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**POLLEN CONCENTRATIONS AND PREVALENCE OF ASTHMA AND ALLERGIC RHINITIS IN ITALY:
EVIDENCE FROM THE GEIRD STUDY**

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1 **Title**

2 POLLEN CONCENTRATIONS AND PREVALENCE OF ASTHMA AND ALLERGIC
3 RHINITIS IN ITALY: EVIDENCE FROM THE GEIRD STUDY.

4

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46

47 **ABSTRACT**

48 *Background:* Pollen exposure has acute adverse effects on sensitized individuals.
49 Information on the prevalence of respiratory diseases in areas with different pollen
50 concentrations is scanty.

51 *Aim:* We performed an ecologic analysis to assess whether the prevalence of allergic
52 rhinitis and asthma in young adults varied across areas with different pollen concentrations
53 in Italy.

54 *Methods:* A questionnaire on respiratory diseases was delivered to random samples of 20-
55 44 year-old subjects from six centers in 2005-2010. Data on the daily air concentrations of
56 7 major allergologic pollens (*Poaceae*, *Urticaceae*, *Oleaceae*, *Cupressaceae*, *Coryloideae*,
57 *Betula* and *Ambrosia*) were collected for 2007-2008. Center-specific pollen exposure
58 indicators were calculated, including the average number of days per year with pollens
59 above the low or high concentration thresholds defined by the Italian Association of
60 Aerobiology. Associations between pollen exposure and disease prevalence, adjusted for
61 potential confounders, were estimated using logistic regression models with center as a
62 random-intercept.

63 *Results:* Overall, 8834 subjects (56.8%) filled in the questionnaire. Allergic rhinitis was
64 significantly less frequent in the centers with longer periods with high concentrations of at
65 least one (OR per 10 days =0.989, 95%CI: 0.979-0.999) or at least two pollens
66 (OR=0.974, 95%CI: 0.951-0.998); associations with the number of days with at least one
67 (OR=0.988, 95%CI: 0.972-1.004) or at least two (OR=0.985, 95%CI: 0.970-1.001) pollens
68 above the low thresholds were borderline significant. Asthma prevalence was not
69 associated with pollen concentrations.

70 *Conclusions:* Our study does not support that the prevalence of allergic rhinitis and asthma
71 is greater in centers with higher pollen concentrations. It is not clear whether the observed
72 ecologic associations hold at the individual level.

73

74

75 **Highlights**

- 76 • The chronic effects of pollens on allergic disease prevalence are poorly known
- 77 • We calculated center-specific indicators of long-term pollen exposure
- 78 • We studied if pollen levels are related to allergic rhinitis and asthma in Italy
- 79 • Allergic rhinitis was less frequent in centers with higher pollen loads
- 80 • There was no ecologic association of pollen exposure with asthma prevalence

81

82

83 **Keywords** (max 6)

84 Aeroallergen, adult, allergy, ecologic study, public health, respiratory.

85

86 **INTRODUCTION**

87 Asthma and rhinitis are allergic respiratory diseases affecting, respectively, 5-15% and 20-
88 30% of adults in Europe (Bauchau and Durham, 2004; Jarvis et al. 2012). The prevalence
89 of both diseases shows great heterogeneity both between and within countries (Burney et
90 al., 1994; Björnsson et al., 1994). Geo-climatic factors seem to account for part of this
91 variability (Pesce et al. 2016). Climatic and meteorological conditions influence the
92 regional flora and intensity of pollination, the dispersion of pollens and the duration of the
93 pollen season (Latorre and Caccavari, 2009, Mandrioli and Negrini in D'Amato, 1991).
94 Climate change may be in part responsible for the observed increases in asthma and
95 allergic rhinitis prevalence in the last decade (Zanolin et al., 2004, de Marco et al. 2012),
96 possibly through its effects of altering pollination (De Sario et al., 2013; D'Amato et al.,
97 2014).

98 Exposure to pollens and other aeroallergens may cause allergy, which is a hyperreactivity
99 reaction of the respiratory tract and eye conjunctiva mediated by immunological (mostly
100 IgE-dependent) inflammation. In sensitized individuals, exposure to pollens leads to
101 release of bioactive molecules such as histamine and lipid mediators that can cause
102 smooth muscle contraction, increased vascular permeability, mucus secretion, and attract
103 inflammatory cells (Plotz et al. 2004, Bernstein et al. 2016).

104 Pollens are one of several environmental factors that trigger symptoms of respiratory
105 allergic diseases, along with meteorological conditions (extreme temperatures,
106 thunderstorms) and chemical air pollutants (D'Amato et al. 2000; Celenza et al. 1996).
107 Nonetheless few studies have investigated whether the prevalence of respiratory diseases
108 varies across areas with different airborne pollen concentrations. All published studies
109 investigated children (Silverberg et al. 2015; Burr et al., 2003; Yoshida et al., 2013).
110 Inconsistent results from these studies showed either positive, null or negative
111 associations between pollen concentrations and respiratory diseases, which may partly

112 relate to the different populations and age groups examined, as well as to the different
113 vegetation and climatic conditions of the geographical areas.

114 The aim of this ecologic study is to describe the cross-sectional relationship between
115 annual concentrations of major allergologic pollens and the prevalence of allergic rhinitis
116 and asthma in the Italian centers participating in the GEIRD (Gene Environment
117 Interactions in Respiratory Diseases) study.

118

119 **METHODS**

120 **Study design**

121 The phase one of the GEIRD multicenter study had a cross sectional design. Three
122 thousands subjects of the Italian young adult general population aged 20-44 years (male
123 to female ratio equal to 1) were selected from six centers between 2005 and 2010 (de
124 Marco et al., 2010). Three centers (Turin, Pavia and Verona), in northern Italy, have a
125 subcontinental climate (Köppen classification: CFA). The other three centers (Ancona,
126 Sassari and Salerno) are coastal cities in central, insular and southern Italy respectively,
127 and they are characterized by a mediterranean climate (Köppen classification: CSA). The
128 subcontinental zone has a lower annual average temperature and a higher annual
129 temperature range than the mediterranean zone (Pesce et al. 2016).

130

131 **Questionnaire and outcomes**

132 A brief postal questionnaire was self-administered for up to three times. In the case of final
133 non response, a phone interview was carried out. The questionnaire (available at
134 www.geird.org) investigated respiratory symptoms and diseases, socio-economic factors,
135 smoking habits and exposure to vehicular traffic. The questions were derived from the
136 European Community Respiratory Health Survey (de Marco et al., 1999). Each center
137 obtained approval from the Ethics committee. All participants were fully informed about all
138 aspects of the research project and consented to take part in the survey. A subject was
139 considered to have:

- 140 • **Allergic rhinitis** if he/she answered “yes” to the question: “Do you have any nasal
141 allergies including hay fever?”.
- 142 • **Asthma** if he/she answered “yes” to both questions: “Have you ever had asthma?” and
143 “Was this confirmed by a doctor?”.

144

145 **Pollen data**

146 Data on the daily air concentrations of seven pollens from five vegetal families (*Poaceae*,
147 *Urticaceae*, *Oleaceae*, *Cupressaceae*), one subfamily (*Coryloideae*), and two genera
148 (*Betula* and *Ambrosia*) were collected from local monitoring stations. The monitoring
149 stations were within city centers, with the exception of Salerno, which had no local
150 monitoring station. In this case we used data from the closest station (Napoli Portici) to
151 derive pollen indicators (see graphical abstract, left panel). All the monitoring stations used
152 a volumetric sampler of the Hirst type. The device consists of a pump which operates
153 continuously for seven days and is calibrated to aspirate 10 l/min of air (14.4 m³) in 24h.
154 The air is directed on a sampling surface constituted by a metallic drum which rotates at
155 the speed of 2 mm/h, on which a plastic adhesive tape of silicone oil retains airborne
156 particles. After seven days, the sampling drum with the adherent atmospheric particles is
157 cut into fragments corresponding to the monitoring days. Each fragment is placed on a
158 slide and covered with glycerin jelly mixed with basic fuch sine (Odgen et al. 1974) and
159 examined under a microscope at 400x magnification. The daily pollen concentration is
160 determined as the number of pollen grains per cube meter of air (grains/m³).

161 Missing data in the time-series of pollen concentrations were considered to be non-
162 randomly allocated over time, since they could be generated by temporary instrumental
163 breakdowns and maintenance. For this reason we decided to input them using the k-
164 Nearest Neighbor algorithm (Fix and Hodges, 1951; Dixon, 1979). This algorithm assigns
165 missing values based on their similarity to k non-missing values according to a Euclidean
166 distance function. In our data, we set k=9 and we implemented the similarity function
167 accounting for year, month, day, and calendar day.

168

169 **Ecologic indicators of pollen exposure**

170 For each pollen taxa and for each center, we calculated the number of days, over a
171 calendar year, when pollen concentrations were above the low and high concentration
172 thresholds defined by the Italian Aerobiological Monitoring Network (*Rete Italiana di*
173 *Monitoraggio in Aerobiologia*) of the Italian Association of Aerobiology (*Associazione*
174 *Italiana di Aerobiologia*) [<http://www.ilpolline.it/>]. Low and high thresholds in grains/m³ are:
175 *Poaceae*, 0.6 and 30; *Urticaceae*, 2 and 70; *Oleaceae*, 0.6 and 25; *Cupressaceae*, 4 and
176 90; *Coryloideae* and *Betula*, 0.6 and 50; and *Ambrosia*, 0.1 and 25. We also computed the
177 number of days, over a calendar year, when the concentrations of *at least one* and *at least*
178 *two pollens* were above the low and high thresholds, respectively. Finally, we calculated
179 “pollen intensity” as the sum of daily concentrations over a calendar year.

180 In the main analysis, center-specific proxy indicators of long-term pollen exposure were
181 obtained by averaging the previously mentioned indicators over years 2007 and 2008,
182 which is an intermediate period during questionnaire data collection. However, under the
183 hypothesis that self-reporting of allergic diseases may be influenced by the level of
184 symptoms at the time of participation, alternative exposure indicators were calculated
185 using daily data from the years of questionnaire administration in each center (ranging
186 from 2005-2006 in Ancona to 2009-2010 in Turin, see supplementary figure S1) and used
187 for sensitivity analysis.

188

189 **Statistical analysis**

190 . The associations (OR with 95% Confidence Interval, 95%CI) between the pollen
191 exposure indicators and the prevalence of allergic rhinitis and asthma were assessed
192 using two-level logistic regression models, with center as a random intercept. All the

193 analyses were adjusted for gender, age (mean centered), smoking habits (non-smokers,
194 ex-smokers, smokers with <15 cigarette pack-years, and smokers with ≥15 pack-years),
195 education level (lower school, high school, degree), heavy traffic near home (never/rare,
196 frequent/constant), and climatic zone (subcontinental, mediterranean). To improve the
197 comparability across study centers, we also adjusted for the following design variables:
198 season of response, type of contact for questionnaire administration (mail, phone),
199 percentile rank of response (mean centered). The latter was included to account for
200 differences in response rates between centers [de Marco et al., 1994] The analysis on
201 asthma was also adjusted for the presence of allergic rhinitis.

202

203 **RESULTS**

204 Overall, 8834 subjects filled in the questionnaire with a 56.8% of response (range: 37.1%
205 Pavia - 67.7% Verona), 47.5% of them were males, and the median age was 35.2 years
206 (Interquartile range: 11.8 years). Subjects from the mediterranean zone were more likely to
207 be males, young, smokers and exposed to high traffic levels than subjects from the
208 subcontinental zone (supplementary table S1).

209 The crude prevalence of diseases by center and climatic zone is shown in figure 1. Allergic
210 rhinitis was more frequent in the mediterranean zone with respect to the subcontinental
211 zone, 27.6% vs 25.3% ($p=0.02$). Across centers, the highest prevalence was in Salerno
212 (29.0%; 95%CI: 26.9-31.1%) and the lowest in Verona (24.4%; 95%CI: 22.5-26.5%).

213 Similarly, asthma prevalence was higher in the mediterranean than in the subcontinental
214 zone (11.3% vs 9.2%, $p=0.001$) and it ranged from 8.3% (95%CI: 6.7-10.2%) in Pavia to
215 12.5% (95%CI: 10.7-14.4%) in Sassari.

216 Pollen concentrations in 2007-2008 for each center are shown in supplementary figure S2.

217 The distributions of pollen exposure indicators by center and climatic zone are reported in
218 table 1 and supplementary table S2. With respect to the subcontinental zone, in the
219 mediterranean zone the number of days with pollens above the low concentration
220 threshold was higher for *Urticaceae*, *Oleaceae* and *Cupressaceae*, and lower for *Betula*
221 and *Ambrosia* (Figure 2); the number of days at high concentration was higher for
222 *Poaceae*, *Oleaceae* and *Cupressaceae*, and lower for *Betula* and *Ambrosia*.

223 The number of days with specific pollens above the low threshold were not significantly
224 associated with the prevalence of allergic rhinitis (table 2); however, we found consistent
225 negative associations (ORs below 1) of the number of days with high concentrations and
226 pollen intensities with allergic rhinitis. In particular, these associations were statistically
227 significant in the case of *Poaceae* (OR=0.977, $p=0.024$, for days with high concentrations;
228 OR=0.983, $p=0.025$, for pollen intensity) and *Cupressaceae* (OR= 0.996, $p=0.047$ for

229 pollen intensity) (table 2). When looking at exposure indicators based on concentrations of
230 at least one or two pollens (figure 3), we found that centers with a longer period with high
231 concentrations had significantly less allergic rhinitis: disease prevalence was 1.1% and
232 2.6% lower per 10 more days per year with high concentrations of at least one (OR=0.989,
233 $p=0.024$) or at least two pollens (OR=0.974, $p=0.028$), respectively. The associations for
234 the number of days with pollens above the low threshold were negative and borderline
235 significant (figure 3).

236 The associations between pollen exposure indicators and asthma were not consistent
237 (ORs were both greater and lower than 1), and none was statistically significant (table 2
238 and figure 3).

239 The sensitivity analyses performed using the indicators calculated over the specific years
240 of questionnaire administration confirmed the main analyses (supplementary Figure S3),
241 although there were some shifts in statistical significance in pollen-specific associations
242 (supplementary tables S3 and S4).

243

244

245 **DISCUSSION**

246 In this cross-sectional multicenter study we report evidence on the ecologic associations
247 between pollen exposure indicators and the prevalence of allergic respiratory diseases in
248 young adults from the general Italian population. Our disease definitions were based on
249 widely used questions in international epidemiological surveys such as ECRHS (Burney et
250 al., 1994) or GA₂LEN (Björnsson et al., 1994). We were able to account for many
251 individual determinants that are known risk factors for allergic respiratory disease and that
252 may have confounded the associations.

253 Overall, our findings indicate that the centers with a higher pollen load (i.e. days with high
254 concentrations and pollen intensities) had a lower prevalence of allergic rhinitis, and this
255 result was fairly consistent across the different analyses carried out. The presence (i.e.
256 concentrations above the low thresholds) of specific pollens was not consistently
257 associated with the prevalence of allergic rhinitis, although borderline significant negative
258 associations of the number of days with at least one/two pollens suggest a lack of
259 statistical power.

260 The fact that the centers with a higher pollen load had a lower prevalence of allergic
261 rhinitis may seem counterintuitive, because of the well-known adverse short-term effects of
262 aeroallergens, which induce nasal and conjunctival symptoms in sensitized subjects,
263 increase hospital and emergency room admissions for asthma, and even respiratory and
264 cardiovascular mortality (Bono et al. 2016; Brunekreef et al., 2000; Caillaud et al., 2014;
265 Cakmak et al., 2012; Cirera et al. 2012; Eriksson and Holmen, 1996; Sakaida et al., 2014;
266 Tobias et al. 2004). However, data on the long-term effect of pollens on the prevalence of
267 allergic diseases are scarce and inconsistent. Our findings on adults are in agreement with
268 an ecologic analysis on children within the ISAAC study (Burr et al., 2003), where the
269 prevalence of allergic rhinitis was inversely associated with pollen exposure. The authors
270 hypothesized that childhood exposure to high pollen concentrations might give some

271 protection against respiratory allergy. This mechanism has also been proposed to explain
272 the induction of tolerance to perennial allergens in children (Ownby et al., 2003). On the
273 other hand, another study performed in the US found a positive association between total
274 pollen counts and hay fever in children (Silverberg et al., 2015). The lack of a positive
275 relationship between pollens and rhinitis may also entail that other risk factors, such as
276 exposure to perennial allergens, are important. About half of allergic rhinitis patients are
277 sensitized to house dust mites, even if they only have a seasonal disease, and
278 questionnaire definitions are unable to disentangle between seasonal and perennial rhinitis
279 in the absence of clinical data (Olivieri et al., 2002).

280 To our knowledge, only one ecologic study in Japan assessed the long-term association
281 between pollens and asthma (Yoshida et al., 2013). It documented a positive association
282 between cedar pollen counts and childhood asthma prevalence. In our study on adults,
283 there was no association between pollen concentrations and asthma prevalence. In a
284 recent study on the same population, we reported that there is a substantial variability of
285 asthma prevalence in Italy, and that this variability can be explained to a large extent by a
286 “climate indicator” obtained by factor analysis on data from all 110 main Italian cities
287 (Pesce et al., 2016). In Italy, asthma prevalence is greater in areas where annual
288 temperatures are higher and temperature ranges are smaller, which are typical features of
289 the mediterranean climate (de Marco, 2002; Zanolin et al. 2004; Pesce et al., 2016). The
290 effect of climate may be partly related to the levels of perennial allergens, as indoor levels
291 of house dust mite allergens are lower in areas with colder winters (Zock et al., 2006), but
292 dietary and lifestyle determinants may also have a role (Pesce et al. 2016).

293 We observed a distribution of pollen concentrations that is consistent with the pattern of
294 vegetation in the country. *Oleaceae* (e.g. olive, ash, jasmine) and *Cupressaceae* (e.g.
295 cypress) are typical of the temperate and warm region, whereas *Betula* (birch) and
296 *Ambrosia* (ragweed) are more common in northern Italy. *Poaceae* (e.g. grass) and

297 *Urticaceae* (e.g. nettle), the most common herbaceous families in Italy, are spread all over
298 the peninsula, given their ability to grow in very different climatic conditions. *Coryloideae*
299 (e.g. hornbeam, hophornbeam, and hazel) are mainly spread in the central and northern
300 regions (Pre-Alps and Apennines). Among the indicators calculated, the number of days
301 with pollens above the low thresholds represents the presence of measurable pollen levels
302 during a year, under the hypothesis that even small pollen concentrations may affect
303 disease prevalence at the population level. On the other hand, the number of days with
304 high concentrations and pollen intensity are proxies of pollen load especially during the
305 pollination season.

306 There was agreement between the analyses based on pollen data from 2007-08 and the
307 analyses of data matched to the years of questionnaires administration, supporting that the
308 results are robust to the method used to derive pollen exposure indicators. Also, the
309 analyses based on pollen-specific concentrations and on concentrations of any pollen type
310 were in a relative agreement. Differences in statistical significance may be explained by
311 the low power due to the small number of centers included.

312 In the interpretation of our study findings, caution should be used. Diseases were defined
313 using simple questionnaire items, since no clinical or laboratory data were available, and
314 we had no information on the confirmation of allergic rhinitis by a doctor. Nonetheless,
315 Olivieri et al. have documented that atopy is present among most (79%) of subjects
316 reporting allergic rhinitis, and only in a minority (21%) of subjects who do not report allergic
317 rhinitis (Olivieri et al., 2002). The ecologic associations observed at the center level may
318 not reflect biologic associations at the individual level (the “ecologic fallacy”, Rothman et
319 al., 2008). In particular, our study was unable to consider the spatial variability in pollen
320 distribution within centers. As a consequence, we have no direct evidence to test the
321 hypothesis that a more exposed individual is more likely to have the disease. As we only
322 had data from a small number of centers, we had limited power to investigate center-level

323 variables (such as pollen concentrations), we could only study one center-level variable at
324 a time, and we had to assume that these variables had linear effects on log odds of
325 disease. Since we had no data on air pollution exposure, we adjusted the analyses for
326 self-reported exposure to traffic. Besides, we acknowledge that using data from Napoli
327 Portici to derive pollen indicators for Salerno may have introduced further exposure
328 misclassification (Katelaris et al., 2004).

329 In conclusion, evidence from this study does not support that allergic rhinitis and asthma
330 are more frequent in centers with a greater pollen concentration. This suggests that, while
331 pollen exposure is known to trigger acute effects in sensitized individuals, allergen
332 sensitization and the development of allergic diseases may be less influenced by living in
333 areas with a greater pollen concentration. Whether these ecologic associations hold at the
334 individual level is still unknown.

335

336

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352 Daily data on pollen concentrations for the years described in figure S1 are available for
353 research purposes upon approval of the GEIRD Steering Committee, in line with the data
354 sharing principle of the GEIRD study (www.geird.org), and the previously mentioned
355 institutions. For data queries please contact the corresponding author.

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Tables

Table 1. Average number of days per year with pollens above the relative low/high concentration threshold in 2007-2008 by study center.

Pollen		Centers					
Taxa	Concentration threshold	Verona	Pavia	Torino	Ancona	Sassari	Salerno
<i>Poaceae</i>	low	220	251	119	215	122	131
	high	31	47	2	60	75	1
<i>Urticaceae</i>	low	213	207	119	263	359	303
	high	46	73	3	23	64	17
<i>Oleaceae</i>	low	67	153	77	125	156	107
	high	9	9	14	20	66	9
<i>Cupressaceae</i>	low	74	81	50	122	233	85
	high	13	7	2	30	97	4
<i>Coryloideae</i>	low	105	116	79	107	82	92
	high	3	10	1	15	0	2
<i>Betula</i>	low	114	90	71	40	0	38
	high	16	17	1	7	0	0
<i>Ambrosia</i>	low	78	121	40	20	0	40
	high	0	25	1	0	0	0

Table 2. Associations[†] of the number of days per year with pollens above the low/high concentration threshold and pollen intensities (2007-2008) with allergic rhinitis.

Pollen Taxa	N. days above low threshold	N. days above high threshold	Pollen intensity
	OR (95% CI) per 10 days	OR (95% CI) per 10 days	OR (95% CI) per 1000 grains/m ³
<i>Poaceae</i>	0.994 (0.983-1.005)	0.977 (0.958-0.997)	0.983 (0.969-0.998)
<i>Urticaceae</i>	0.991 (0.978-1.004)	0.979 (0.958-1.001)	0.991 (0.983-1.000)
<i>Oleaceae</i>	0.986 (0.968-1.005)	0.977 (0.949-1.006)	0.996 (0.992-1.001)
<i>Cupressaceae</i>	0.989 (0.978-1.000)	0.983 (0.965-1.001)	0.996 (0.991-0.999)
<i>Coryloideae</i>	0.985 (0.944-1.027)	0.973 (0.881-1.074)	0.977 (0.919-1.038)
<i>Betula</i>	1.006 (0.978-1.036)	0.940 (0.851-1.038)	0.969 (0.921-1.021)
<i>Ambrosia</i>	1.000 (0.979-1.022)	0.977 (0.909-1.051)	0.970 (0.881-1.067)

[†] OR were adjusted for gender, age, smoking habits, education level, heavy traffic near home, season of response, type of contact, percentile rank of response, climatic zone. OR with p<0.05 are in bold

Table 3. Associations[†] of the number of days per year with pollens above the low/high concentration threshold and pollen intensities (2007-2008) with asthma.

Pollen Taxa	N. days above low threshold	N. days above high threshold	Pollen intensity
	OR (95% CI) per 10 days	OR (95% CI) per 10 days	OR (95% CI) per 1000 grains/m ³
<i>Poaceae</i>	0.995 (0.979-1.012)	1.011 (0.981-1.042)	1.010 (0.989-1.033)
<i>Urticaceae</i>	1.014 (0.994-1.035)	1.016 (0.983-1.051)	1.008 (0.994-1.022)
<i>Oleaceae</i>	0.999 (0.971-1.029)	1.030 (0.987-1.074)	1.005 (0.998-1.012)
<i>Cupressaceae</i>	1.012 (0.995-1.028)	1.019 (0.993-1.047)	1.004 (0.998-1.011)
<i>Coryloideae</i>	0.975 (0.915-1.041)	0.907 (0.781-1.054)	0.943 (0.859-1.036)
<i>Betula</i>	0.988 (0.946-1.032)	0.992 (0.850-1.157)	0.998 (0.920-1.082)
<i>Ambrosia</i>	0.987 (0.954-1.021)	0.954 (0.849-1.071)	0.937 (0.803-1.093)

[†] OR were adjusted for gender, age, smoking habits, education level, heavy traffic near home, allergic rhinitis, season of response, type of contact, percentile rank of response, climatic zone.

Figures

Figure 1. Crude prevalence of allergic rhinitis (A) and asthma (B) by study center and climatic zone.

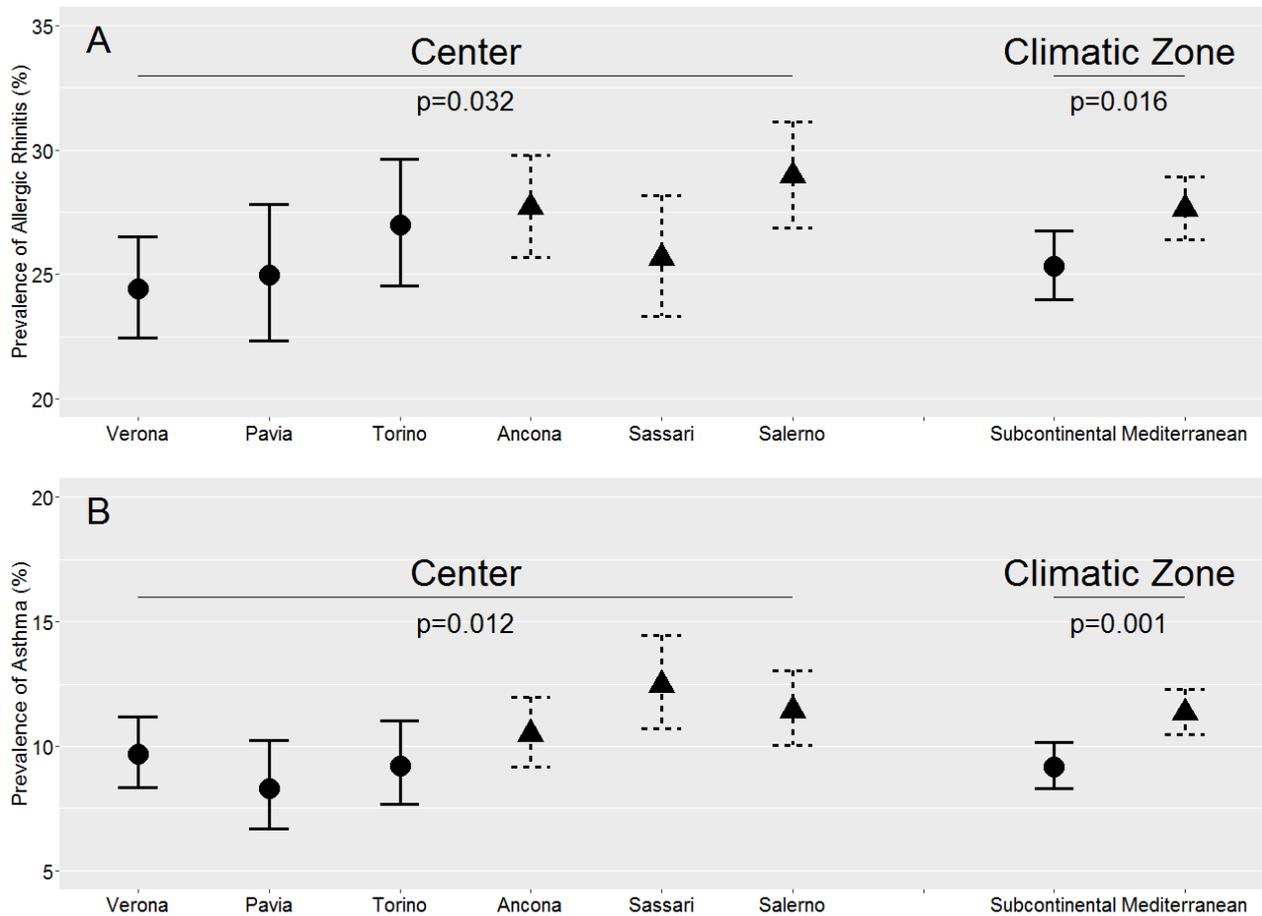


Figure 2. Average number of days per year with pollen above the low and high thresholds in 2007-2008 by climatic zone.

Figure 3. Associations[†] between the number of days per year with at least one/two pollens (2007-2008) above the low/high thresholds and the prevalence of allergic rhinitis and asthma.

[†] OR for 10 days/year. Adjusted for gender, age, smoking habits, education level, heavy traffic near home, season of response, type of contact, percentile rank of response, climatic zone. OR for asthma are also adjusted for allergic rhinitis.

ONLINE SUPPLEMENTARY MATERIAL

Table S1. Distribution of subjects' characteristics by study center and climatic zone.

Covariates	Centers						p*	Climatic zone		p*
	Verona (n=1746)	Pavia (n=966)	Torino (n=1205)	Ancona (n=1866)	Sassari (n=1245)	Salerno (n=1806)		Subcontinental (n=3917)	Mediterranean (n=4917)	
Male gender(%)	47.0	46.4	44.4	48.4	47.7	49.8	0.082	46.0	48.8	0.011
Age (years) (median; IQR)	35.4; 11.5	35.9; 10.6	36.7; 12.1	34.3; 11.7	35.0; 11.2	34.4; 12.3	<0.001	35.9; 11.5	34.5; 11.8	<0.001
Smoking habits (%)	non smokers	54.4	58.3	58.4	58.4	52.7		56.6	57.6	
	ex-smokers	19.1	17.8	15.5	15.7	19.6		17.7	15.0	
	Smokers (<15 packs-year)	16.0	14.1	15.1	15.0	14.8	<0.001	15.2	15.1	0.002
	smokers (≥15 packs-year)	10.6	9.9	11.1	10.9	13.0		10.5	12.3	
Level of education(%)	lower	21.8	23.7	19.2	17.3	25.2		21.5	20.0	
	higher	52.4	51.5	51.3	59.4	48.2	<0.001	51.9	54.2	<0.001
	degree	25.8	24.8	29.5	23.3	26.5		26.7	27.9	
Frequent/ constant heavy traffic near home(%)	39.7	28.4	53.9	41.2	37.6	53.7	<0.001	41.2	44.8	0.001
Season of response(%)	spring	33.9	57.7	45.6	59.8	55.2		43.4	44.7	
	summer	3.6	23.3	32.1	24.5	8.7		17.2	17.7	
	autumn	50.3	17.9	18.3	1.3	30.4	<0.001	32.5	20.8	<0.001
	winter	12.1	1.1	4.0	14.4	5.8		6.9	16.8	
Type of contact (%)	postal (vs. phone)	84.1	93.3	93.7	100.0	85.5	<0.001	89.3	86.0	<0.001

IQR, interquartile range. *p-values were computed using Pearson's Chi-square test, except for variable age where Kruskal-Wallis test was used.

Table S2. Average pollen intensities in 2007-2008 (grains/m³) by study center and climatic zone.

Pollen taxa	Centers						Climatic zone	
	Verona	Pavia	Torino	Ancona	Sassari	Salerno	Subcontinental	Mediterranean
<i>Poaceae</i>	3642	5805	731	7341	11754	590	3393	6561
<i>Urticaceae</i>	13361	17658	1581	7147	18245	6652	10867	10681
<i>Oleaceae</i>	865	1098	895	2190	34973	1124	952	12762
<i>Cupressaceae</i>	4988	3456	1104	20626	42302	2272	3183	21733
<i>Coryloideae</i>	826	2440	555	2892	753	794	1273	1479
<i>Betula</i>	3241	3824	424	791	0	110	2496	300
<i>Ambrosia</i>	135	2003	136	62	0	21	758	27

Table S3. Associations[†] of the number of days per year with pollens above the low/high thresholds and pollen intensities (for the years of questionnaire administration in each center) and allergic rhinitis.

Pollen Taxa	N. days above low threshold	N. days above high threshold	Pollen intensity
	OR (95% CI) per 10 days	OR (95% CI) per 10 days	OR (95% CI) per 1000 grains/m ³
<i>Poaceae</i>	0.998 (0.987-1.009)	0.980 (0.956-1.004)	0.980 (0.964-0.998)
<i>Urticaceae</i>	0.993 (0.982-1.004)	0.979 (0.959-0.999)	0.989 (0.979-0.999)
<i>Oleaceae</i>	0.985 (0.964-1.006)	0.967 (0.935-1.000)	0.997 (0.994-1.001)
<i>Cupressaceae</i>	0.990 (0.980-1.000)	0.986 (0.971-1.002)	0.995 (0.990-0.999)
<i>Coryloideae</i>	0.983 (0.951-1.016)	0.968 (0.869-1.077)	0.964 (0.894-1.039)
<i>Betula</i>	0.996 (0.976-1.016)	0.938 (0.842-1.044)	0.971 (0.919-1.026)
<i>Ambrosia</i>	1.004 (0.981-1.027)	0.979 (0.920-1.042)	0.972 (0.894-1.056)

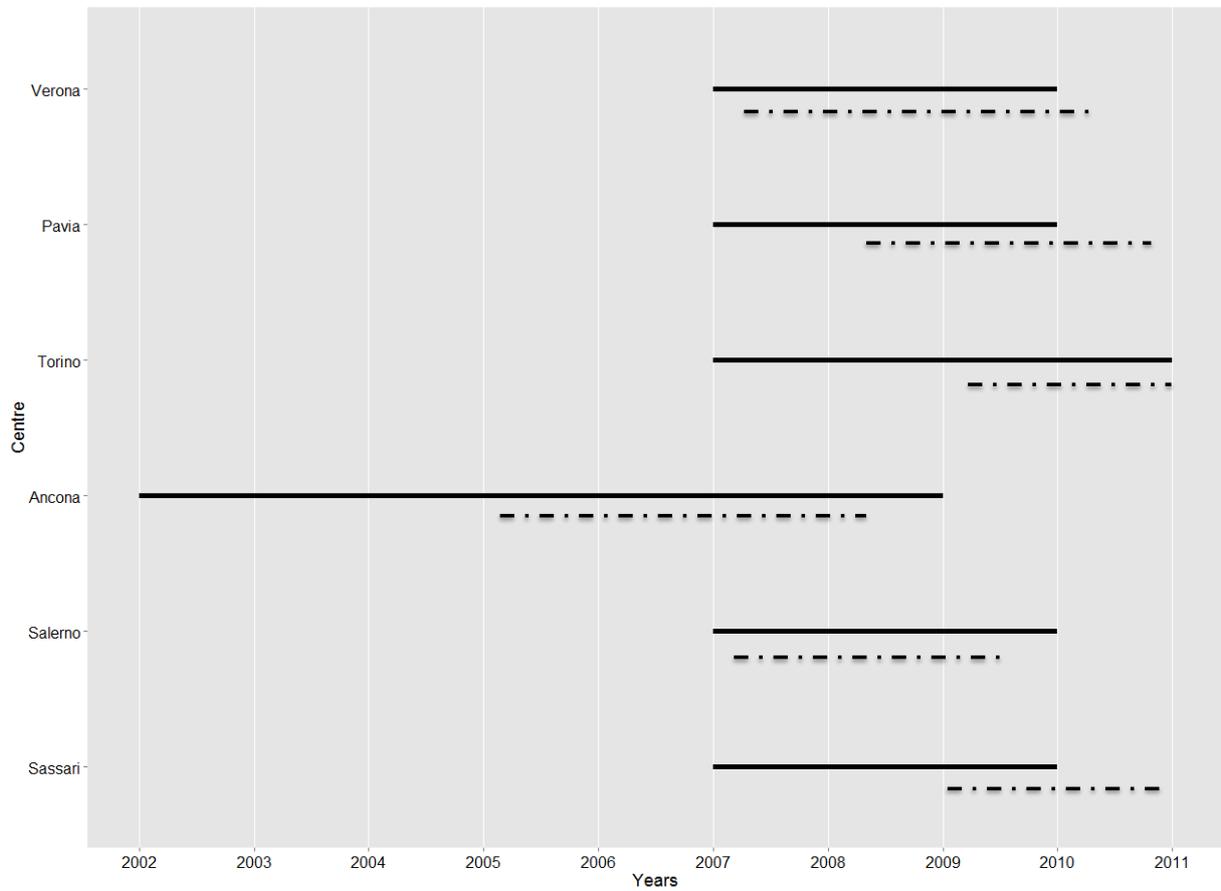
[†] OR were adjusted for gender, age, smoking habits, education level, heavy traffic near home, season of response, type of contact, percentile rank of response, climatic zone. OR with p<0.05 are in bold

Table S4. Associations[†] of the number of days per year with pollens above the low/high thresholds and pollen intensities (for the years of questionnaire administration in each center) and asthma.

Pollen Taxa	N. days above low concentration threshold	N. days above high concentration threshold	Pollen intensity
	OR (95% CI) per 10 days	OR (95% CI) per 10 days	OR (95% CI) per 1000 grains/m ³
<i>Poaceae</i>	0.993 (0.977-1.010)	1.010 (0.974-1.048)	1.014 (0.989-1.040)
<i>Urticaceae</i>	1.013 (0.996-1.030)	1.006 (0.975-1.038)	1.006 (0.990-1.022)
<i>Oleaceae</i>	0.999 (0.966-1.032)	1.031 (0.981-1.082)	1.004 (0.999-1.008)
<i>Cupressaceae</i>	1.011 (0.996-1.026)	1.017 (0.994-1.040)	1.004 (0.996-1.011)
<i>Coryloideae</i>	1.006 (0.954-1.060)	0.903 (0.768-1.063)	0.944 (0.842-1.059)
<i>Betula</i>	1.001 (0.971-1.033)	1.032 (0.872-1.222)	1.022 (0.937-1.115)
<i>Ambrosia</i>	0.982 (0.948-1.017)	0.954 (0.863-1.055)	0.934 (0.817-1.068)

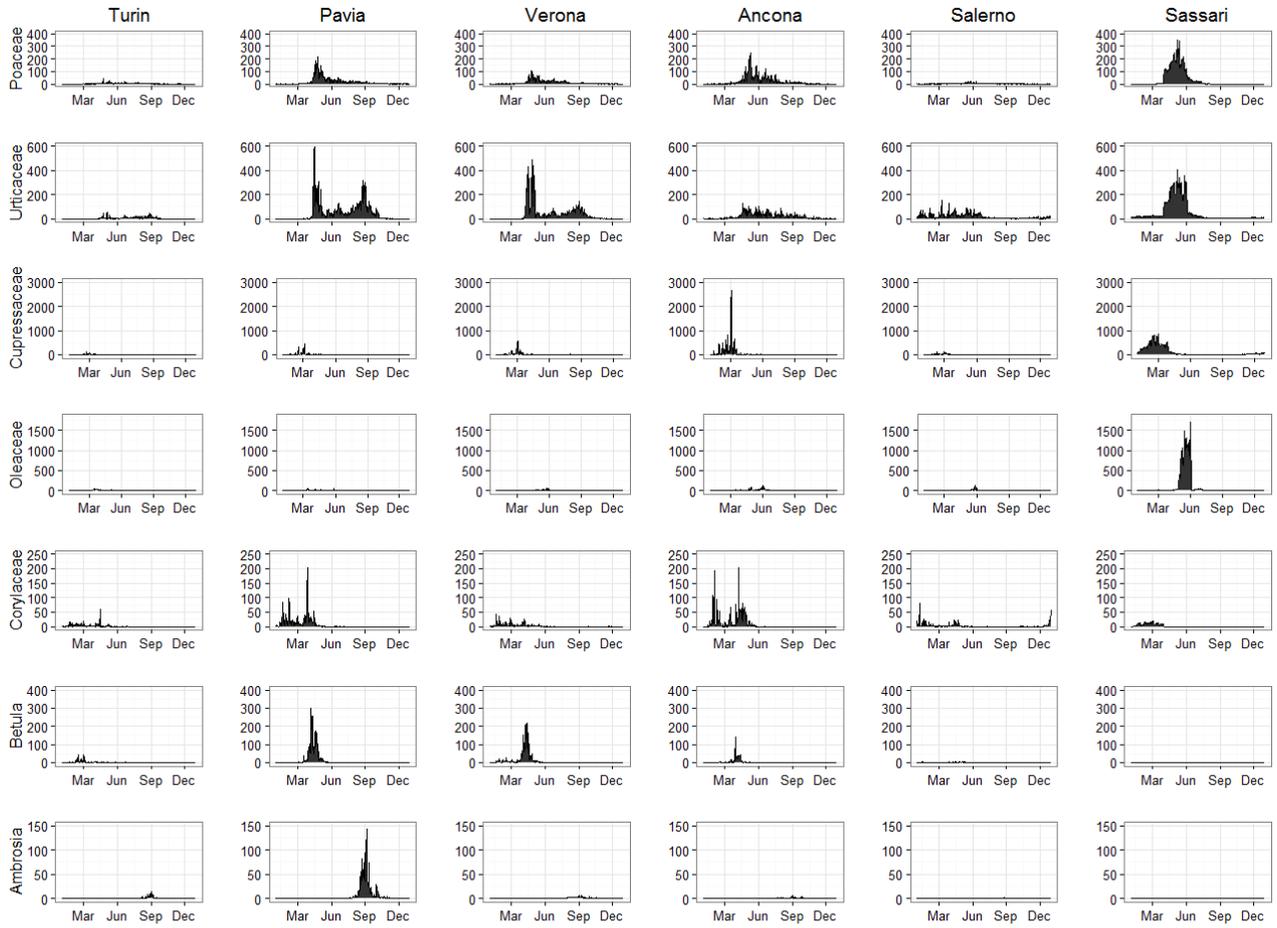
[†] OR were adjusted for gender, age, smoking habits, education level, heavy traffic near home, allergic rhinitis, season of response, type of contact, percentile rank of response, climatic zone.

Figure S1. Period when questionnaire and pollen data were collected by study center. †



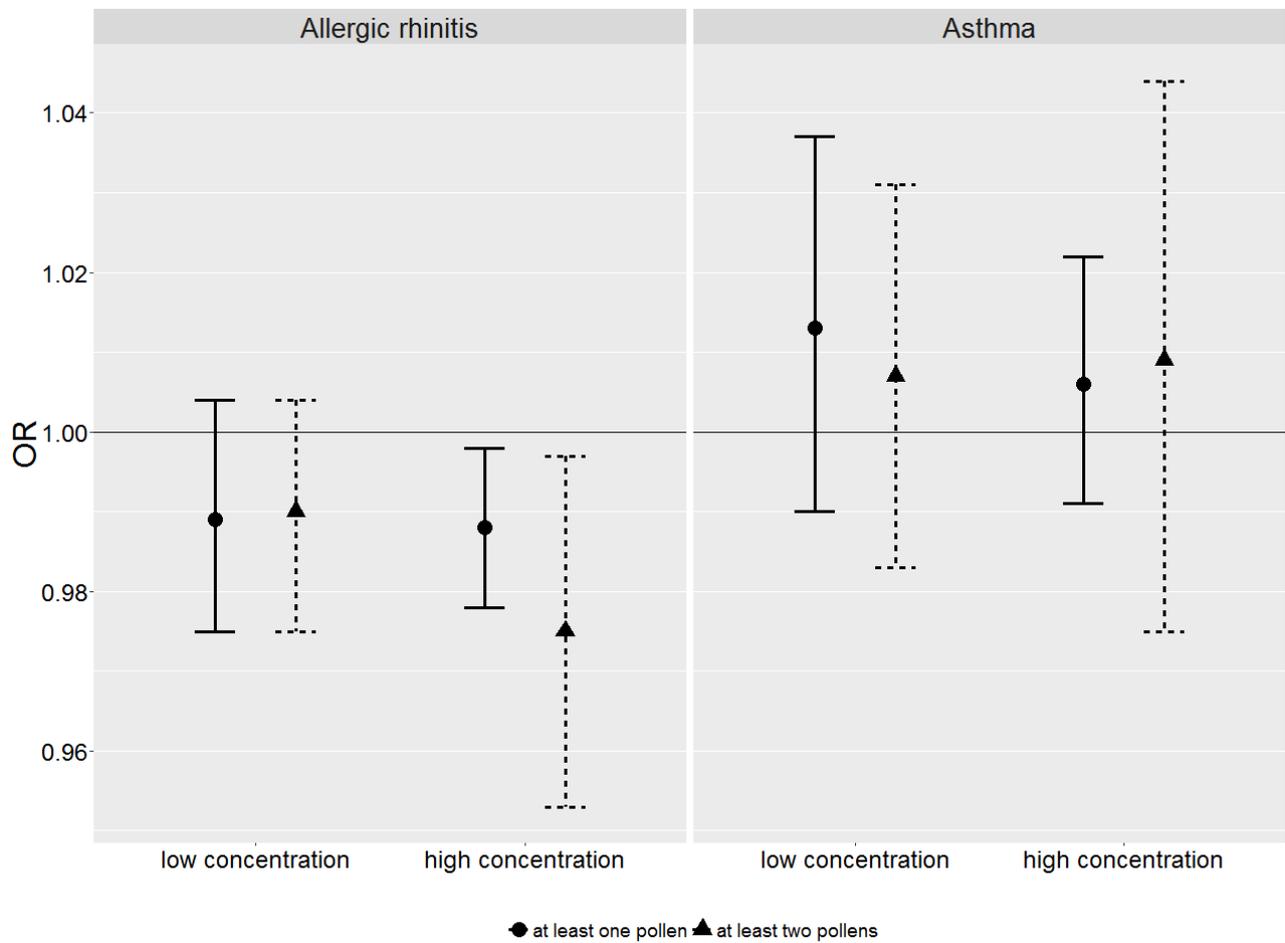
† Solid lines represent pollen data, dashed-dot lines represent the periods when questionnaires were collected.

Figure S2. Distribution of daily[†] pollen concentrations in 2007-2008 (grains/m³) by study center.



[†] pollen concentrations for a given calendar day were averaged between 2007 and 2008 for descriptive purposes

Figure S3. Associations[†] of the number of days with at least one/two pollens above the low/high thresholds (for the years of questionnaire administration in each center) with the prevalence of allergic rhinitis and asthma.



[†] OR for 10 days/year. Adjusted for gender, age, smoking habits, education level, heavy traffic near home, season of response, type of contact, percentile rank of response, climatic zone. OR for asthma are also adjusted for allergic rhinitis.