

Smoking and New-Onset Asthma in a Prospective Study on Italian Adults

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Key Words

Asthma incidence · Smoking habits · Allergic rhinitis · Reverse causation · Italy

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:** We aimed 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 a 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 the 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.

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Introduction

The effect of smoking on asthma onset in adults is still a matter of debate. Most longitudinal studies have 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 inci-

dence 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 the 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] reports 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 favour smoking cessation among people more susceptible to the noxious effects of smoking [17].
- 2 The definition of asthma that is 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 Consideration of smoking status at baseline may not be adequate, if a substantial proportion of the studied population change their smoking behaviour during the follow-up. Hence, some authors [10] have handled smoking as a time-dependent variable in their statistical analysis.
- 5 Not taking into account socio-economic status as a potential confounder could bias the estimates of the smoking-asthma association. Indeed, in the latest phase of the smoking epidemic, cigarette smoking has become mainly confined to the lower socio-economic classes [20], who, in turn, are at a high risk for respiratory diseases [21].

In addition, the association between smoking and asthma can be modified by atopic status, and the effects of this modification could contribute to the 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 non-smokers among the atopics (OR = 1.45, 95% CI 0.81–2.61),

while the opposite trend was observed among non-atopics (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 OR of asthma onset in smokers with respect to non-smokers increased from 1.8 (0.8–4.2) among atopics to 5.7 (1.7–19.2) among non-atopics.

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 association was modified by allergic rhinitis (a proxy of atopy) [24], a change in the definition of smoking (smoking status assessed at baseline only or both at baseline and at the end of follow-up), a change in the definition of asthma (asthma attack/asthma drug vs. asthma attack/asthma drug/wheezing) and adjustments for occupational status.

Materials and Methods

Recruitment of Studied Cohorts

The incidence of asthma and its determinants were studied in 3 population-based cohorts. Two cohorts were recruited from the framework of the Italian Study on Asthma in Young Adults (ISAYA) conducted in Verona in northern Italy and Sassari on the Mediterranean island of Sardinia [25]. The third cohort was recruited from the framework of the Italian Study on the Incidence of Asthma (ISIA) in Verona [12]. Briefly, the ISAYA cohorts originated from samples of 3,000 subjects (1,500 males and 1,500 females) randomly selected from the general population (aged 20–44 years), and comprising responders to a screening questionnaire conducted first by mail and then by phone in 1998–2000. The questionnaire enquired about socio-demographic characteristics, respiratory symptoms, smoking habits and socio-economic 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, but within the framework of the ECRHS. The 2,713 responders to the ECRHS screening questionnaire in 1991–1993 were contacted again in 1998–2000 and administered the same questionnaire used in ISAYA.

The response was 63% (1,712/2,713) in Verona-ISIA, 74% (2,166/2,927) in Verona-ISAYA and 70% (2,055/2,925) in Sassari-ISAYA. At the baseline in 1998–2000, the 3 cohorts comprised 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 had asthma attacks during the last 12 months or currently taking medicines for asthma. 'Past asthma' was considered present when a subject reported that they had had asthma, but there had been no attacks during the previous year and they were not 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 also considered as those subjects whose asthma developed during follow-up and who then underwent remission.

Other respiratory disorders were considered as potential determinants of asthma onset, i.e. 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. Subjects who did not have asthma but reported at least 1 asthma-like symptom were 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?', and 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 participated in the baseline study, 692 subjects were excluded because they had either current ($n = 309$) or past ($n = 322$) asthma at baseline or information about their asthma status was lacking ($n = 61$). Hence, a 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 2008–2009, subjects who had participated in ISAYA or ISIA were administered the GEIRD screening questionnaire by mail/phone. This was the same as the previous questionnaire, with the addition of questions about level of education, outdoor exposure, a history of asthma, rhinitis, chronic bronchitis and eczema and any life impairment [23] (<http://www.geird.org>). The (mean $\pm$ SD) duration of follow-up was 9.1 ± 0.8 years [median 9.4, interquartile range (IQR) 8.5–9.7].

Assessment of Smoking Habits

The subjects considered were: (1) current smokers if they reported to have smoked at least 1 cigarette/day or 1 cigar/week for 1 year and also in the last month, (2) ex-smokers if they had smoked at least 1 cigarette/day or 1 cigar/week for 1 year, but not in the last month and (3) never-smokers. 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 $\kappa = 0.93$) had been found between self-reported smoking 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 ($n = 90$).

Statistical Analysis

To evaluate the significance of differences among different groups (responders/non-responders, current/never-/ex-smokers), Fisher's exact test or the χ^2 test were used for categorical vari-

ables and the Wilcoxon-Mann-Whitney rank-sum test for continuous variables. Verona was considered as 2 separate cohorts, Verona-ISIA and Verona-ISAYA.

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

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

STATA(R) software (v13.0, Texas, USA) was used for statistical analysis, and statistical significance was set at $p < 0.05$.

Results

At baseline, the (mean $\pm$ SD) age of the cohort was 34.7 ± 7.8 years (range 20–54 years) and the proportion of men was 45%.

Response to the Follow-Up Survey

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 (68–77%) than in Sassari (40%) (table 1). The response was higher amongst women, lower amongst the unemployed and students, and it 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 to respond. As regards smoking habits, the response percentage was the highest among never-smokers and the lowest among current smokers (table 1).

Baseline Characteristics of Responders to Follow-Up Survey according to Baseline Smoking Status

Among the responders to follow-up, 28.7% (910/3,167) were current smokers at baseline. They had started smok-

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

Characteristics	Respondents	Non-respondents	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 group			<0.001
20–29 years	830 (26.0)	750 (36.5)	
30–39 years	1,336 (41.9)	881 (42.9)	
40–54 years	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)	
Worker	517 (16.3)	288 (14.3)	
Student	251 (7.9)	232 (11.5)	
Other	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)	

Values denote n (%).

^a Significance of differences was evaluated by Fisher's exact test or χ^2 test.

ing at a mean age of 17.6 ± 3.6 years, 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 (IQR 3.9–17.9). 47.1% (425/902) of current smokers consumed >10 cigarettes/day. Ex-smokers had quit smoking for a median of 8.3 years (IQR 3.1–14.0).

Current smoking was more prevalent among men, as expected (table 2). Overall, the number of ever-smokers (i.e. current + ex-smokers) increased with increasing age, but while ex-smokers comprised only one quarter of the

number of current smokers in people aged 20–29 years, they approached the same number 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 workers and businessmen. The proportion of current smokers was the lowest among housewives, while ex-smokers were rare among students and the unemployed. Smoking habits were significantly associated with respiratory disturbances. About half of 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). The incidence rate of asthma was 5.2/1,000 person-years (4.9/1,000 in men and 5.5/1,000 in women).

Cumulative incidence was not significantly affected by study centre, sex, age or occupation (table 3). Cumulative incidence of asthma was doubled in people with asthma-like symptoms and increased 3-fold in people with allergic rhinitis ($p < 0.001$). 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 the 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 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 OR of asthma incidence in ex-smokers or current smokers with respect to never-smokers remained substantially unchanged, i.e. 1.24 (1.07–1.44) and 1.04 (0.75–1.44), respectively.

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

	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				<0.001
20–29 years	491 (29.1)	69 (12.2)	269 (29.6)	
30–39 years	724 (42.8)	243 (42.9)	357 (39.2)	
40–54 years	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)	
Worker	224 (13.3)	117 (20.7)	172 (19.0)	
Student	167 (9.9)	15 (2.7)	69 (7.6)	
Other	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)	

Values denote n (%). Information on smoking habits was missing in 20 subjects.

^a Significance of differences was evaluated by Fisher's exact test or χ^2 test.

^b Information on occupation, chronic bronchitis and allergic rhinitis was missing for 14, 28 and 27 subjects, 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-smokers or current smokers, was confined to subjects with allergic rhinitis or asthma-like symptoms (table 4).

Changes in Classification of Smoking Habits or Definition of Outcome

When smoking habits were re-classified by considering smoking both at baseline and at follow-up, there was no significant increase in the risk of new-onset asthma in ex-smokers at baseline or in those quitting smoking during the follow-up (table 5). On the other hand, the influence of allergic rhinitis and study 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, the number of new cases during the follow-up was 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).

Main Results of the Study

1 The incidence of asthma was not affected by active smoking. This result was consistent among subjects with or without allergic rhinitis and 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, but the interactions between smoking habits and respiratory disorders were not significant.

4 Allergic rhinitis was the most important risk factor for asthma incidence.

Discussion

Both the asthma-smoking and smoking-asthma relations present a high variability in the current literature, with studies even yielding opposite results. While the effect of asthma on smoking initiation is expected to change largely according to cultural background and health education [29], the large variability in the effect of smoking on asthma is more difficult to explain. Several reasons have been put forward to explain this, i.e. 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] and modification of effects by atopic status [2, 11].

In this study, the impact of the healthy smoker effect was likely attenuated by the long time that elapsed since smoking initiation (mean $\pm$ SD = 17.7 $\pm$ 8.3 years). The risk of asthma incidence was about the same among nev-

Table 3. Population at risk, new cases of asthma, cumulative incidence, crude and adjusted OR of asthma onset as a function of baseline predictors

Covariates	New cases/ population 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				
20–29 years	42/823	5.1 (3.8–6.8)	1	1
30–39 years	67/1,302	5.1 (4.1–6.5)	1.01 (0.68–1.50)	1.13 (0.75–1.70)
40–54 years	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)
Worker	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)
Other	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 for 64 subjects was missing. Significant estimates (p < 0.05) are reported in bold type.

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

^b Computed by 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

	OR (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)	

OR and p value were computed by a logistic regression model, controlling for study cohort, gender, age group, occupation and chronic bronchitis. Significant estimates ($p < 0.05$) are reported in bold type.

^a Computed by Wald's test.

Table 5. Cumulative incidence of asthma and adjusted OR, 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)	OR ^a (95% CI)
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 and relapsed smoker	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 Computed by logistic regression model, adjusting for cohort, sex, age group, occupation and respiratory disorders (asthma-like symptoms, chronic bronchitis and allergic rhinitis).

er-smokers and current smokers, regardless of whether current smokers were those smoking at baseline or at both baseline and follow-up. The relation between smoking habits and asthma incidence did not change irrespective of including or excluding occupation in the multi-variable 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 definition of outcome was expanded to include a new onset of wheezing, in agreement with previous studies on adults [18] and adolescents [19].

Past smoking was associated with a small but significant increase in asthma incidence. In the current litera-

ture, ex-smokers have been reported to present with 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 in previous 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 this study, allergic rhinitis at baseline emerged as the most important risk factor for new-onset asthma, being associated with a 4-fold increase in asthma incidence, similar 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 to asthma incidence during adulthood [31]. However, most GPs are not aware of the importance of allergic rhinitis as a risk factor for asthma [32].

Strengths and Limitations

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

The study has some limitations. First, only 61% of eligible subjects participated in the follow-up, and the re-

sponse was affected by nearly all the variables considered, including respiratory disorders and smoking habits. As expected, the response percentage was lower among current smokers [33]. Hence, although a recent study reported that loss to follow-up, while affecting prevalence estimates, does not modify exposure-outcome associations [34], our 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 study. Indeed, a sample of 3,187 subjects, 30% of whom 30% are exposed to the risk factor considered, has 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 power of this 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 (1.09–1.49) in ex-smokers ($p = 0.002$).

Third, smoking abstinence of just 1 month was required to define an ex-smoker according to the ECRHS questionnaire [26], and the shortness of this time period could have favoured reverse causation.

Fourth, smoking habits were assessed by questionnaire. However, in 1 of the cohorts (Verona-ISIA) self-reported smoking was verified by serum cotinine levels and a good agreement was found (Cohen's $\kappa = 0.93$) [27].

Conclusions

Notwithstanding the relatively high loss to follow-up, our study suggests that current smoking does not affect the incidence of asthma when a rigorous definition of asthma is adopted, i.e. based on asthma attacks and the use of medicines for asthma. This negative finding persisted when controlling for potential confounders, such as socio-economic status, and for potential effect modifiers, such as allergic rhinitis, or when considering smoking status both at baseline and 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.

Appendix

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Statement of Ethics

Ethics approval was obtained in each centre involved in the 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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