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1 **TITLE PAGE**

2 **SMOKING AND NEW-ONSET ASTHMA IN A PROSPECTIVE STUDY ON ITALIAN**
3 **ADULTS**

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16 **Keywords:** asthma incidence; smoking habits; allergic rhinitis; reverse causation; adult
17 population; Italy.

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19 **Abbreviations:** ECRHS: European Community Respiratory Health Survey; GEIRD: Gene-
20 Environment Interactions in Respiratory Diseases; IQL: interquartile range; ISAYA: Italian Study
21 on Asthma in Young Adults; ISIA: Italian Study on the Incidence of Asthma; SD: standard
22 deviation.

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31 authors declare that they have no competing interests.

32

33 **Abstract**

34 *Background:* The existence of a cause-effect relation between active smoking and new-onset
35 asthma in adults, although supported by several studies, has not been proven yet.

36 *Aims:* To prospectively study asthma incidence as a function of smoking habits in the Italian adult
37 population.

38 *Methods:* A population-based cohort of 5,241 non-asthmatics was enrolled in Verona and Sassari
39 in 1998–2000. The cohort was contacted again in 2007–2009 within the Gene-Environment
40 Interactions in Respiratory Diseases study, and 3,187 subjects (60.8%) answered a screening
41 questionnaire on smoking habits and respiratory disorders. The relation between smoking habits
42 and self-reported new-onset asthma, defined as asthma attacks/use of medicines for asthma, was
43 investigated by a multivariable logistic model.

44 *Results:* During follow-up 145 new cases of asthma were observed, yielding a cumulative
45 incidence of 4.6% (95% CI 3.9–5.4); cumulative incidence of asthma did not significantly differ
46 among never smokers (76/1,666=4.6%), ex-smokers (30/554=5.4%) and current smokers
47 (39/883=4.4%) (p=0.641). In multivariable analysis the most important risk factor for asthma
48 onset was allergic rhinitis (OR=4.00, 95% CI 3.68–4.35). Compared to never smokers, the risk of
49 asthma onset was slightly increased in ex-smokers (OR=1.28, 1.09–1.49) but not in current
50 smokers (OR=1.01, 0.66–1.53). Current smoking became a significant predictor only when both
51 new-onset wheezing and new-onset asthma were considered as outcome (OR=2.03, 1.35–3.05).

52 *Conclusions:* In this prospective study current smoking was not a risk factor for new-onset
53 asthma, unless new-onset wheezing was also considered. The increase in asthma incidence among
54 ex-smokers was likely due to reverse causation.

55

56 **Introduction**

57 The effect of smoking on asthma onset in adults is still a matter of debate. Most longitudinal
58 studies found an increased risk of new-onset asthma among current smokers with respect to never
59 smokers [1–7], the relative risk ranging between 1.4 and 3. However a few studies report no effect
60 of current smoking on asthma onset [8–11], or even a protective effect [12]. A few studies found
61 different effects according to gender: an increased incidence of asthma among current smokers has
62 been found only in women by some Western studies [13,14] and only in men by a Japanese study
63 [15].

64 A recent report of Surgeon General by the Centers for Disease Control and Prevention [16]
65 concluded that “*the evidence is sufficient to infer a causal relationship between active smoking*
66 *and exacerbation of asthma in adults*”, but not “*between active smoking and incidence of asthma*”,
67 as “*the evidence is suggestive but not sufficient*”.

68 The current literature [7,10,16] found several reasons that could bias the estimates of the
69 smoking-asthma association and lead to discrepant reports:

- 70 1) The “healthy smoker effect” could reduce smoking initiation or favor smoking cessation
71 among people more susceptible to smoking noxious effects [17].
- 72 2) The definition of asthma adopted can largely influence the results: for instance in the
73 British 1958 birth cohort current smoking was associated with incident asthma only when
74 wheezing was also considered as an outcome [18]. Likewise in Swedish adolescents ever
75 smoking turned out to be a risk factor for wheezing but not for asthma [19]. In the elderly
76 the relation between smoking and asthma onset could be biased by a misclassification
77 between asthma and COPD [1].
- 78 3) Passive smoking has been reported to increase the risk of adult-onset asthma among never
79 smokers [7]. In most studies passive smoking among never smokers has been seldom
80 considered, possibly causing an underestimation of active smoking on asthma incidence.
- 81 4) Considering smoking status at baseline could not be adequate, if a substantial proportion of
82 the studied population change his smoking behavior during the follow-up. Hence, some
83 authors [10] handled smoking as a time-dependent variable in statistical analysis.
- 84 5) Not taking into account socioeconomic status as a potential confounder could bias the
85 estimates of smoking-asthma association. Indeed in the late phase of smoking epidemic,
86 cigarette smoking becomes mainly confined to lower socioeconomic classes [20], who in
87 turn are at high risk for respiratory diseases [21].

88 In addition, the association between smoking and asthma can be modified by atopic status and
89 this effect modification could contribute to discrepancies observed in the current literature. In the

90 European Community Respiratory Health Survey (ECRHS) the incidence of adult-onset asthma
91 was higher in smokers than in nonsmokers among the atopics (OR=1.45, 95% CI 0.81–2.61),
92 while an opposite trend was observed among nonatopics (OR=0.67, 0.40–1.15) [11]. Accordingly,
93 an increased risk of asthma onset among smokers was found in an Italian cohort of subjects with
94 allergic rhinitis [22]. At variance, in a Swedish study [2] the odds ratio (OR) of asthma onset in
95 smokers with respect to nonsmokers increased from 1.8 (0.8–4.2) among atopics to 5.7 (1.7–19.2)
96 among nonatopics.

97 The impact of smoking on asthma onset in adults was prospectively investigated, using data
98 from the Gene-Environment Interactions in Respiratory Diseases (GEIRD) study [23]. In addition,
99 it was verified whether the smoking-asthma relation was modified by allergic rhinitis (a proxy of
100 atopy) [24], change in smoking definition (smoking status assessed at baseline only or both at
101 baseline and at the end of follow-up), change in asthma definition (asthma attack/asthma drug vs
102 asthma attack/asthma drug/wheezing) and adjustment for occupational status.

103

104 **Materials and Methods**

105 **Recruitment of studied cohorts**

106 The incidence of asthma and its determinants were studied in three population-based cohorts.
107 Two cohorts had been recruited in the frame of the Italian Study on Asthma in Young Adults
108 (ISAYA) in Verona, Northern Italy, and Sassari, Mediterranean island of Sardinia [25]. The third
109 cohort had been recruited in the frame of the Italian Study on the Incidence of Asthma (ISIA) in
110 Verona [12]. Briefly ISAYA cohorts originated from samples of 3,000 subjects (1,500 males,
111 1,500 females) randomly selected from the general population aged 20–44 years and were
112 comprised of responders to a screening questionnaire administered first by mail and then by phone
113 in 1998–2000. The questionnaire enquired about socio-demographic characteristics, respiratory
114 symptoms, smoking habits and socioeconomic burden [26].

115 The recruitment of the ISIA cohort was more complex, as the cohort originated from a random
116 sample selected in Verona with the same protocol in the frame of the ECRHS. The 2,713
117 responders to the ECRHS screening questionnaire in 1991–93 were contacted again in 1998–2000
118 and administered the same questionnaire used in ISAYA.

119 Response percentage had been 63% (1712/2713) in Verona-ISIA, 74% (2166/2927) in Verona-
120 ISAYA and 70% (2055/2925) in Sassari-ISAYA. At the baseline in 1998-2000 the three cohorts
121 were comprised of 5,933 subjects overall.

122 **Assessment of asthma and other respiratory disorders at baseline**

123 Subjects with current or past asthma at baseline were excluded from the analysis. “Current
124 asthma” was assumed when a subject reported having asthma attacks during the last 12 months or
125 currently taking medicines for asthma. “Past-asthma” was considered present when a subject
126 reported ever asthma during the lifespan, but neither attack during the previous year nor currently
127 taking medicines for asthma.

128 In the main analysis, “incident asthma” was defined as a new case of current asthma reported at
129 follow-up. Incident cases were considered also those subjects whose asthma developed during
130 follow-up and underwent remission during the same period.

131 Other respiratory disorders were considered as potential determinants of asthma onset: asthma-
132 like symptoms, allergic rhinitis and chronic bronchitis. Asthma-like symptoms included wheezing,
133 tightness in the chest, and shortness of breath in the last 12 months. A subject who did not have
134 asthma but reported at least one asthma-like symptom, was categorized as having asthma-like
135 symptoms. Allergic rhinitis was defined by a positive answer to the question “*Do you have any*
136 *nasal allergies including hay fever?*”. Chronic bronchitis was assumed if the subject answered
137 affirmatively to the question “*Have you had cough and phlegm on most days for a minimum of*
138 *three months a year and for at least two successive years?*”.

139 **Selection and follow-up of non-asthmatic cohorts**

140 Of 5,933 subjects who had participated in the baseline study, 692 subjects were excluded because
141 they had either current (n = 309) or past (n = 322) asthma at baseline or lacked information on
142 asthma status (n = 61). Hence new onset of asthma and its determinants were prospectively
143 investigated in 5,241 subjects without a history of asthma at baseline. Of note, subjects with
144 asthma-like symptoms but without current/past asthma were retained.

145 In 2008–09 subjects who had participated in ISAYA or ISIA were administered by mail/phone the
146 GEIRD screening questionnaire, which is the same as the previous one with the addition of
147 questions on education level, outdoor exposure, history of asthma, rhinitis, chronic bronchitis and
148 eczema, and life impairment [23] (available at <http://www.geird.org>). Duration of follow-up was
149 9.1 ± 0.8 years (mean \pm SD) (median 9.4, interquartile range 8.5–9.7).

150 **Assessment of smoking habits**

151 Subjects were considered: 1) current smokers if they reported to have smoked at least one
152 cigarette per day or one cigar a week for a year, and also in the last month; 2) ex-smokers if they
153 had smoked at least one cigarette per day or one cigar a week for a year, but not in the last month;
154 3) never smokers otherwise. To evaluate cumulative smoke exposure, pack-years were calculated
155 as years of smoking multiplied by the average daily consumption of 20-cigarette packs. Self-
156 reported smoking status had been validated in the survey performed in Verona in 1991–93, where

157 a good agreement (Cohen's $k = 0.93$) had been found between self-reported smoking consumption
158 and serum cotinine levels [27].

159 To evaluate changes in smoking habits, subjects were also classified as follows [28]: 1) never
160 smoker (if so at both surveys), 2) starter/restarter if a never smoker or ex-smoker at baseline
161 reported to be a smoker at follow-up, 3) ex-smoker if a never smoker at baseline became an ex-
162 smoker at follow-up or an ex-smoker remained an ex-smoker, 4) quitter if a current smoker
163 became an ex-smoker at follow-up and 5) current smoker, if so at both surveys. Subjects having
164 inconsistent answers were excluded from the analysis (90 subjects).

165 **Statistical analysis**

166 To evaluate significance of differences among different groups (responders/non-responders,
167 never/ex/current smokers) the Fisher's exact test or chi-squared test were used for categorical
168 variables and the Wilcoxon-Mann-Whitney rank-sum test for continuous variables. Verona was
169 considered as two separated cohorts, Verona-ISIA and Verona-ISAYA.

170 To compute asthma incidence, timing of first asthma attack was considered. Information on the
171 date of asthma onset had not been reported by 32.1% of new cases (48/145), for these subjects the
172 middle of the follow-up was assumed as time to event.

173 A logistic regression model was used to estimate the influence of smoking habits and
174 respiratory disorders (asthma-like symptoms, allergic rhinitis, chronic bronchitis) at baseline on
175 asthma onset during the follow-up, controlling for gender, age class (20–29, 30–39, 40–54 years),
176 occupation (clerk, businessman, workman, unemployed, housewife, student, other). Standard
177 errors were adjusted for intra-cohort correlation. Significance of the interaction between smoking
178 habits and the other variables in the model was also tested.

179 A sensitivity analysis was performed by modifying the outcome or the main explanatory
180 variable tested. First, the analysis was repeated by considering as outcome not only the onset of
181 current asthma but also the onset of wheezing; for this purpose, only subjects without both
182 current/past asthma and wheezing were included in the analysis ($n = 2,850$). Second, the analysis
183 was repeated by using the smoking definition which took into account also changes in smoking
184 status during the follow-up.

185 Stata(R) software (Texas, USA, version 13.0) was used for statistical analysis, and statistical
186 significance was set at $p < 0.05$.

187

188 **Results**

189 At baseline the age of the cohort was 34.7 ± 7.8 years (mean \pm SD) (range: 20-54 years) and the
190 proportion of men was 45%.

191 **Response to the follow-up**

192 Out of 5,241 subjects without current/past asthma at baseline, 3,187 answered the screening
193 questionnaire at follow-up. Participation in the follow-up survey was higher in Verona, ranging
194 from 68 to 77%, than in Sassari (40%) (Table 1). Response percentage was higher in women and
195 lower in unemployed and students, and increased with advancing age. The association between
196 respiratory disorders and participation rate was not consistent, as subjects with asthma-like
197 symptoms were more likely to respond, while those with chronic bronchitis were less likely. As
198 regards smoking habits, response percentage was the highest among never smokers and the lowest
199 among current smokers (Table 1).

200 **Baseline characteristics of responders to follow-up according to baseline smoking status**

201 Among responders to follow-up, 28.7% (910/3167) were current smokers at baseline. They had
202 started smoking at the age of 17.6 ± 3.6 years (mean \pm SD), corresponding to a smoking duration
203 of 17.7 ± 8.3 years, consumed 12.7 ± 7.9 cigarettes/day and had a median cumulative smoking
204 exposure of 9.1 pack-years with an interquartile range (IQL) of 3.9–17.9. 47.1% (425/902) of
205 current smokers consumed more than 10 cigarettes/day. Ex-smokers had quit smoking for a
206 median of 8.3 years (IQL 3.1–14.0).

207 Current smoking was more prevalent among men as expected (Table 2). Overall ever smokers
208 (current + ex-smokers) increased with increasing age, but while ex-smokers were one fourth of
209 current smokers in people aged 20–29 years, they approached the number of current smokers in
210 people aged 40–54 years. Accordingly, ex-smokers were more prevalent in the older cohort
211 (Verona-ISIA). Both current and past smoking was more common among workmen and
212 businessmen. The proportion of current smokers was the lowest among housewives, while ex-
213 smokers were rather rare among students and unemployed. Smoking habits were significantly
214 associated with respiratory disturbances. About half the subjects reporting asthma-like symptoms
215 or chronic cough and sputum were current smokers, while this proportion decreased to 23%
216 among people reporting allergic rhinitis.

217 **Cumulative incidence and incidence rate of asthma during the follow-up**

218 During the follow-up 145 new cases of asthma were observed, yielding a cumulative incidence
219 of 4.6% (95% CI 3.9–5.4). Incidence rate of asthma was 5.2/1,000 person-years, 4.9/1,000 person-
220 years in men and 5.5/1,000 person-years in women.

221 Cumulative incidence was not significantly affected by centre, sex, age, occupation (Table 3).
222 Cumulative incidence of asthma was doubled in people with asthma-like symptoms and increased
223 three-folds in people with allergic rhinitis ($p < 0.001$). Also people with chronic bronchitis
224 experienced a 50% increase in asthma incidence, but the effect was not significant. As regards

225 smoking habits, cumulative incidence in ex-smokers (30/554=5.4%) was slightly higher, although
226 not significantly, than in current smokers (39/883=4.4%) and never smokers (76/1,666=4.6%)
227 (p=0.641).

228 The pattern of risk estimates was partly modified in multivariable analysis, after adjusting for
229 other potential determinants. Allergic rhinitis was confirmed as the most important risk factor for
230 asthma onset, but the presence of asthma-like symptoms, although increasing the OR of asthma
231 onset by 80%, was no longer significant. New significant risk factors emerged: with respect to
232 never smokers, the risk of asthma onset was increased in ex-smokers (OR=1.28, 1.09–1.49) but
233 not in current smokers (OR=1.01, 0.66–1.53). In addition, the risk of asthma onset significantly
234 varied across different cohorts, and it was slightly decreased among housewives.

235 The relation between smoking habits and asthma incidence did not change when occupation
236 was not included in the multivariable model. Indeed the ORs of asthma incidence in ex- or current
237 smokers with respect to never smokers were substantially unchanged: 1.24 (1.07–1.44) and 1.04
238 (0.75–1.44) respectively.

239 No significant interaction was detected between smoking habits and any of the other factors
240 considered. Of note, the increase in asthma incidence, observed among ex-smokers with respect to
241 never or current smokers, was confined to subjects with allergic rhinitis or with asthma-like
242 symptoms (Table 4).

243 **Changes in smoking habits classification or in outcome definition**

244 When smoking habits were re-classified by considering smoking both at baseline and at follow-
245 up, the risk of new-onset asthma was significantly increased neither in ex-smokers at baseline nor
246 in those quitting smoking during the follow-up (Table 5). On the other hand, the influence of
247 allergic rhinitis and centre on new-onset asthma remained unchanged

248 Among the 3,187 subjects without current/past asthma at baseline and taking part in the follow-
249 up, 332 reported wheezing at baseline. Hence, the composite outcome of new asthma onset and
250 new wheezing onset was investigated on 2,855 subjects without asthma or wheezing at baseline.
251 With this enlarged outcome, new cases during the follow-up were 311, yielding a cumulative
252 incidence of 10.9% (9.8–12.0%). With this new approach current smoking became a strong
253 predictor of new-onset asthma/wheezing doubling the risk of asthma incidence (OR = 2.03, 1.35–
254 3.05), while ex-smoking lost its significance (OR = 1.04, 0.75–1.43).

255

256 **Discussion**

257 The main results of the present study are:

- 258 1. The incidence of asthma was not affected by active smoking. The result was consistent among
259 subjects with or without allergic rhinitis, did not change after adjusting for socio-economic
260 status, or when considering people smoking both at baseline and at follow-up.
- 261 2. Current smoking at baseline became a significant risk factor only when the outcome was
262 expanded to include both new-onset asthma and new-onset wheezing.
- 263 3. Ex-smokers experienced a higher risk of asthma onset. The increased risk seemed to be
264 confined to ex-smokers with asthma-like symptoms or allergic rhinitis, although the
265 interactions between smoking habits and respiratory disorders were not significant.
- 266 4. Allergic rhinitis was the most important risk factor for asthma incidence.

267 Both the asthma-smoking and smoking-asthma relations presented a high variability in the
268 current literature, with studies yielding even opposite results. While the effect of asthma on
269 smoking initiation is expected to largely change according to the cultural background and health
270 education [29], the large variability in the effect of smoking on asthma is more difficult to explain.
271 Anyway, several reasons have been put forward to explain also the latter variability: the “healthy
272 smoker effect” [17], different definitions of asthma [18,19], considering smoking status as a static
273 variable measured at baseline or as a time-dependent variable [10], a confounding effect of socio-
274 economic status [20,21], effect modification by atopic status [2,11].

275 In the present study the impact of the healthy smoker effect was likely attenuated by the long
276 time elapsed since smoking initiation (mean \pm SD = 17.7 \pm 8.3 years). The risk of asthma
277 incidence was about the same among never and current smokers, regardless of whether current
278 smokers were those smoking at baseline, or those smoking both at baseline and at follow-up. The
279 relation between smoking habits and asthma incidence did not change irrespective of including or
280 excluding occupation in the multivariable model. The relation was not modified by allergic
281 rhinitis, a proxy of atopy [24], as denoted by the lack of a significant interaction between smoking
282 habits and allergic rhinitis.

283 Current smoking at baseline became a strong predictor (OR=2.03, 1.35–3.05) only when the
284 outcome definition was expanded to include also new onset of wheezing, in agreement with
285 previous studies on adults [18] or adolescents [19].

286 In the present study, past smoking was associated with a small but significant increase in
287 asthma incidence. In the current literature ex-smokers have been reported to present both an
288 increase [3,5,9,14], a decrease [12], or no change [8,13] in asthma incidence. Of note, the increase
289 in asthma incidence recorded in the present survey (OR=1.28, 1.09–1.49) was lower than the
290 increase reported by the former studies, where the OR ranged from 1.49 (1.12–1.97) [14] to 2.50
291 (1.58–3.96) [5].

292 It is well known that most asthmatic subjects also suffer from allergic rhinitis [24,30]. In the
293 present study allergic rhinitis at baseline emerged as the most important risk factor for new-onset
294 asthma, being associated with a four-fold increase in asthma incidence, similarly to a previous
295 prospective Italian study [12]. Interestingly, this effect persisted, although to a lesser extent, when
296 allergic rhinitis during childhood was put in relation with asthma incidence during adulthood [31].
297 However, most GPs are not aware of the importance of AR as a risk factor for asthma [32].

298 **Strengths and limitations**

299 The main strength of the present study is its prospective design which allows to elucidate the
300 temporal relation between smoking and asthma. This is particularly important as not only smoking
301 habits could influence asthma incidence and prognosis, but also asthma in childhood can influence
302 smoking initiation among teenagers [29]. Moreover the analysis took into account several
303 potential confounders and/or effect modifiers (allergic rhinitis, socio-economic status, changes in
304 smoking habits during the follow-up).

305 The present study has some limitations. First, only 61% of eligible subjects participated in the
306 follow-up, and response was affected by nearly all variables considered, including respiratory
307 disorders and smoking habits: response percentage was lower among current smokers, as expected
308 [33]. Hence, although a recent study reported that loss to follow-up, while affecting prevalence
309 estimates, does not modify exposure-outcome associations [34], the present findings should be
310 interpreted with caution.

311 Second, the lack of association between current smoking and new onset asthma could be
312 attributed to the limited power of the present study. Indeed, a sample of 3187 subjects, of whom
313 30% are exposed to the risk factor considered, has an 81% power to detect an increase in
314 cumulative incidence of at least 57% (from 4.6% to 7.2%) with a 5% significant level.
315 Nevertheless, the study power of the present study was enough to assess as significant the mild
316 association between past smoking and new onset asthma: compared to never smokers, the OR of
317 asthma onset was 1.28 (95% CI 1.09-1.49) in ex-smokers (p=0.002).

318 Third, in the present survey an abstinence of just one month was required to define an ex-
319 smoker according to the ECRHS questionnaire [26] and the shortness of this time period his could
320 have favored reverse causation. Fourth, smoking habits was assessed by questionnaire. However,
321 in one cohort (Verona-ISIA) self-reported smoking consumption had been verified by serum
322 cotinine levels and a good agreement had been found (Cohen's $k = 0.93$) [27].

323

324 **Conclusions**

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327 Notwithstanding the relatively high loss to follow-up, the present study suggests that current
328 smoking does not affect the incidence of asthma when a rigorous definition of asthma is adopted,
329 based on asthma attacks and use of medicines for asthma. This negative finding persisted when
330 controlling for potential confounders, such as socioeconomic status, and for potential effect
331 modifiers, such as allergic rhinitis, or when considering smoking status both at baseline and at
332 follow-up. Current smoking was a strong risk factor only when a composite end-point was
333 considered by joining new-onset asthma and new-onset wheezing.

334

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361 **Ethical approval**

362 Ethics approval was obtained in each centre involved in GEIRD study from the appropriate ethics
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367

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473 **List of tables:**

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488 **Table 1:** Baseline characteristics of non-asthmatics at baseline (n = 5,241), who did participate (n
 489 = 3,187) or did not participate (n = 2,054) in the follow-up.

Characteristics	Respondents n (%)	Non-respondents n (%)	p value ^a
Cohort			< 0.001
Verona - ISIA	1,174 (36.8)	343 (16.7)	
Verona - ISAYA	1,285 (40.3)	610 (29.7)	
Sassari - ISAYA	728 (22.8)	1,101 (53.6)	
Sex			< 0.001
Male	1,442 (45.2)	1,149 (55.9)	
Female	1,745 (54.8)	905 (44.1)	
Age class (years)			< 0.001
[20 – 30)	830 (26.0)	750 (36.5)	
[30 – 40)	1,336 (41.9)	881 (42.9)	
[40 – 54)	1,021 (32.0)	423 (20.6)	
Occupation			< 0.001
Clerk	1,161 (36.6)	614 (30.4)	
Housewife	364 (11.5)	182 (9.0)	
Businessman	425 (13.4)	317 (15.7)	
Unemployed	140 (4.4)	193 (9.6)	
Workman	517 (16.3)	288 (14.3)	
Student	251 (7.9)	232 (11.5)	
Others	315 (9.9)	193 (9.6)	
Asthma-like symptoms			0.023
No	2,709 (85.0)	1,697 (82.6)	
Yes	478 (15.0)	357 (17.4)	
Chronic bronchitis			< 0.001
No	2,855 (90.4)	1,758 (86.9)	
Yes	303 (9.6)	265 (13.1)	
Allergic rhinitis			0.332
No	2,643 (83.6)	1,723 (84.7)	
Yes	517 (16.4)	312 (15.3)	
Smoking			< 0.001
Never smoker	1,690 (53.4)	945 (46.3)	
Ex-smoker	567 (17.9)	357 (17.5)	
Current smoker	910 (28.7)	737 (36.1)	

490 ^a Significance of differences was evaluated by the Fisher's exact test or the chi-squared test.

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495 **Table 2:** Baseline characteristics of 3,167 responders to follow-up according to smoking habits at
 496 baseline. Results are presented as absolute frequency with percentage in parentheses.

	Never smokers (n = 1,690)	Ex-smokers (n = 567)	Current smokers (n = 910)	p value ^a
Cohort				0.002
Verona - ISIA	613 (36.3)	246 (43.4)	301 (33.1)	
Verona - ISAYA	679 (40.2)	211 (37.2)	393 (43.2)	
Sassari - ISAYA	398 (23.6)	110 (19.4)	216 (23.7)	
Sex				< 0.001
Male	660 (39.1)	297 (52.4)	476 (52.3)	
Female	1,030 (60.9)	270 (47.6)	434 (47.7)	
Age at baseline (years)				< 0.001
[20 – 30)	491 (29.1)	69 (12.2)	269 (29.6)	
[30 – 40)	724 (42.8)	243 (42.9)	357 (39.2)	
[40 – 54)	475 (28.1)	255 (45.0)	284 (31.2)	
Occupation ^b				< 0.001
Clerk	650 (38.6)	190 (33.6)	316 (35.0)	
Housewife	201 (11.9)	69 (12.2)	90 (10.0)	
Businessman	196 (11.6)	93 (16.4)	132 (14.6)	
Unemployed	85 (5.1)	14 (2.5)	40 (4.4)	
Workman	224 (13.3)	117 (20.7)	172 (19.0)	
Student	167 (9.9)	15 (2.7)	69 (7.6)	
Others	160 (9.5)	68 (12.0)	85 (9.4)	
Asthma-like symptoms				< 0.001
No	1,530 (90.5)	489 (86.2)	673 (74.0)	
Yes	160 (9.5)	78 (13.8)	237 (26.0)	
Chronic bronchitis ^b				< 0.001
No	1,587 (94.2)	509 (91.5)	745 (83.0)	
Yes	98 (5.8)	47 (8.5)	153 (17.0)	
Allergic rhinitis ^b				< 0.001
No	1,365 (81.4)	477 (84.9)	782 (86.8)	
Yes	312 (18.6)	85 (15.1)	119 (13.2)	

497 Information on smoking habits was missing in 20 subjects.

498 ^a Significance of differences was evaluated by the Fisher's exact test or the chi-squared test.

499 ^b Information on occupation, chronic bronchitis, allergic rhinitis was missing in 14, 28, 27 subjects
 500 respectively.

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504 **Table 3:** Population at risk, new cases of asthma, cumulative incidence, crude and adjusted ORs
 505 of asthma onset as a function of baseline predictors.

Covariates	New cases of asthma / pop. at risk (n = 3,123)	Cumulative incidence (95% CI)	Crude OR (95% CI)	Adjusted OR ^a (95% CI)
Cohort				
Verona - ISIA	51/1,154	4.4 (3.4–5.8)	1	1
Verona - ISAYA	50/1,249	4.0 (3.0–5.2)	0.91 (0.61–1.34)	0.81 (0.68–0.98)
Sassari - ISAYA	44/720	6.1 (4.6–8.1)	1.41 (0.93–2.13)	1.27 (1.09–1.49)
		p = 0.099 ^b		
Sex				
Male	61/1,405	4.3 (3.4–5.5)	1	1
Female	84/1,718	4.9 (4.0–6.0)	1.13 (0.81–1.59)	1.18 (0.84–1.66)
		p = 0.394		
Age class (years)				
[20 – 30)	42/823	5.1 (3.8–6.8)	1	1
[30 – 40)	67/1,302	5.1 (4.1–6.5)	1.01 (0.68–1.50)	1.13 (0.75–1.70)
[40 – 54)	36/998	3.6 (2.6–5.0)	0.70 (0.44–1.10)	0.85 (0.66–1.08)
		p = 0.159		
Occupation				
Clerk	53/1,142	4.6 (3.6–6.0)	1	1
Housewife	15/355	4.2 (2.6–6.9)	0.91 (0.50–1.63)	0.88 (0.82–0.94)
Businessman	19/417	4.6 (2.9–7.0)	0.98 (0.57–1.68)	0.95 (0.70–1.30)
Unemployed	8/136	5.9 (3.0–11.4)	1.28 (0.60–2.76)	1.02 (0.52–2.00)
Workman	17/500	3.4 (2.1–5.4)	0.72 (0.41–1.26)	0.84 (0.32–2.23)
Student	16/249	6.4 (4.0–10.2)	1.41 (0.79–2.51)	1.15 (0.99–1.33)
Others	14/310	4.5 (2.7–7.5)	0.97 (0.53–1.78)	1.10 (0.68–1.79)
		p = 0.625		
Asthma-like symptoms				
No	106/2,654	4.0 (3.3–4.8)	1	1
Yes	39/469	8.3 (6.1–11.2)	2.18 (1.49–3.19)	1.81 (0.84–3.89)
		p < 0.001		
Chronic bronchitis				
No	124/2,801	4.4 (3.7–5.3)	1	1
Yes	19/294	6.5 (4.2–9.9)	1.49 (0.91–2.46)	0.93 (0.59–1.44)
		p = 0.080		
Allergic rhinitis				
No	82/2,589	3.2 (2.6–3.9)	1	1
Yes	61/507	12.0 (9.5–15.2)	4.18 (2.96–5.91)	4.00 (3.68–4.35)
		p < 0.001		
Smoking habits				
Never smoker	76/1,666	4.6 (3.7–5.7)	1	1
Ex-smoker	30/554	5.4 (3.8–7.6)	1.20 (0.78–1.85)	1.28 (1.09–1.49)
Current smoker	39/883	4.4 (3.2–6.0)	0.97 (0.65–1.43)	1.01 (0.66–1.53)
		p = 0.641		

506 The analysis was performed on 3,123 subjects, as information on asthma onset was missing in 64
 507 subjects. Significant estimates ($p < 0.05$) are reported in bold.

508 ^a Adjusted for all the other variables in the model.

509 ^b p values were computed by the Fisher's exact test.

510

511 **Table 4:** Association between smoking habits and new onset of asthma, as a function of asthma-
 512 like symptoms and allergic rhinitis. Odds ratios and p values were computed by a logistic
 513 regression model, controlling for study cohort, gender, age group, occupation and chronic
 514 bronchitis.

		ORs (95% CI)			p value ^a
		Never smoker	Ex-smoker	Current smoker	
Asthma-like symptoms	No	1	0.97 (0.82–1.15)	1.23 (0.61–2.46)	0.609
	Yes	1.77 (0.94–3.34)	4.46 (2.36–8.44)	1.23 (0.59–2.59)	
Allergic rhinitis	No	1	1.00 (0.51–1.96)	1.09 (0.68–1.74)	0.840
	Yes	3.83 (3.09–4.74)	6.80 (4.34–10.66)	3.14 (2.39–4.14)	

515 Significant estimates ($p < 0.05$) are reported in bold.

516 ^a p values were computed by the Wald test.

517

518 **Table 5:** Cumulative incidence of asthma and adjusted ORs, as a function of changes in smoking
 519 habits during the follow-up.

Changes in smoking habits	New cases / Population at risk	Cumulative incidence (95% CI)	ORs (95% CI) ^a
Never smoker	75/1,564	4.8 (3.8–6.0)	1
Ex-smoker	25/513	4.9 (3.3–7.1)	1.02 (0.72–1.45)
Starter & relapse	5/105	4.8 (2.0–11.0)	0.96 (0.36–2.56)
Quitter	12/266	4.5 (2.6–7.8)	0.96 (0.44–2.10)
Current smoker	26/569	4.6 (3.1–6.6)	0.98 (0.60–1.59)

520 ^a ORs were computed by a logistic regression model, adjusting for cohort, sex, age class,
 521 occupation and respiratory disorders (asthma-like symptoms, chronic bronchitis, allergic rhinitis).

522