

## The sensitization pattern differs according to rhinitis and asthma multimorbidity in adults: the EGEA study.

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1 **The sensitization pattern differs according to rhinitis and asthma**  
2 **multimorbidity in adults: the EGEA study**

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36 **Abstract:**

37 **Background:** Mono- and polysensitization are different IgE-mediated allergic phenotypes in children.  
38 Allergic sensitization is associated with both allergic asthma and allergic rhinitis, however,  
39 associations between the sensitization pattern and particularly polysensitization with asthma and  
40 rhinitis remains poorly studied in adults.

41 **Aim:** The aim of this study was to assess how the allergic sensitization pattern associates with asthma,  
42 rhinitis and their multimorbidity.

43 **Methods:** 1,199 adults from the EGEA study, with extensive phenotypic characterization and all data  
44 available on skin prick tests to 10 allergens, total IgE and blood eosinophils were included. Using  
45 questionnaires only, participants were classified into 6 groups: asymptomatic (no asthma, no rhinitis),  
46 non-allergic rhinitis alone, allergic rhinitis alone, asthma alone, asthma+non-allergic rhinitis and  
47 asthma+allergic rhinitis. Mono- and polysensitization were defined by a positive skin prick test to one  
48 or more than one allergen respectively.

49 **Results:** Asymptomatic participants and those with non-allergic rhinitis alone were mostly non-  
50 sensitized (around 72%) while around 12% were polysensitized. Between 32 and 43% of participants  
51 with allergic rhinitis alone, asthma alone and asthma+non-allergic rhinitis were non-sensitized and  
52 between 37 and 46% of them were polysensitized. 65% of the participants with asthma+allergic  
53 rhinitis were polysensitized. The level of total IgE followed a similar trend to that of allergic  
54 sensitization. Eosinophils were increased in asthma, especially when associated with rhinitis. Nasal  
55 symptoms were more severe and eczema more common in participants with both asthma and allergic  
56 rhinitis than in the other groups.

57 **Conclusions:** Allergic sensitization and particularly polysensitization rates widely differ according to  
58 asthma and rhinitis status. This study emphasized the importance of taking into account  
59 multimorbidity between asthma and rhinitis and showed that allergic sensitization is not a dichotomic  
60 variable.

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62  
63

64 **Key words:** allergic sensitization, asthma, rhinitis, multimorbidity, monosensitization,  
65 polysensitization

66

67 **Abbreviations**

68 AR: Allergic rhinitis

69 ARIA: Allergic Rhinitis and its Impact on Asthma

70 BHR: Bronchial Hyperresponsiveness

71 D.Pteronyssinus: Dermatophagoides pteronyssinus

72 EGEA: Epidemiological study of the Genetics and Environment of Asthma

73 IgE: Immunoglobulin E

74 MeDALL: Mechanisms of the Development of ALLergy

75 NAR: Non-allergic rhinitis

76 SPT: Skin Prick Test

77

## 78 **Introduction**

79 According to the World Allergy Organization (1), IgE-mediated allergic diseases, including allergic  
80 respiratory diseases such as rhinitis (2) and asthma are complex (3). These diseases are associated  
81 with both allergen-specific IgE and non-allergic mechanisms that may coexist in the same patient. In  
82 addition, they tend to cluster and patients may present concomitant or consecutive diseases (allergic  
83 multimorbidity) (4) as shown in children within the European MeDALL project (5).

84 Most epidemiological studies define allergic status as being sensitized or not (thus as having at least  
85 one positive skin prick test or at least one specific IgE>0.35kU/L). Nevertheless, sensitization to an  
86 allergen does not necessary imply nasal symptoms (6) and, conversely, nasal symptoms may  
87 possibly be due to a non-allergic rhinitis despite an allergic sensitization. Over 70% of symptomatic  
88 patients are sensitized to more than one allergen i.e polysensitized as found in both children and  
89 adults (7-9). Important clinical and immunological differences exist between mono and  
90 polysensitized patients suggesting that polysensitization is the expression of a distinct disease both  
91 in children and adults (5,10,11). Moreover, persistence of allergic diseases over time is associated  
92 with multimorbidity and/or allergic polysensitization (2). A recent study in Finnish adults showed  
93 that polysensitization -but not monosensitization- was associated with asthma (12). All of these  
94 studies emphasize phenotypic differences between mono and poly sensitized subjects, as recently  
95 summarized in a review (6). However, to our knowledge, no study has ever specifically assessed the  
96 sensitization pattern (mono- vs polysensitization, total IgE rate, eosinophil counts, severity of the  
97 symptoms) according to asthma and rhinitis status in adults.

98 In adults, using an unsupervised approach, we have previously identified three clusters of rhinitis  
99 with similar characteristics similar to those known by clinicians but differing in term of allergic  
100 sensitization, and this whatever the asthma status (13). Furthermore, in the cluster combining asthma  
101 and allergic rhinitis, participants showed a particularly high rate of polysensitization compared to  
102 the other clusters. This finding prompted us to perform a study assessing allergic sensitization in  
103 relation to asthma and rhinitis. Our hypothesis is that allergic sensitization, and particularly  
104 polysensitization, differ according to asthma and rhinitis status comorbidity and, in adults, this  
105 confirms the MeDALL concept that has previously been shown in children (5).

106 The aim of this study was to assess how the allergic sensitization pattern, assessed by mono- vs  
107 polysensitization, total IgE, eosinophil counts and severity of the symptoms, associates with asthma,  
108 rhinitis and their multimorbidity in 1199 adults of the EGEA (Epidemiological study of the Genetics  
109 and Environment of Asthma) study.

## 110 **Methods**

111 *Study design*

112 The EGEA study is a French case-control and family study based on an initial group of asthma cases  
113 and their first-degree relatives, as well as a group of controls (EGEA1, n=2047;  
114 <https://egeanet.vjf.inserm.fr>).

#### 115 *Setting and participants*

116 The protocol and descriptive characteristics of the EGEA study have been previously published (14).  
117 Briefly, EGEA is a 20-year follow-up study combining a case-control study with a family study of  
118 asthma cases (children or adults). 2047 children (<16 years) and adults from five French cities were  
119 enrolled between 1991 and 1995. The participants included 348 cases with current asthma recruited in  
120 chest clinics, their 1244 first-degree relatives, and 415 population-based controls. A follow-up of the  
121 initial cohort was conducted between 2003 and 2007 (EGEA2) (15). Among the alive cohort (n =  
122 2,002), 92% (n = 1,845) completed a short self-administered questionnaire and among them 1,601 had  
123 a complete examination (1570 adults). All participants responded to questionnaires based on  
124 international standardized tools to characterize asthma, respiratory and allergic symptoms and  
125 treatments, and environmental exposures.

126 Ethical approval was obtained from the relevant institutional review board committees (Cochin Port-  
127 Royal Hospital and Necker-Enfants Malades Hospital, Paris). Written informed consent was signed by  
128 all participants.

#### 129 *Variables*

##### 130 *Allergic sensitization*

131 Skin-prick tests (SPTs) to 10 of the most common aero-allergens (cat, *Dermatophagoides*  
132 *pteronysinus*, olive, birch, *Parietaria judaica*, timothy grass, *Cupressus*, ragweed pollen,  
133 *Cladosporium herbarum*, *Alternaria tenuis*, Stallergènes, Antony, France) were selected for the  
134 analysis (16,17). Negative (uncoated) and positive (histamine) SPT controls were assessed. SPT with a  
135 mean wheal diameter 3mm  $\geq$  than the negative control was considered as positive (16). SPTs  
136 assessment was performed by trained professionals and in the same way for all adult participants,  
137 whatever the center. SPTs to *Blattella germanica* and *Aspergillus* were also available but not included  
138 in the analysis as the quality of the reagents was insufficient.

##### 139 *Asthma and Allergic rhinitis definitions*

140 Asthma status was based on a positive answer to either “*Have you ever had attacks of breathlessness*  
141 *at rest with wheezing?*” or “*Have you ever had asthma attacks?*” or as being recruited as an asthma  
142 case. Allergic Rhinitis (AR) ever was defined by a positive answer to nasal symptoms: “*Have you had*  
143 *a problem with sneezing or runny or blocked nose when you did not have a cold or the flu?*” and a  
144 positive answer to “*Have you ever had allergic rhinitis?*” or “*Have you ever had hay fever?*”. Non-  
145 allergic Rhinitis (NAR) ever was defined by a positive answer to nasal symptoms and a negative

146 answer to “*Have you ever had allergic rhinitis?*” and “*Have you ever had hay fever?*”.

147 The quantitative asthma symptom score, as defined by Pekkannen *et al.* was used to describe the  
148 phenotype of asthma and as a proxy of severity of asthma (18).

149 Participants were classified into 6 groups, based only on their responses to the questionnaire: no  
150 asthma and no rhinitis (Reference group), non-allergic rhinitis (NAR) only, allergic rhinitis (AR) only,  
151 asthma only (As+), asthma+NAR (As+NAR), and asthma+AR (As+AR). These groups are similar to  
152 those highlighted by a clustering approach, but using only two questions on rhinitis and not using  
153 allergic sensitization (13).

154 Nasal symptoms were considered, similarly to the ARIA guidelines (2), as intermittent if they occur  
155 more than one month per year but less than 4 days per week or as persistent if they occur more than a  
156 month per year and more than 4 days per week. Moreover, if the symptoms occurred less than one  
157 month per year, persistence of nasal symptoms was considered as rare. Severity of nasal symptoms  
158 was assessed using the answers to the question “*Have these nose problems disturbed you daily*  
159 *activities?*”. This enabled a score of disturbance to be obtained from 0 to 3 (0: no, 1: a little bit, 2:  
160 moderately, 3: a lot).

161 *Other phenotypes - definition*

162 Eczema, conjunctivitis or sinusitis were defined as a positive answer to “*Have you ever had eczema?*”  
163 (respectively conjunctivitis or sinusitis).

164 *Biological phenotypes*

165 Total IgE were assessed by the UniCAP system (Pharmacia®) from blood samples in a centralized  
166 laboratory, and expressed in international units (IU) per milliliter.

167 Eosinophil cell counts were obtained from white blood cell counts.

168 *Study size*

169 The present analysis was conducted in 1199 adult participants of EGEA2 who had available data on  
170 asthma status, rhinitis status, SPT, total Immunoglobulin E (IgE), and blood eosinophils. Since this is  
171 an exploratory study, no power calculation was needed.

172 *Bias*

173 Analyses were also performed using the 12 allergens including *Aspergillus* and *Blatta Germanica*, and  
174 results were very similar, with similar percentages of mono- and polysensitization according to the  
175 groups (data not shown).

176 Due to the familial design of the study, a sensitivity analysis was conducted in a sub-sample of the  
177 population with one randomly-selected member per family. These analyses with 566 participants have  
178 shown very similar results to those of the study on the 1199 participants (data not shown).

179 *Statistical analysis*

180 To test whether general, phenotypic and allergic characteristics differ among the groups and differs  
181 from the reference group (no asthma no rhinitis), the Chi2 test and univariate polytomous logistic  
182 regression with no further adjustment were performed. For variables available only in subjects with  
183 rhinitis (such as age of onset, persistence or severity) or asthma (such as age of onset), these tests were  
184 performed only among the adequate population (i.e subjects with rhinitis or asthma).

185 To test whether some groups tend to be more non-sensitized (no positive SPT) or monosensitized (1  
186 positive SPT) than poly-sensitized ( $\geq 2$  SPTs), a polytomous logistic regression was used, adjusting  
187 results on several variables: age, sex, smoking status and educational level, chosen as they differed  
188 significantly according to the six groups. The reference class was the group with neither asthma nor  
189 rhinitis. This same methodology was used to compare sensitization to each of the 10 allergens among  
190 the groups. Severity and persistence of nasal symptoms, total IgE level and eosinophil count were  
191 compared group by group using logistic regression adjusted for age, sex, smoking status and  
192 educational level.

193 As a sensitivity analysis, we also adjusted the results using occupation instead of educational level,  
194 adjusting on parental asthma and childhood spent on a farm.

195 All the analyses were performed using the R statistical software (19).

196 **Results**

197 *Characteristics of the participants*

198 Participants were classified into 6 groups: no asthma no rhinitis (Reference group, N=362), NAR  
199 alone (NAR, N=169), AR alone (AR, N=167), asthma alone (As+, N=65), asthma+NAR (As+NAR,  
200 N=78) and asthma+AR (As+AR, N=358). The characteristics are presented in Table I. The  
201 participants of the groups with asthma were younger (p-value As vs non-As:  $<0.001$ ), and more likely  
202 to be male (p-value As vs non-As: 0.015). The participants who had asthma and rhinitis – allergic or  
203 non-allergic - declared a younger age of onset than those without asthma (p-value rhinitis vs  
204 rhinitis+As:  $<0.001$ ). The participants with As+AR had a higher prevalence of eczema to those in the  
205 other groups (p-value $<0.05$  whatever the group).

206 *Allergic sensitization evaluated by SPT*

207 Participants without symptoms of rhinitis or asthma and those with NAR had no allergic sensitization  
208 in over 71%, and less than 14% were sensitized to over 2 allergens (Figure 1). Participants with AR  
209 alone or As+ alone had no allergic sensitization in about 33% of cases whereas about 42% of them  
210 were sensitized to over 2 allergens. Participants with As+NAR had no positive SPT in 43.6% of cases  
211 and 37.0% of them were sensitized to over 2 allergens. Participants with As+AR had no positive SPT  
212 in 14.8% of cases and 65% of them were sensitized to over 2 allergens.



213 Compared to the participants without asthma and rhinitis, polysensitization (*versus* non or mono-  
214 sensitized) was highly associated with AR alone and even more so with As+AR (crude and adjusted  
215 odds-ratios in Table 2). Lower aORs were observed for As+ and As+NAR and no significant  
216 association was found for NAR alone. Using different levels of adjustment did not modify the results  
217 (see Table E1 in the Online Repository)

#### 218 *Sensitization according to different allergens*

219 The repartition of the allergic sensitization according to the group and to the 10 allergens is given in  
220 figure 2. *D.pteronysinus*, cat, and allergens related to hay/pollen were the most common allergens.  
221 The sensitization rate to *D.pteronysinus* was higher in all groups of symptomatic participants i.e. AR  
222 alone, As+ alone, As+NAR and As+AR groups as compared to the reference group (no asthma no  
223 rhinitis). The sensitization rate to cat was higher in all groups of symptomatic participants except for  
224 the NAR alone group. For hay/pollen allergens, the sensitization rate was particularly high for  
225 participants with AR alone and As+AR, whatever the allergen. Sensitization to timothy grass was the  
226 most common allergen for hay/pollen, followed by Olive tree. Sensitization rates to *Parietaria* and  
227 Cypress were low in all groups. Sensitization to *Cladosporium* and *Alternaria* was over 10% only in  
228 the As+ alone and As+AR groups.

#### 229 *Persistence and severity of nasal symptoms*

230 Nasal symptoms were more persistent in As+AR participants compared to As+NAR (p-value adjusted  
231 <0.001) or NAR alone (adjusted p-value=0.018) and slightly more persistent compared to AR alone  
232 (adjusted p-value=0.14). There was no difference between NAR alone and As+NAR (adjusted p-  
233 value=0.81). Nasal symptoms were more severe in participants with As+AR compared to As+NAR  
234 (p-adjusted<0.001), NAR alone (p-value<0.001) or AR alone (adjusted p-value=0.010). Nasal  
235 symptoms were also more severe in participants with As+NAR than in those with NAR alone  
236 (adjusted p-value=0.036) (Table 1).

#### 237 *Blood eosinophils and total IgE*

238 Blood eosinophil counts were higher in all symptomatic groups compared to the reference group (no  
239 asthma, no rhinitis). AR alone and As+ alone had a similar level whereas eosinophils were even higher  
240 when asthma was associated with rhinitis, allergic or non-allergic. Total IgE levels followed a similar  
241 trend to allergic sensitization, with a higher value in participants with As+AR, compared to  
242 participants without asthma and rhinitis or NAR alone, whereas participants with As+ alone, As+NAR  
243 and As+AR had intermediate levels (Table 1).

## 244 **Discussion**

245 In the present study, using new analyses, we showed that polysensitization was the highest among  
246 participants with asthma and allergic rhinitis multimorbidity by comparison to asthma or rhinitis

247 alone. Asymptomatic participants or those with non-allergic rhinitis are in the vast majority, non-  
248 sensitized or sensitized to one allergen. Levels of total IgE followed a similar trend to allergic  
249 sensitization. Eosinophil counts were increased in asthma alone, and the greatest number was found  
250 when asthma was associated with rhinitis. Nasal symptoms were more severe in participants with  
251 As+AR than in participants from other groups.

252 This study presents several strengths and limitations. It was performed among over 1000 adults from  
253 the EGEA study that is not representative of the French population, but enriched in participants with  
254 asthma, allowing a good statistical power to address allergic multimorbidities. This particular design  
255 (case control and family study) and the age differences at inclusion between cases, relatives and  
256 controls explains in part that participants with asthma were younger than participants without asthma  
257 (20). The age of onset of nasal symptoms differs according to the group, and is significantly lower in  
258 participants with allergic rhinitis. This result is not surprising because allergic rhinitis often appears at  
259 a younger age than non-allergic rhinitis whereas non-allergic rhinitis is often characterized by onset  
260 after the age of 20 years (21). The age of onset of nasal symptoms is also lower in participants with  
261 asthma, and this can be explained by the concomitance of two facts: (i) rhinitis and asthma are  
262 strongly related, often coexist, and one often leads to the other; (ii) the mean age of onset of asthma is  
263 generally lower than 20 years and, even more, often occurs during childhood. Thereupon, the age of  
264 onset of nasal symptoms was the lowest in participants with asthma+AR. The extensive phenotypic  
265 characterization regarding respiratory health, and particularly rhinitis and asthma, is clearly a strength.  
266 Rhinitis was not diagnosed by a physician but was defined by self-reported symptoms, as is mostly the  
267 case in epidemiological studies. Thereby, using self-reported questionnaires leads to a possible  
268 misclassification of the subjects due to a poor knowledge of the disease. However, to classify our  
269 participants we used their answers to questions from an interviewer-based, standardized and validated  
270 questionnaire from the European Community Respiratory Health Study (ECRHS). Several  
271 epidemiological studies have already used these self-reported symptoms to define rhinitis (22-24).  
272 Using self-reported questionnaires also leads to another possible misclassification due to recall bias, as  
273 is often the case in epidemiology. The differentiation between allergic and non-allergic rhinitis was  
274 also based on self-reported symptoms and did not take allergic sensitization into account. This  
275 classification could be surprising at first glance, as some participants have unusual characteristics such  
276 as in the NAR or no rhinitis groups where some reported hay fever or allergic rhinitis or in the AR  
277 group where some were not sensitized to any of the 10 allergens. This definition, although unusual,  
278 enabled us to refine questionnaire-based phenotypes and our results support that choice. In our  
279 previous unsupervised study, we found 3 clusters of rhinitis (13) whatever the asthma status. Whereas  
280 characteristics of the participants were similar to the phenotypes of rhinitis known by clinicians, the  
281 allergic sensitization differed strongly among the three phenotypes. In this study, we have put forward  
282 3 groups based only on two frequent rhinitis questions. The level of allergic sensitization was similar

283 to the one found in the cluster analysis as opposed to the classical phenotypes, and this confirms the  
284 interest of taking this particular definition of rhinitis. Another limitation of our study is the difficulty  
285 to distinguish allergic asthma from non-allergic asthma phenotypes. First, because we stratified  
286 asthma sub-groups according to rhinitis, and secondly because of the inherent difficulty to  
287 differentiate between both types of asthma in epidemiological settings. However, participants with co-  
288 occurrence of allergic asthma and non-allergic rhinitis should exist and this may be one explanation as  
289 to why participants with asthma+NAR were sensitized.

290 In this study, we decided to define allergic sensitization using SPTs rather than specific-IgE – because  
291 the SPTs have a better predictive value for rhinitis (25). Thus, some differences may be found with  
292 other studies, since the two methods are not exactly comparable (2). Furthermore, SPTs were defined  
293 at the extract level (i.e. IgE reactivity to several non-related - or not obviously related - allergenic  
294 source materials) and not at the molecular level (i.e. IgE reactivity to several nonrelated - or non-  
295 obviously related - allergenic molecules) (5). This could have changed the way of defining  
296 polysensitization and may have increased the number of allergenic molecules detected. As allergic  
297 sensitization is a transient phenotype and as asthma is a complex disease that changes over time, it  
298 would have been interesting to perform a longitudinal analysis. However, EGEA1 questionnaires  
299 regarding rhinitis were slightly different to those in EGEA2 and 30% of the participants were children,  
300 and no SPT were available at the second-follow-up of EGEA. This disabled the opportunity to  
301 perform the longitudinal analysis in EGEA, but the question remains of interest.

302 Among the 10 studied allergens, the most frequently involved were *D.pteronysinus*, cat, Timothy  
303 grass and Olive tree, and this whatever the group. Participants with As+AR had the highest rate of  
304 sensitization to cat and *D.pteronysinus*, but also to all the allergens related to hay/pollen and  
305 *Alternaria*. Participants with AR alone and As+AR were particularly sensitized to allergens related to  
306 hay/pollen which bring out the “hay fever” part of allergic rhinitis. Participants with asthma seem to  
307 be particularly sensitized to *Alternaria* and *Cladosporium*, which is concordant with the literature  
308 (26,27). The 10 allergens tested were chosen for being the most common, but it is possible that  
309 participants are sensitized to other allergens such as dog or *Dermatophagoides farinae* (28), and then,  
310 considering these other allergens may increase the number of positive SPT. However, it is unlikely  
311 that adding more allergens would increase the number of sensitized participants as it has been shown  
312 that using from eight to ten allergens allowed the identification of the majority of sensitized subjects  
313 (29). Overall, participants of the As+ alone and As+NAR groups had significantly higher rates for  
314 *D.pteronysinus*, cat, Timothy grass and Olive tree than the reference group. This suggests that these  
315 allergens are not only related to nasal symptoms or allergic rhinitis, but also to asthma itself.

316 In the present study, we showed that mono- and polysensitized individuals represent different  
317 phenotypes of allergic diseases. This was found for children in the EU-FP7 MeDALL project (5,30)  
318 and now also extends to adults. More specifically, we confirmed that asymptomatic subjects are often

319 monosensitized as shown in Russian and Finnish children for House Dust Mite monosensitization  
320 (31). Furthermore, allergic sensitization was lower in asymptomatic subjects than in symptomatic  
321 ones as found in a Finnish adult case-control on asthma study (12). We have also found that the  
322 polysensitization rate is the highest among participants with both allergic rhinitis and asthma, which is  
323 concordant with previous studies among European adults (32,33). Recent studies in genetics, including  
324 one using the EGEA study data (34,35), have also shown that genetic variants associated with asthma  
325 plus hay fever or asthma plus allergic rhinitis were different from those associated with only asthma or  
326 hay fever. This again suggests that asthma plus allergic rhinitis is a very specific phenotype. The  
327 As+AR group seems to have a specific phenotype - characterized by a high level of polysensitization,  
328 total IgE and eosinophil counts, and severe symptoms. This group is also the one with the youngest  
329 age of onset of asthma and rhinitis.

330 Interestingly, one could note a trend in the number of positive SPTs: being the lowest in asymptomatic  
331 and NAR alone participants, the highest in multimorbid diseases (participants with As+AR), and with  
332 intermediate levels in participants with AR alone, As+ alone or As+NAR. This trend was also found  
333 when looking at each allergen separately. Moreover, nasal symptoms were more severe among  
334 participants with As+AR, compared to the other groups with rhinitis. We showed that the As+AR  
335 group is the most polysensitized group. This result is concordant with the following studies where  
336 polysensitization was associated with more severe symptoms: (i) 9044 children aged 0-18 years in the  
337 Netherlands (10), (ii) 2415 young Italian adults with allergic rhinitis (8), (iii) 3225 Spanish and  
338 Portuguese patients with allergic rhinitis aged 10-50 years (33), (iv) 130 Korean patients with  
339 childhood asthma (36). On the contrary, other studies have shown no change in severity according to  
340 polysensitization, neither in the 784 children aged 6-18 years in primary care diagnosed with allergic  
341 rhinitis (9), nor in the 523 Finnish adults with asthma from a population-based case-control (12).  
342 These discordant results do not seem to be due to the differences in the age of the participants, to the  
343 size of the samples, or to geography, as the studies were conducted in both children and adults in  
344 America, Europa or Asia. However, the different protocols used to define asthma or rhinitis (by  
345 questionnaire, by relevant medication use, by history of symptoms, by lung function test, by a  
346 physician or GP, by GINA or by ARIA classification), and allergic sensitization (by SPT or by  
347 specific-IgE) may partly explain the between-study discrepancies. Furthermore, we also found that  
348 participants with As+NAR had more severe nasal symptoms compared to those with NAR only,  
349 meaning that severity is not related only to sensitization, but also to multimorbidity diseases. These  
350 results suggest that multimorbidity and polysensitization are two different aspects of allergic disease,  
351 probably interacting together.

352 The MeDALL study in birth cohorts showed that multimorbid-polysensitized participants have a  
353 more persistent disease, and the authors suggested that a recurrence of a Th2 pathway may partly  
354 explain the results (5). The current study confirms the findings of the MeDALL study in adults, with

355 a multimorbid-polysensitized phenotype associated with an earlier onset and a greater severity  
356 compared to other phenotypes. Therefore, the same hypothesis may be proposed to explain, at least  
357 in part, our results. Our results suggest that this multimorbid-polysensitized phenotype could  
358 constitute a specific phenotype. A key unanswered question is the extent to which a particular  
359 phenotype (pattern) profile may identify "treatable" traits. Further researches is required to explore  
360 this possibility. Overall, this study emphasized the importance of taking into account multimorbidity  
361 between asthma and rhinitis and showed that allergic sensitization should not be used as a  
362 dichotomic variable. This result may lead to a different classification of allergic phenotypes in  
363 future epidemiological studies.

364

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392 **Supporting Information**

393 Additional Supporting Information may be found in the online version of this article:

394 Table E1: OR with different adjustments of the association between polysensitization (*versus* no or  
395 monosensitized) and the 6 groups

396 Table E2: adjusted OR of the association between allergic sensitization to each of the 10 allergen and  
397 the 6 groups

398

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Table 1: Characteristics of the participants

		No asthma, no rhinitis	NAR alone	AR alone	Asthma alone (As+)	Asthma +NAR	Asthma + AR	p crude, overall
<b>N</b>		362	169	167	65	78	358	
<b>Age, mean±sd</b>		46.8±16.3	47.2±16.3	45.2±14.8	40.8±17.1	40.2±17.9	38.4±16.0	<0.0001
<b>Sex, % women</b>		50.0	60.9	57.5	47.7	43.6	48.0	0.02
<b>Tobacco status, %</b>	Non-smoker	49.7	50.3	52.7	41.5	50.0	51.1	0.51
	Ex-smoker	29.2	26.0	26.9	35.4	23.1	22.9	
	Smoker	21.1	23.7	20.4	23.1	26.9	26.0	
<b>BMI, mean±sd</b>		24.6±3.8	23.9±3.8	24.1±3.5	24.8±3.7	25.0±4.4	23.7±3.9	
<b>Educational level, %</b>	Low	30.9	27.8	21.0	21.5	29.5	16.3	0.0008
	Medium	23.8	25.4	22.8	24.6	21.8	32.6	
	High	45.3	46.7	56.3	53.8	48.7	51.1	
<b>Current nasal symptoms, %</b>			84.4	87.3		85.5	90.7	0.17
<b>Eyes symptoms associated, %</b>			32.1	76.6		47.4	80.4	<0.0001
<b>Persistence of nasal symptoms %</b>	Rare		50.7	42.5		53.6	30.4	<0.0001
	Intermittent		17.8	26.7		17.4	31.0	
	Persistent		31.5	30.8		29.0	38.7	
<b>Severity of nasal symptoms (disturbance), %</b>	No		76.7	50.7		64.7	40.4	<0.0001
	Low		17.1	33.6		22.1	32.4	
	Medium		4.8	13.0		5.9	18.3	
	High		1.4	2.7		7.4	9.0	
<b>Age of onset of nasal symptoms, mean±sd</b>			32.7±18.8	25.1±15.0		23.2±17.7	14.2±12.2	<0.0001
<b>Eczema, %</b>		22.7	25.6	35.3	38.5	38.5	52.7	<0.0001
<b>Conjunctivitis, %</b>		13.8	22.3	46.7	26.6	25.7	55.5	<0.0001
<b>Sinusitis, %</b>		34.9	47.6	59.3	47.7	50.0	58.0	<0.0001

Allergic rhinitis, %		5.5	0	73.7	0	0	81.3	<0.0001
Hay fever, %		10.8	0	77.8	0	0	78.2	<0.0001
Current asthma, %		0	0	0	91.5	96.6	97.1	0.17
Asthma Symptom score, %	0	77.6	66.2	62.5	27.7	22.4	17.6	<0.0001
	1	19.9	25.4	31.2	36.2	36.2	27.6	
	2	2	7	3.8	25.5	13.8	22.8	
	3	0.5	1.4	2.5	6.4	19	20.2	
	4	0	0	0	4.3	6.9	9.9	
	5	0	0	0	0	1.7	1.8	
BHR, % of yes		23.7	28.4	29.8	55.8	69.8	67.8	<0.0001
FEV1, % predicted $\pm$ sd		107	106	109	94.9	95.5	98.2	0.0006
Age of onset of asthma, mean $\pm$ sd					15.8 $\pm$ 15.5	19.9 $\pm$ 16.3	13.9 $\pm$ 14.3	0.0015
Eosinophils, *, mean $\pm$ sd		149 $\pm$ 106	178 $\pm$ 145	191 $\pm$ 123	196 $\pm$ 129	249 $\pm$ 198	253 $\pm$ 192	<0.0001
Total IgE, *, IU/mL, geometric mean $\pm$ sd		33.9 $\pm$ 3.7	47.9 $\pm$ 4.6	79.4 $\pm$ 3.6	72.4 $\pm$ 5.1	100.0 $\pm$ 5.6	166.0 $\pm$ 3.6	<0.0001
Number of positive SPT, mean $\pm$ sd		1.4 $\pm$ 0.9	1.5 $\pm$ 1.1	2.7 $\pm$ 1.7	2.6 $\pm$ 1.6	2.3 $\pm$ 1.5	3.5 $\pm$ 1.8	<0.0001

NAR: Non-allergic rhinitis, AR: Allergic rhinitis, sd: standard deviation

FEV1: Forced Expiratory Volume in one second, BHR: Bronchial Hyper Responsiveness (Methacholine test, PD<sub>20</sub>≤4 mg, Methacholine challenge test was not performed if baseline FEV1 <80% predicted, PD= Provocative Dose), IgE: Immunoglobulin E, SPT: skin prick test

Table 2: Odds Ratio of the association between polysensitization (*versus* no or monosensitized) and the 6 groups

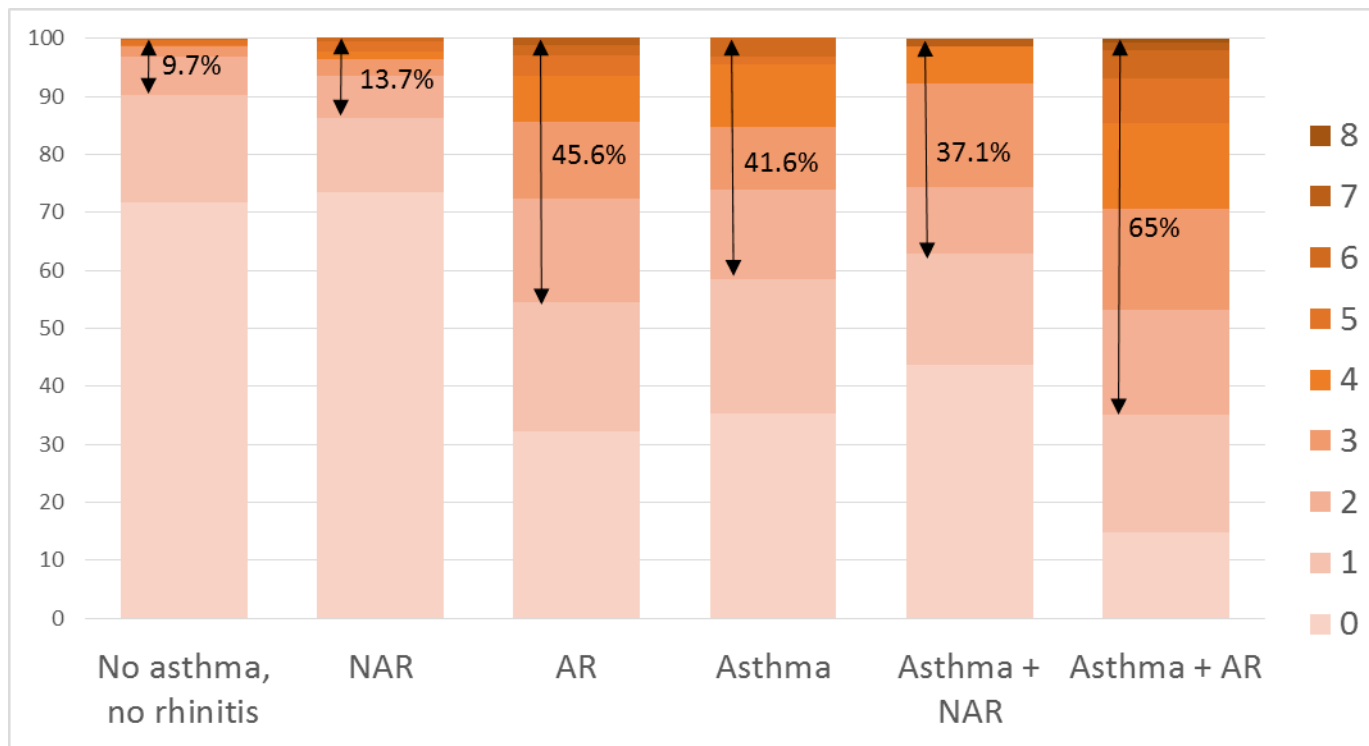
OR [95% CI]	No asthma, no rhinitis	NAR alone	AR alone	Asthma alone (As+)	Asthma +NAR	Asthma + AR	p-value
<b>crude OR</b>	1 (ref)	1.47[0.84-2.58]	7.8[4.91-12.40]	6.64[3.63-12.14]	5.53[3.11-9.84]	17.34[11.50-26.15]	
<b>aOR (on age, sex and education)</b>	1 (ref)	1.59 [0.89-2.84]	8.62[5.30-14.02]	6.01[3.20-11.31]	4.79[2.62-8.75]	15.24[9.95-23.34]	

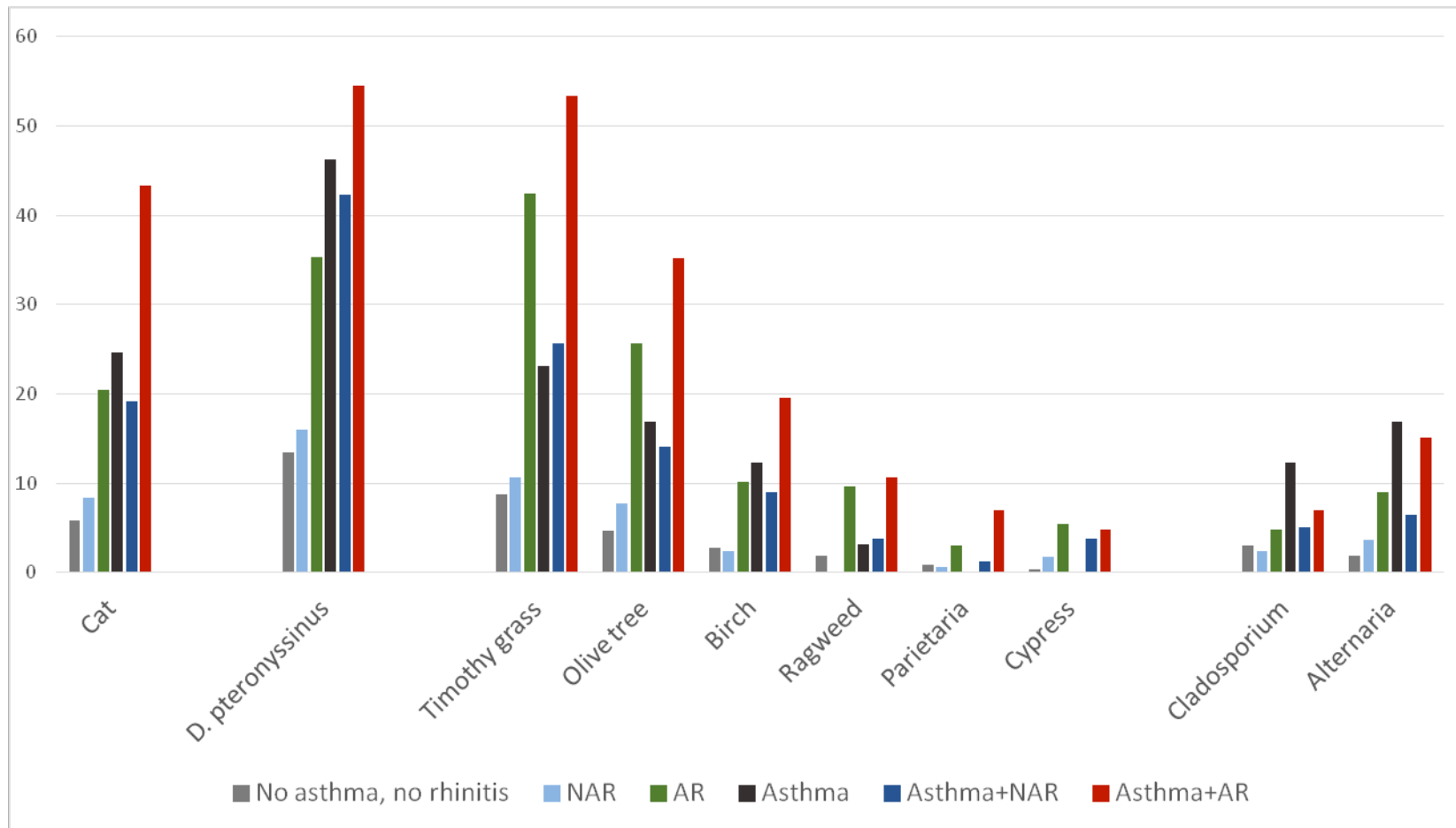
aOR: adjusted Odd Ratio, NAR: Non-allergic rhinitis, AR: Allergic rhinitis.

**Figure legends:**

Figure 1: Number of allergic sensitization –Number of positive SPT- according to the group and percentage of polysensitization

Figure 2: Rate of allergic sensitization to the 10 allergens according to the group







## **The sensitization pattern differs according to rhinitis and asthma multimorbidity in adults: the EGEA study**

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Supplementary material

***Respiratory phenotypes***

A lung function test with methacholine challenge was performed using a standardized protocol with similar equipment across centers according to the ATS/ERS guidelines (E1).

Methacholine challenge was performed unless baseline FEV<sub>1</sub> <80% predicted.

E1. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. *Eur Respir J*. 2005 Aug;26(2):319–38.

**Table E1:** OR with different adjustments of the association between polysensitization (*versus* no or monosensitized) and the 6 groups

<b>OR [95% CI]</b>	<b>No asthma, no rhinitis</b>	<b>NAR alone</b>	<b>AR alone</b>	<b>Asthma alone(As+)</b>	<b>Asthma +NAR</b>	<b>Asthma + AR</b>
<b>crude OR</b>	1 (ref)	1.5[0.8-2.6]	7.8[4.9-12.4]	6.6[3.6-12.1]	5.5[3.1-9.8]	17.3[11.5-26.2]
<b>aOR (on age, sex and education)</b>	1 (ref)	1.6[0.9-2.8]	8.6[5.3-14.0]	6.0[3.2-11.3]	4.8[2.6-8.8]	15.2[9.9-23.3]
<b>aOR (on age, sex, education, childhood life in farm, parental asthma)</b>	1(ref)	1.7[0.9-3.1]	10.6[6.3-17.8]	6.8[3.5-13.1]	4.8[2.5-9.1]	17.2[10.9-27.1]
<b>aOR (on age, sex, occupation, childhood life in farm, parental asthma)</b>	1(ref)	1.7[0.9-3.2]	10.8[6.4-18.1]	7.2[3.7-13.9]	4.7 [2.4-8.9]	17.5[11.0-27.6]

aOR: adjusted Odd Ratio, NAR: non-allergic rhinitis, AR: allergic rhinitis.

**Table E2:** adjusted OR of the association between allergic sensitization to each of the 10 allergen and the 6 groups

	<b>Group</b>	<b>aOR[95%]</b>
<b>Reference</b>	<b>No asthma, no rhinitis</b>	<b>1.0 (reference)</b>
<b>Cat</b> (n=255 with positive SPT)	NAR	1.46 [ 0.72-2.97 ]
	AR	3.98 [ 2.21-7.17 ]
	Asthma	4.45 [ 2.15-9.22 ]
	Asthma+NAR	3.42 [ 1.65-7.08 ]
	Asthma+AR	10.49 [ 6.39-17.22 ]
<b><i>Cladosporium herbarum</i></b> (n=60 with positive SPT)	NAR	0.74 [ 0.23-2.38 ]
	AR	1.48 [ 0.58-3.77 ]
	Asthma	4.12 [ 1.57-10.81 ]
	Asthma+NAR	1.71 [ 0.52-5.56 ]
	Asthma+AR	2.29 [ 1.09-4.80 ]
<b>Olive tree</b> (n=221 with positive SPT)	NAR	1.81 [ 0.85-3.86 ]
	AR	7.19 [ 3.91-13.22 ]
	Asthma	3.7 [ 1.62 -8.43 ]
	Asthma+NAR	2.8 [ 1.24 -6.32 ]
	Asthma+AR	9.32 [ 5.42-16.02 ]
<b>Birch</b> (n=116 with positive SPT)	NAR	0.91 [ 0.28-2.97 ]
	AR	3.92 [ 1.74-8.86 ]
	Asthma	4.12 [ 1.54-11.03 ]
	Asthma+NAR	2.74 [ 1 -7.54 ]
	Asthma+AR	6.8 [ 3.4 -13.57 ]
<b>Ragweed</b> (n=66 with positive SPT)	NAR	NC
	AR	5.34 [ 2.14-13.33 ]
	Asthma	1.44 [ 0.29-7.13 ]
	Asthma+NAR	1.8 [ 0.45 -7.19 ]
	Asthma+AR	5.77 [ 2.51-13.26 ]
<b><i>Dermatophagoides pteronyssinus</i></b> (n=393 with positive SPT)	NAR	1.32 [ 0.78-2.24 ]
	AR	3.63 [ 2.3 -5.72 ]
	Asthma	4.94 [ 2.72-9.00 ]
	Asthma+NAR	4.06 [ 2.3 -7.15 ]
	Asthma+AR	6.46 [ 4.41-9.46 ]
<b><i>Alternaria tenuis</i></b> (n=98 with positive SPT)	NAR	1.87 [ 0.62-5.68 ]
	AR	4.78 [ 1.9-12.03 ]
	Asthma	9.14 [ 3.37-24.83 ]
	Asthma+NAR	2.97 [ 0.91-9.69 ]
	Asthma+AR	7.42 [ 3.3-16.69 ]
<b>Timothy grass</b> (n=347 with positive SPT)	NAR	1.33 [ 0.71-2.49 ]
	AR	8.48 [ 5.16-13.96 ]
	Asthma	2.62 [ 1.29-5.31 ]
	Asthma+NAR	2.91 [ 1.52-5.57 ]
	Asthma+AR	9.94 [ 6.45-15.33 ]

<b><i>Parietaria judaica</i></b> <b>(n=35 with positive SPT)</b>	NAR	0.69 [ 0.07-6.68 ]
	AR	3.39 [0.79-14.44 ]
	Asthma	NA
	Asthma+NAR	1.38[0.14-13.59 ]
	Asthma+AR	8.03[2.38-27.17 ]
<b>Cypress</b> <b>(n=33 with positive SPT)</b>	NAR	6.27[0.65-60.88 ]
	AR	19.68[2.47-157.14]
	Asthma	NC
	Asthma+NAR	13.24[1.35-130.21]
	Asthma+AR	16.99[2.23-129.27]
<b>aOR: adjusted OR on age, sex, smoking status and educational level, NAR: non-allergic rhinitis, AR: allergic rhinitis, NC: not calculable (sample too small)</b>		