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1 **The asthma-rhinitis multimorbidity is associated with IgE**

2 **polysensitization in adolescents and adults**

3

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24

25 **Short Title**

26 Asthma-rhinitis multimorbidity and IgE polysensitization

27

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40 **Abstract**

41 **Background:** Children with multimorbid asthma and rhinitis show IgE polysensitization to
42 several allergen sources. This association remain poorly studied in adolescents and adults
43 using defined allergen molecules. We investigated IgE sensitization patterns towards a broad
44 panel of aeroallergen components in adults and adolescents with a focus on individuals with
45 asthma and rhinitis multimorbidity.

46 **Methods:** IgE reactivity to 64 microarrayed aeroallergen molecules was determined with the
47 MeDALL-chip in samples from the French EGEA study (n=840, age=40.7±17.1) and the Swedish
48 population-based birth cohort BAMSE (n=786, age=16±0.26). The age- and sex-adjusted
49 associations between the number of IgE-reactive allergen molecules (≥ 0.3 ISU) and the
50 asthma-rhinitis phenotypes were assessed using a negative binomial model.

51 **Results:** Groups representing four phenotypes were identified: no asthma-no rhinitis (A-R-;
52 30% in EGEA and 54% in BAMSE), asthma alone (A+R-; 11% and 8%), rhinitis alone (A-R+; 15%
53 and 24%), and asthma-rhinitis (A+R+; 44% and 14%). The numbers of IgE-reactive aeroallergen
54 molecules significantly differed between phenotypes (median in A-R-, A+R-, A-R+ and A+R+:
55 0, 1, 2 and 7 in EGEA and 0, 0, 3, and 5 in BAMSE). As compared to A-R- subjects, the adjusted
56 ratio of the mean number of IgE-reactive molecules was higher in A+R+ than in A+R- or A-R+
57 (10.0, 5.4 and 5.0 in EGEA and 7.2, 0.7 and 4.8 in BAMSE).

58 **Conclusion:** The A+R+ phenotype combined the sensitization pattern of both the A-R+ and
59 A+R-phenotypes. This multimorbid polysensitized phenotype seems to be generalizable to
60 various ages and allergenic environments and may be associated with specific mechanisms.

61

62

63 **Key words**

64 Allergens, Epidemiology, Multimorbidity, Polysensitization, Specific-IgE

65

66 **Abbreviations**

67 A: Asthma

68 EGEA: Epidemiological study of the Genetics and Environment of Asthma, bronchial

69 hyperresponsivness and atopy

70 FP7: Framework Programme 7 (European Union)

71 IgE: Immunoglobulin E

72 ISAC: Immuno solid-phase allergen chip

73 ISU: Standardized units for specific IgE

74 MeDALL: Mechanisms of the development of allergy

75 R: Rhinitis

76 **Introduction**

77 Allergic diseases are complex and represent multiple phenotypes (1) such as clinically silent
78 IgE sensitization, isolated phenotypes such as only rhinitis, asthma, dermatitis, food allergy,
79 and multimorbidities associating several conditions in the same subject.

80 In children, multimorbidities of allergic diseases share common causal mechanisms that are
81 partly IgE-mediated.(2) IgE sensitization is heterogeneous and important clinical and
82 immunological differences exist between mono- and poly- sensitized patients.(3-5) An
83 important result from the FP7-funded project MeDALL (Mechanisms of the Development of
84 Allergy) was the identification of the multimorbid polysensitized phenotype of allergic
85 diseases in children, characterized by children with asthma presenting both allergic
86 polysensitization and other allergic diseases, mainly rhinitis.(5) Although polysensitization and
87 allergic-related multimorbidity were known, they had not been associated in a single
88 phenotype. In MeDALL, using hypothesis and data-driven methods, this novel phenotype was
89 shown to be associated with some important features of allergic diseases including a low
90 probability of remission of IgE sensitization and symptoms,(6-8) elevated levels of total and
91 specific IgE,(9) high levels of blood eosinophils, and a high rate of allergy in family history. This
92 newly described phenotype is also associated with the severity of asthma,(10-13) rhinitis,(11-
93 13) atopic dermatitis(14) or food allergy.(15) However, this phenotype needs to be confirmed
94 also in adolescents and adults, to understand whether these associations are transient or
95 persistent along the life course. In a previous analysis in adults from the Epidemiological study
96 of the Genetics and Environment of Asthma, bronchial hyperresponsiveness and atopy - EGEA
97 study, first evidence was provided that polysensitization is associated with multimorbid
98 asthma and rhinitis.(16) However, the analysis was limited by use of allergen extracts which

99 represent mixtures of source-specific genuine allergen molecules and cross-reactive allergens
100 so that a true discrimination of co- and cross-sensitization could not be made (17, 18) and by
101 the fact that only a limited number of allergen extracts could be tested by skin prick testing.
102 Until recently, the IgE sensitization profiling in allergic multimorbidity has been based on a
103 limited number of allergens. Currently, the allergen micro-array technology makes it possible
104 to measure allergen-specific IgE antibody responses to a large number of allergen molecules.
105 In MeDALL, the immunoCAP ISAC chip technology (19, 20) was refined to increase its
106 sensitivity and to incorporate new allergens.(20) The resulting MeDALL chip has been
107 validated and tested in birth cohorts and allows measuring IgE responses to more than 170
108 allergen components with a sensitivity similar to that of the traditional ImmunoCAP as
109 validated using the major birch pollen allergen Bet v 1-specific IgE.(21-23)
110 The present cross-sectional study investigates if the multimorbid polysensitized phenotype
111 suspected in children could be generalized to adults and adolescents living in two different
112 allergenic environments (France and Sweden) using different cohort designs (i.e., a cohort
113 following a case-control study: EGEA, France (24) and a birth cohort: BAMSE, Sweden (25)).
114 IgE sensitization patterns towards a large variety of respiratory allergen components were
115 measured using the MeDALL micro-array technology.(21, 23)

116

117 **Methods**

118 ***Populations and study setting***

119 The present analysis relies on two populations, the EGEA study and the BAMSE birth cohort.

120 The EGEA1 study is composed of a group of 388 individuals with asthma enrolled in chest

121 clinics, 1,244 first-degree relatives and 415 control individuals.(26)Participants were recruited
122 through self-completed questionnaires and had a complete examination including pulmonary
123 function tests.(24) About 11 years later, 1,601 participants (77.1% of the original cohort + 58
124 new family members) took part in a complete examination (EGEA2). The analysis of IgE was
125 conducted with serum samples from 840 adults at EGEA2 (463 with and 377 without asthma).
126 Written consent was obtained from all participants. Ethical approval was obtained from the
127 ethics committees (Necker-Enfants Malades Hospital, Paris for EGEA2).

128 BAMSE is a population-based birth cohort comprising 4,089 children from representative
129 areas of Stockholm.(25) For this study, questionnaire data from baseline (2 months), 1, 2, 4,
130 8, 12 and 16 years were used. Blood was drawn at 4, 8 and 16 years. Sera were available for
131 64%, 60%, and 62% of the population.(6, 7) In 1,699 children, 42% of the original cohort, blood
132 samples were available from all three clinical follow-ups (4, 8 and 16 years). Of these children,
133 a subset of 800 was randomly selected. Permission for the study was obtained from the
134 Regional Ethical Review board at Karolinska Institutet at each follow up and parents of
135 participating children gave their informed consent.

136

137 ***Definition of asthma, allergic rhinitis and atopic dermatitis***

138 Validated questionnaires were used in both studies. In EGEA, ever asthma was defined by a
139 positive answer to either *“Have you ever had attacks of breathlessness at rest with*
140 *wheezing?”* or *“Have you ever had asthma attacks?”* or being recruited as an asthma case.
141 Allergic rhinitis ever was defined by a positive answer to *“Have you ever had allergic rhinitis?”*
142 or *“Have you ever had hay fever?”*. The age of asthma onset was estimated by
143 questionnaire.(27) Age of rhinitis onset could not be evaluated since the questionnaire did not

144 include this information. Atopic dermatitis was defined by a positive response to “Have you
145 ever had atopic dermatitis?”.

146 In BAMSE asthma at age 1 and 2 years was defined as at least three episodes of wheeze in
147 combination with inhaled corticosteroids and/or signs of bronchial hyperreactivity without
148 concurrent upper respiratory infection the past year before follow-up.(9) Asthma at 4, 8, 12
149 and 16 years was defined as more than 3 episodes of wheeze in the last 12 months prior to
150 the date of questionnaire and/or at least 1 episode of wheeze in the last 12 months in
151 combination with inhaled steroids occasionally or regularly. Allergic rhinitis was defined as
152 symptoms of sneezing, a runny or blocked nose, or itchy, red and watery eyes after exposure
153 to furred pets or pollen in the past 12 months and/or doctor's diagnosis of allergic rhinitis
154 since last follow up. Participants that fulfilled rhinitis definition or asthma definition at least
155 one during the follow-ups at 1, 2, 4, 8, 12 or 16 years were classified as rhinitis ever and asthma
156 ever. Atopic dermatitis was defined as dry skin, itchy rashes with age-specific location for 2
157 weeks or more in the past 12 months and/or doctor’s diagnosis of atopic dermatitis.

158 Participants from EGEA and BAMSE were grouped in four phenotypes: no asthma & no rhinitis
159 (A-R-), asthma alone (A+R-), rhinitis alone (A-R+), and asthma & rhinitis (A+R+). Multimorbidity
160 was defined as having both asthma and rhinitis. For an exploratory analysis, we further
161 considered atopic dermatitis.

162

163 ***Allergen-specific IgE measurement***

164 IgE reactivity to microarrayed allergens was determined in anonymized samples with the
165 MeDALL-chip (multiplex microarray) in EGEA2 samples and in the 16-years old samples in
166 BAMSE.(21, 23, 28, 29) The MeDALL-chip comprises 176 allergen components including aero-

167 and food allergen components. In the present study IgE responses to 64 defined clinically
168 relevant respiratory allergenic molecules were studied (Table S1 in the *Supplements*). The
169 measurement of allergen-specific IgE was performed as described.(6, 21) Results are given in
170 ISU. According to previous studies, the positivity of each allergen-specific IgE was defined with
171 a threshold of 0.3 ISU IgE.(6, 21, 22). As previously shown, the agreement between SPT and
172 allergen-specific IgE in EGEA was strong (Cohen Kappa coefficient ≥ 0.65), with slightly higher
173 prevalences using the MeDALL-chip (except for ragweed) (Table S2 in the *Supplements*).⁽²⁸⁾
174 In BAMSE, agreement for allergen-specific IgE between Immunocap and the MeDALL-chip
175 components was high (Cohen Kappa coefficient ≥ 0.75) for the most prevalent allergens
176 (thimothy grass, birch and cat) and moderate for the less prevalent allergens (house dust mite,
177 horse and mugwort), as expected given the link between the kappa and the prevalence (Table
178 S3 in the *Supplements*).

179 Within each study, respiratory allergenic molecules recognized by $\geq 3\%$ of subjects were
180 considered to address the sensitization profiles of asthma and rhinitis phenotypes (Table S1).

181

182 ***Biases***

183 In both studies, allergen-specific IgE was measured in a subset of samples (for cost issues),
184 randomly selected among the BAMSE samples and in EGEA among the non-asthma and
185 asthma samples separately. Within each group, the selection process was unrelated to the
186 allergen exposure and the allergen-specific IgE reactivity, minimizing the risk for selection bias
187 (Fig. S1 and S2).

188

189 ***Statistical methods***

190 Demographic results are given in means \pm SD or n (%). For the analysis of the number of
191 positive allergen-specific IgE, results are given in medians and 25-75 percentiles (Q1 and Q3).
192 The level of allergen-specific IgE for each positive allergen molecule were compared between
193 phenotypes using the non-parametric Kruskal Wallis test. Negative binomial regression model
194 was applied to estimate age and sex adjusted associations with the number of positive
195 allergen-specific IgE. This regression models the ratio of the mean number of positive allergen-
196 specific IgE (and its 95% confidence interval) between the asthma and rhinitis phenotypes. For
197 example, a ratio of 5.0 for asthma means that those with asthma had a 5-fold higher mean
198 number of positive allergen-specific IgE, as compared with those without asthma. Logistic
199 regression models were used to estimate Odds Ratio (OR) and their 95% CI associated with
200 positive allergen-specific IgE.

201

202 **Results**

203 *Demographic characteristics of participants*

204 There were 840 adult participants to the French EGEA study (463 with and 377 without
205 asthma) and 786 adolescents of the Swedish BAMSE cohort (Fig. S1 and S2). In BAMSE and
206 within the asthma and the non-asthma group in EGEA, participants included in the analysis
207 did not differ to those non-included regarding allergy related characteristics (Tables S4 and
208 S5). In the BAMSE study, included participants had more often asthma than non-included ones
209 (22.9% vs. 18.0%, $p=0.02$). The demographic characteristics of the participants are presented
210 in Table 1. In EGEA, mean age of asthma onset was higher in the A+R- than in the A+R+ (19.4
211 (± 16.0) vs. 13.7 (± 14.6), $p=0.002$). The frequency of asthma-rhinitis multimorbidity (A+R+)

212 was 44% in EGEA and 14% in BAMSE. Asthma only (A+R-) and rhinitis only (A-R+) were found
213 in 11% and 15% in EGEA and 8% and 24% in BAMSE.

214

215 ***IgE reactivity to allergen molecules***

216 We identified 39 and 18 allergens recognized by IgE in at least 3% of the EGEA population and
217 the BAMSE population, respectively ([Table S1](#)). IgE-reactivities to olive Ole e 1 and house dust
218 mite Der p 1 were frequent in EGEA (20.4% and 26.4% respectively) and infrequent in BAMSE
219 (1.2% and 1.3%). IgE-reactivity to birch Bet v 1 was frequent in BAMSE. IgE-reactivities to
220 animal (cat, dog and horse) and grass pollen allergens were similar in both populations
221 irrespective of age difference between the two studies.

222

223 ***Multimorbidity and polysensitization***

224 The number of subjects with IgE reactivity to at least one allergen and the number of IgE-
225 reactive allergens differed significantly between the asthma-rhinitis phenotypes in both
226 studies. IgE sensitizations to few allergens were observed in the A-R- phenotype whereas the
227 greatest number of IgE-reactive allergens was found in the multimorbid A+R+ phenotype
228 ([Table 2, Fig. 1-A](#)). The A+R- and A-R+ phenotypes showed IgE reactivity to significantly fewer
229 allergens than the A+R+ phenotype ($p < 0.001$). As compared to A-R- subjects, the age and sex
230 adjusted ratio of the mean number of IgE sensitizations was significantly higher in A+R+ than
231 in A+R- or A-R+, in both cohorts ([Table 2](#)). There was a difference between EGEA and BAMSE
232 since the A+R- group showed IgE reactivity to significantly more allergens in EGEA than in
233 BAMSE.

234 In EGEA, the number of allergen molecules associated with specific IgE was significantly higher
235 in childhood-onset asthma than in adult-onset asthma (median were 9.0 and 2.0, respectively,
236 $p < 0.0001$) (Fig. 1B and Table 2). In both childhood and adult-onset asthma, the A+R+
237 phenotype exhibited IgE reactivity to a higher number of allergens than the A+R- ($p < 0.001$ in
238 childhood-onset asthma and $p = 0.002$ in adult-onset asthma) (Table 2). Among subjects with
239 rhinitis, the number of allergen recognized by IgE was higher among subjects with childhood-
240 onset asthma as compared to adult-onset asthma ($p < 0.0001$).

241 In both studies, the prevalence of subjects with IgE reactivity to at least one allergen and the
242 number of IgE-reactive allergens increased gradually with the number of diseases (asthma and
243 rhinitis and atopic dermatitis) (Table 3). For each additional allergic disease phenotype, the
244 number of IgE-reactive allergens increased significantly. However, among subjects with
245 asthma and rhinitis, atopic dermatitis was not associated with the number of IgE-reactive
246 allergens (age and sex adjusted relative change [95% CI] = 1.1 [0.9-1.3], $p = 0.29$ in EGEA and
247 1.2 [0.8-1.7], $p = 0.41$ in BAMSE). The median level of allergen-specific IgE among positive
248 allergen molecule increased with the number of diseases ($p < 0.0001$ in EGEA and BAMSE, Table
249 3), although in EGEA the trend was not linear, with a median level of similar magnitude in
250 participants with 2 and 3 diseases.

251

252 ***Sensitization patterns between asthma and rhinitis phenotypes***

253 The patterns of IgE sensitizations differed between the phenotypes and populations (Fig. 2
254 and 3). In the A-R- phenotype, IgE-reactivity frequency was below 10% for all allergen
255 components in both cohorts, except for Phl p 1 in BAMSE (Fig. 2-A, 3-A). In the A+R-
256 phenotype, Phl p 1, most of the Der p allergens and Fel d 1 were over 10% in EGEA (Fig. 2-B),

257 whereas only Phl p 1 was over the threshold of 10% in BAMSE (Fig. 3-B). In the A-R+
258 phenotype, pollen allergens and Fel d 1 were over 10% in both EGEA and BAMSE (Fig. 2-C and
259 3-C). In BAMSE Can f 5 was also over the threshold of 10% recognition in the A-R+ phenotype.
260 In the A+R+ phenotype (Fig. 2-D and 3-D), 24 allergen molecules in EGEA (61.5% of the 39
261 allergens recognised by at least 3% of the EGEA population) and 17 allergens in BAMSE (94.4%
262 of the 18 allergens recognised by at least 3% of the BAMSE population) were over the 10% IgE
263 recognition frequency. Although the A+R- and A-R+ sensitization patterns differed between
264 the EGEA and BAMSE populations, in both studies the A+R+ sensitization pattern results from
265 the combination of the A+R- and A-R+ sensitization patterns.

266 For the three allergens with the highest IgE-reactivity frequency in the A-R- (Phl p 1, Ole e 1,
267 and Der p 23 in EGEA with IgE-reactivity frequency in A-R- of 9.5%, 6.0% and 7.0%; Phl p 1, Bet
268 v 1 and Fel d 1 in BAMSE with IgE-reactivity frequency in A-R- of 15.6%, 7.6% and 5.9%,
269 respectively) we estimated the risk for A-R+, A+R- and A+R+ as compared to A-R- (Fig. 4). In
270 both studies and for each allergen component, the OR was always the highest for A+R+,
271 although the risk in A+R+ did not statistically differ from the risk in A-R+ or A+R-. In EGEA, the
272 OR point estimate for A+R+ was approximately the addition of the OR point estimate for A+R-
273 and A-R+. In BAMSE, none of these three allergen molecules was associated with the asthma
274 only phenotype (OR point estimates were close to 1).

275

276 Discussion

277 Our study shows that the asthma-rhinitis multimorbid phenotype is associated with strong
278 IgE-polysensitisation, both in adolescents and in adults. The asthma-rhinitis multimorbid

279 phenotype combined the sensitization pattern of both the asthma-only phenotype and the
280 rhinitis-only phenotype. In addition, the systematic highest risk observed for allergen specific-
281 IgE reactivity in the asthma-rhinitis multimorbid phenotype as compared to the asthma- or
282 rhinitis-only phenotypes, indicates that the mechanisms involved in the asthma-rhinitis
283 multimorbid phenotype might be partly different or enhanced than those involved in asthma-
284 or rhinitis-only phenotypes. The observation found in two different populations with exposure
285 to different allergen sources, the Swedish BAMSE cohort and the French EGEA population,
286 provides evidence for the generalizability of this “extreme” phenotype to any age or allergenic
287 environment.

288 A major strength of our study is the strategy used, by addressing the research question in two
289 populations differing regarding many features including population age (including adolescents
290 and adults), study design (birth cohort and case-control combined to a family study) and
291 allergen exposure due to different environments (Sweden with a high birch pollen exposure
292 and France with a high mite exposure). Long-term birth cohort studies are essential to
293 understand disease mechanisms and life course of allergic diseases,(30) but in population-
294 based studies individuals with severe disease are rare. Therefore, patient cohorts can be
295 combined with population-based studies to fill gaps of unmet needs of birth cohorts (30) for
296 a better definition of disease phenotypes and stratification. Similar observations in the two
297 populations provide evidence that the observed associations are not due to uncontrolled bias
298 affecting a single study or by chance. A further asset relies in the precise characterisation of
299 the allergic sensitization, by assessing IgE sensitization to well-defined allergen molecules
300 which allow to discriminate co- and cross-sensitization. The MeDALL micro-array has been
301 established and was carefully validated regarding specificity and sensitivity in the FP7-funded
302 EU program MeDALL and has previously been successfully used in several studies including

303 the EGEA and BAMSE cohorts.(7, 22, 28)

304 One limitation, relying on the cross-sectional design of our analyses, is the lack of definite
305 information on the timing of the events and of the successive specific allergens sensitization.
306 This timing of events has been addressed in some birth cohort studies. However, none of these
307 previous studies has used defined allergen molecules but only allergen extracts to detect IgE
308 sensitization. A recent study in the MAS and PASTURE cohorts, which identified different
309 sensitisation profiles characterized by allergen specificity, time course and sIgE level, did not
310 identify clear temporal sensitization pattern between 1 and 6 years of age.(31) The clusters
311 were mainly characterized by allergen specificity and strength of the sIgE sensitization. In the
312 Paris cohort, Gabet et al identified as early as 18 months of age three sensitization profiles,
313 including a “polysensitized” profile which exhibits the highest risk for multimorbidity at 6
314 years.(8) In the EGEA study, we examined the impact of age of asthma onset on the
315 sensitization patterns. When the disease started in childhood, the number of sensitizations
316 was greater than when the disease started later for both A+R- and A+R+ groups. But, the
317 association between the asthma-rhinitis multimorbidity and allergic polysensitization was
318 observed in both childhood- and adult-onset phenotypes. Another limitation could be that
319 IgE measurements on the chip are performed under conditions of low amounts of allergen
320 immobilized to the solid phase which may be affected by allergen-specific IgG antibodies.
321 However, the MeDALL allergen-chip has been carefully evaluated with respect to sensitivity
322 and was found to be more sensitive for detecting IgE sensitization than allergen-extract-based
323 skin prick testing and conventional allergen extract-based serology because significantly more
324 sensitized subjects were detected.(22)

325 Our study is clinically relevant and provides results with a general validity because it examines
326 asthma-rhinitis multimorbidity and polysensitization in depth and confirms the hypothesis
327 raised in the recent paper by Burte et al in the same EGEA cohort using classical IgE tests for
328 12 aeroallergens sources.(16) It is novel as it uses the most advanced method of IgE
329 measurement that is needed to accurately assess true polysensitization, allowing for the
330 assessment of IgE-reactivity to define allergen molecules. Moreover, similar findings were
331 observed in a second cohort which allow the generalizability of the results. For the first time,
332 our study showed that for specific allergens with high IgE recognition frequency in the study
333 populations, the risk of IgE-reactivity was the highest in the asthma-rhinitis multimorbid
334 phenotype as compared to the isolated asthma or rhinitis phenotypes. This might suggest that
335 the biological mechanisms involved in the association between IgE-sensitization and the AR
336 phenotypes are partly different or enhanced in the AR multimorbidity phenotype. Moreover,
337 in the EGEA study we observed that the magnitude of the risk for the AR multimorbidity
338 phenotype was roughly the addition of the risk observed in asthma alone and rhinitis alone
339 phenotypes. This might suggest independent effects of allergen-specific IgE-sensitisation in
340 asthma and in rhinitis (if the effects were mainly shared, the risk in A+R+ would not be higher
341 than the risk in A+R- or A-R+). Our observations provide hypotheses for novel biological
342 explanations which warrants further investigations.

343 The major difference across the two study populations is related to the allergen exposure. In
344 Sweden, exposure to mites is very low, and low level of IgE-reactivity to mite allergens
345 probably explains differences in the total number of allergen recognized between EGEA and
346 BAMSE and the lack of sensitization in A+R- patients in Sweden. Moreover, in Sweden birch
347 pollen is highly prevalent whereas it is not common in most parts of France.(7, 28) Thus, the
348 prevalence of birch-related IgE is higher in Sweden than in France. Finally, Ole e 1 is the major

349 allergen of olive and it displays strong cross-reactivity with Fra e 1, a major ash allergen.(32,
350 33) These two species are common in France but not in Sweden, which explain the low
351 prevalence of Ole e 1-specific IgE in BAMSE as compared to EGEA.

352 If we consider the impact of environmental exposure, the results are similar in both studies
353 and show that allergic multimorbidity is associated with IgE-polysensitization in adults
354 (France) and adolescents (Sweden). Moreover, the levels of allergen-specific IgE are
355 associated with the number of co-existing allergic disease phenotypes. Our study extends to
356 adolescents and adults recent findings in childhood studies and therefore indicates that the
357 allergy multimorbid IgE-polysensitized phenotype starts early in life and does not remit over
358 time, but seems to remain persistent across the life course. In addition, we observed that AR
359 multimorbidity is associated with IgE sensitization to significantly more allergen molecules as
360 compared with asthma alone both in childhood- and adult-onset asthma, emphasizing the
361 generalizability of this phenotype. Recent studies in children showed that this phenotype is
362 associated with the severity of asthma and rhinitis,(11-13, 15) and therefore underline the
363 relevance of this phenotype at the clinical and public health level. By investigating pathways
364 related to asthma severity in children with asthma and rhinitis, Liu et al. showed that allergy
365 was associated with asthma severity through several pathways, from allergic inflammation
366 and subsequently through pulmonary physiology or rhinitis severity.(12)

367 Our study clearly demonstrated different patterns of sensitization according to the asthma
368 and rhinitis phenotypes, with no or few sensitizations in the A-R- group, with no or
369 predominant sensitization to indoor allergens in A+R-, predominant pollen allergens in A-R+,
370 and frequent IgE-sensitization to both pollen and indoor allergens in A+R+. Differences in the
371 A+R- sensitization patterns between EGEA and BAMSE might partly be explained by

372 differences in allergenic environment, in particular the infrequent sensitization to house dust
373 mite allergens in Sweden, and differences in the asthma phenotypes considered (e.g. EGEA
374 also includes adult-onset asthma, which might have different IgE-sensitization pattern).

375 In conclusion, our study provides new insights into the patterns of allergic sensitization across
376 the AR phenotypes in both adolescents and adults. By showing that the allergy multimorbid
377 polysensitized phenotype, previously identified in early life, seems to remain persistent across
378 the life-course, our findings advocate for paying a particular attention to this specific
379 phenotype, to identify its underlying mechanisms and risk factors.

380

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405 **Conflict of interests statements**

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417 V Siroux, C Lupinek, I Pin, J Just, R Nadif, JM Anto, E Melen, R Valenta, M Wickman and J
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Figures legend

FIGURE 1. Distribution of the number of IgE-reactive allergens (≥ 0.3 ISU) according to the asthma and rhinitis phenotypes in EGEA and in BAMSE (A) and taking into account age of asthma onset in EGEA (B) (among the 64 allergen components).

In these box plots, the bottom and the top of the rectangle indicate the first and the third quartile, respectively, and the horizontal line near the middle of the rectangle indicates the median. The vertical lines from the top and the bottom of the rectangle indicate the maximum and minimum values, respectively. The diamond indicates the mean value.

FIGURE 2. IgE recognition frequencies and intensities to respiratory allergens recognized by $>3\%$ of the EGEA samples according to the combined asthma and rhinitis phenotypes in EGEA with: (A) no asthma and no rhinitis (A-R-), (B) asthma but no rhinitis (A+R-), (C) no asthma but rhinitis (A-R+), and (D) asthma and rhinitis (A+R+)

FIGURE 3. IgE recognition frequencies and intensities of respiratory allergens recognized $>3\%$ of the BAMSE samples according to the combined asthma and rhinitis phenotypes in BAMSE with: (A) no asthma and no rhinitis (A-R-), (B) asthma but no rhinitis (A+R-), (C) no asthma but rhinitis (A-R+), and (D) asthma and rhinitis (A+R+)

FIGURE 4. Age- and sex-adjusted association (OR (95% CI)) between the asthma-rhinitis phenotypes and the three allergen components with the highest IgE-reactivity frequency in the A-R- group. A) In EGEA, B) in BAMSE