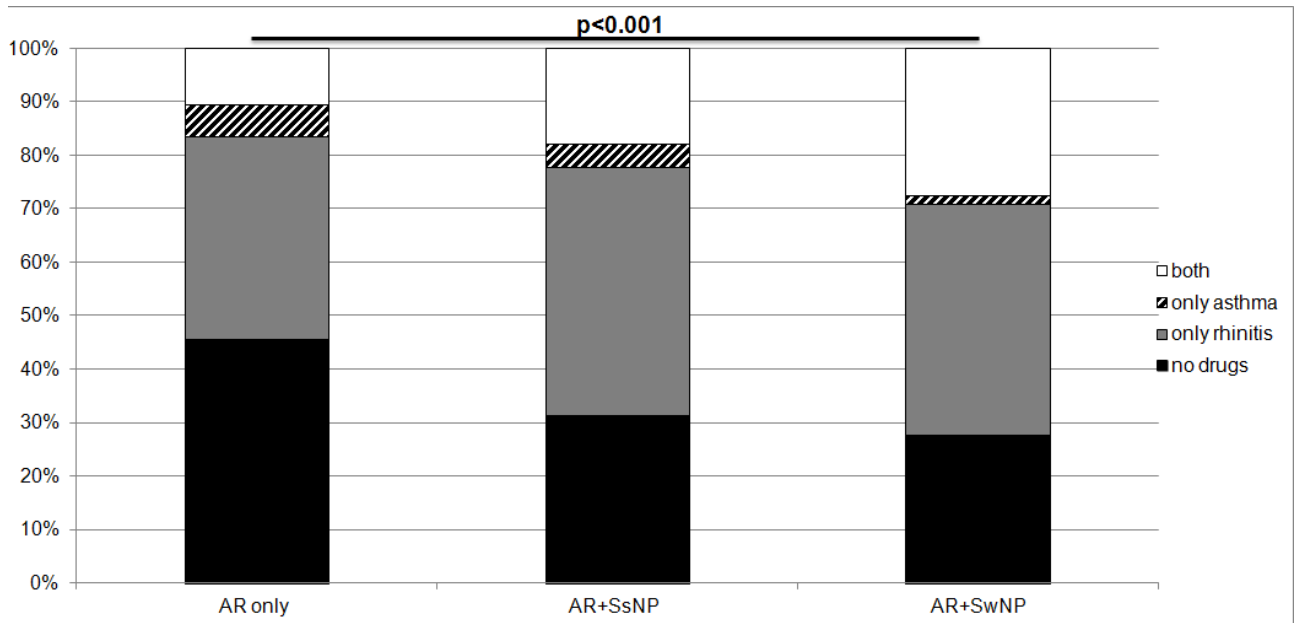
542 RRR: Relative Risk Ratio

543 CI: Confidence Interval

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



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550 AR: Allergic Rhinitis; SsNP: Sinusitis without Nasal Polyps; SwNP= Sinusitis with Nasal  
551 Polyps

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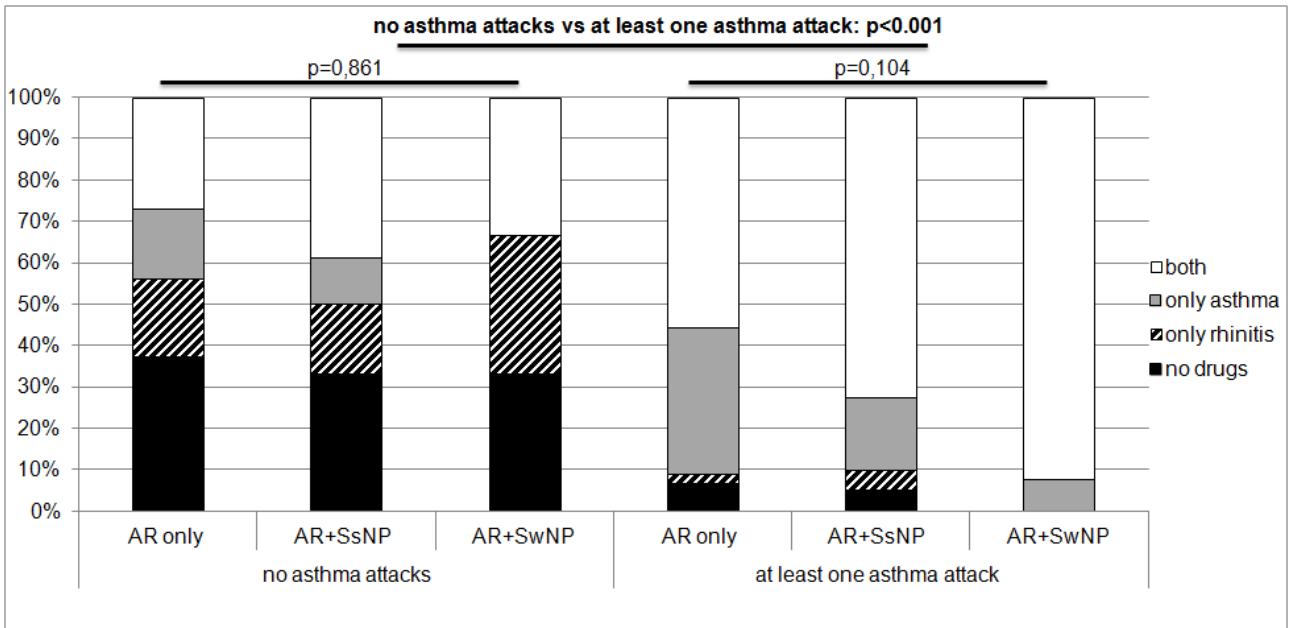
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558 Figure 2. Distribution of subjects with allergic rhinitis who used medication for rhinitis and  
 559 asthma in the last 12 months stratified by categories of rhinitis and asthma attacks



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561 AR: Allergic Rhinitis; SsNP: Sinusitis without Nasal Polyps; SwNP= Sinusitis with Nasal  
 562 Polyps

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