TITLE PAGE

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

Giuseppe Verlato[a] Giang Nguyen[a] Pierpaolo Marchetti[a] Simone Accordini[a] Alessandro Marcon[a] Roberto Marconcini[a] Roberto Bono[b] Alessandro Fois[c] Pietro Pirina[c] Roberto de Marco[a]

[a] Unit of Epidemiology & Medical Statistics, Department of Public Health and Community Medicine, University of Verona, Verona, Italy

[b] Department of Public Health and Pediatrics, University of Turin, Turin, Italy

[c] Institute of Respiratory Diseases, University of Sassari, Sassari, Italy

Corresponding author: Professor Giuseppe Verlato, Unit of Epidemiology & Medical statistics, Department of Public Health and Community Medicine, University of Verona, Strada Le Grazie 8, 37134 Verona, Italy. Tel: +39 045 8027628, Fax: +39 045 8027154; Email: giuseppe.verlato@univr.it

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

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Abstract

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

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

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

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

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

Introduction

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

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

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

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

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

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

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

Materials and Methods

Recruitment of studied cohorts

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

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

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

Assessment of asthma and other respiratory disorders at baseline

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

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

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

Selection and follow-up of non-asthmatic cohorts

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

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

Assessment of smoking habits

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

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

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

Statistical analysis

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

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

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

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

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

Results

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

Response to the follow-up

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

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

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

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

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

During the follow-up 145 new cases of asthma were observed, yielding a cumulative incidence 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-years in men and 5.5/1,000 person-years in women.

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

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

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

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

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

Changes in smoking habits classification or in outcome definition

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

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

Discussion

The main results of the present study are:

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

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

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

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

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

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

Strengths and limitations

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

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

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

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

Conclusions

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

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Ethical approval

Ethics approval was obtained in each centre involved in GEIRD study from the appropriate ethics committee (Comitato di Bioetica dell'Azienda Sanitaria Locale di Sassari; Comitato Etico per la Sperimentazione dell'Azienda Ospedaliera Istituti Ospitalieri di Verona). All participants were fully informed about all aspects of the research project and consented to complete and return the questionnaire.

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List of tables:

Table 1: Baseline characteristics of non-asthmatics at baseline (n = 5,241), who did participate (n = 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)	

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

Table 2: Baseline characteristics of 3,167 responders to follow-up according to smoking habits at 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)	

Information on smoking habits was missing in 20 subjects.

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

[b] Information on occupation, chronic bronchitis, allergic rhinitis was missing in 14, 28, 27 subjects respectively.

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		

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

[a] Adjusted for all the other variables in the model.

[b] p values were computed by the Fisher's exact test.

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

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

[a] p values were computed by the Wald test.

Table 5: Cumulative incidence of asthma and adjusted ORs, as a function of changes in smoking 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)

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