

Increased prevalence of asthma and allied diseases among active adolescent tobacco smokers after controlling for passive smoking exposure. A cause for concern?

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Summary

Background Whereas effects on allergic and respiratory health have been established for passive tobacco smoking, contradictory results still exist for active tobacco smoking.

Objective Whether adolescents with asthma and allied diseases have higher rates of active smoking compared with adolescents without asthma was assessed after controlling for environmental tobacco smoking exposure.

Methods A population-based sample of 14 578 adolescents was enrolled in an epidemiological survey on allergies in France.

Results After controlling for age, sex, geographic region, familial allergy and passive smoking, current (in the past year) wheezing (12.4%), current asthma (5.6%), lifetime asthma (12.3%), current rhinoconjunctivitis (13.9%), lifetime hayfever (14.4%) and current eczema (9.3%) but not lifetime eczema (22.5%) were all significantly related to active smoking (> 1 cigarette/day) (9.3%). A higher risk of current wheezing, current and lifetime asthma or current eczema was seen in smokers exposed to passive smoking compared with smokers not exposed to it using a polychotomous logistic regression model, in which the different modalities of exposure to active and passive smoking constituted the response variable. Passive smoking was significantly associated only with current diseases. Active smoking was also highly related to both severe asthma (OR = 4.02; 95% confidence interval: 1.37, 11.79) and severe rhinoconjunctivitis (OR = 2.95; 1.58, 5.49). The highest rate of adolescents suffering from the co-morbidity of lifetime asthma and hayfever (3.6%) was also seen in active smokers compared with passive and non-smokers (5.5% vs. 3.6% and 3.1%, respectively; $P = 0.001$).

Conclusions Being asthmatic or allergic does not seem to act as a deterrent towards starting active smoking or continuing to smoke in adolescence. Results suggest the need for considering individual allergic status in programming health educational activities aimed at reducing smoking among adolescents.

Keywords active smoking, adolescence, allergic rhinitis, asthma, co-morbidity, eczema, passive smoking, tobacco

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Introduction

For several decades, a documented increase in the incidence of IgE-mediated allergic diseases such as asthma, allergic rhinitis and atopic dermatitis (eczema) has occurred in industrial nations, probably due to environmental changes [1]. The risk factors that might have contributed to this increase include active and passive tobacco smoking, which are on the rise in certain age groups and in females. Effects in

terms of allergic and respiratory consequences have been established for passive tobacco smoking by several rigorous studies [2]. In contrast, findings concerning active tobacco smoking are contradictory [3]. Furthermore, the effects of active smoking have not been separated from those of passive smoking thus far, so that the proper effect of active smoking on asthma and allied diseases has still to be determined.

Based upon data from a large representative population-based sample of adolescents, the present study was intended to determine the relationship of active forms of tobacco smoking to asthma and allied diseases while taking passive tobacco smoking as well as other potential confounding factors of the relationship into account.

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Methods

Population

A questionnaire-based survey on asthma and allied diseases was conducted in 1993–1994 in five centres of France (Bordeaux, Marseilles, Montpellier, Strasbourg, West Marne). Each of the centres studied a group of 3000 eighth and ninth grade school adolescents, the majority of whom were 13 or 14 years of age. The choice of 3000 was made for statistical reasons according to the protocol of the International Study of Asthma and Allergies in Childhood (ISAAC) [4]. The studied groups were selected from strictly limited geographic region.

Authorization by the 'National Commission of Informatics and Civil Liberties (CNIL)' was sought and obtained before conducting the survey. The parents of the teenagers were informed by mail of the purposes and modalities of the survey, and their written assent was requested, in all but one of the centres (Montpellier).

Questionnaire

Adolescents filled out a self-administered standardized questionnaire at school. Questions derived by the ISAAC questionnaire [4] were used to assess the prevalence, severity and management of asthma and allied diseases, namely wheezing, allergic rhinitis and eczema, respectively. Such questions had been previously validated [6–9] and had been translated from English into French by a native French speaker, then back translated into English by a native English speaker. This process had been pursued until the initial English wording had been obtained. Final French wording was provided by consensus among the Allergy and Respiratory Medicine department heads of the participating centres. Furthermore, a study of the reproducibility of answers to the self-administered questionnaire by the teenagers was carried out one year after the main survey in a sample of 345 teenagers by the centre in Marseilles. The degree of accord was significant for the overall set of questions [5]. Questions derived from the British Medical Research Council and the European Community Respiratory Health Survey (ECRHS) were used to assess smoking habits among teenagers and family history of allergy except in Montpellier, which limited the survey to health outcomes.

Health outcomes and risk factors studied

The following health outcomes were considered:

- *current wheezing*: a history of 'chest wheezing or whistling in the chest over the previous 12 months';
- *current asthma*: chest wheezing or whistling over the previous 12 months with a history of asthma at some point in life;
- *lifetime asthma*: a history of asthma at some point in life according to the standardized question 'Have you ever had asthma?';
- *current rhinoconjunctivitis in the past year*: a history of 'nasal symptoms (sneezing, nasal discharge or nasal obstruction) accompanied by tearing and itching eyes in

the absence of a cold or respiratory infection over the previous 12 months';

- *lifetime hayfever*: a history of hayfever at least once in life ('have you ever had hayfever?');
- *current eczema in the past year*: a history of 'an itchy skin rash over the previous 12 months, which had affected the flexures at some time';
- *lifetime eczema*: a history of eczema or atopic dermatitis at least once in life ('Have you ever had eczema?').

Severe current asthma was ascertained as: ≥ 4 attacks of wheezing associated with attacks severe enough to limit speech to only one or two words at a time between breaths, and ever being woken at night by an attack in the past year. Severe current rhinoconjunctivitis was defined as current rhinoconjunctivitis having interfered a lot with daily activities in the past year.

Three tobacco-smoking habits were defined:

1. *Non-smoking*: the subject does not smoke and is not exposed to cigarette smoke from others;
2. *Active cigarette smoking*: smoking at least one cigarette a day for 1 year;
3. *Passive tobacco smoking*: the subject does not smoke but is exposed to tobacco smoke from others. Depending on the information available, two subtypes of passive tobacco smoking were considered: exposure to parental smoking alone or exposure to that of parents and others.

To better separate active from passive smoking, a categorical four-class variable for smoking habits, defined according to whether the teenagers were active smokers exposed to passive smoking, active smokers non-exposed to passive smoking, passive smokers only or non-smokers, respectively, was also considered in the analysis.

The other factors taken into account as potential confounders in the study of the relationship between smoking habits and asthma and allergic disorders were age, sex, geographic region, latitude and family history of allergy (except in the centre of Bordeaux where it was not available).

Statistical analysis

Conventional methods were used for comparing percentages [10]. The logistic regression model was used to determine the risk (odds ratio, OR) between each allergic disorder and active cigarette smoking, after adjustment for potential risk factors [11]. Furthermore, the polychotomous logistic regression model, generally used to establish the ORs when the response variable consists of events that may have more than two outcomes, was employed to estimate the OR between the four-class smoking variable and asthma and allied diseases after allowing for potential confounders.

The population taken into account for the present analysis is represented by the overall group of 13- or 14-year olds surveyed in all centres except for Montpellier, where data on active and passive tobacco smoking were not available.

Results

Participation

The final sample included 15 171 adolescents. The response rate varied from 78% in Bordeaux to 86% in West Marne. The sex ratio was well balanced in all four centres. There was no difference in age in the centres. In all four centres, the girls were younger than the boys and this difference was significant except in Bordeaux. Data on allergic disorders and smoking habits were available for 14 578 adolescents.

Asthma and allied diseases

Eczema was the most frequent disorder among the studied adolescents followed up by allergic rhinitis and asthma (Table 1). A history of asthma at some point in life and of current wheezing (current asthma) was reported by 5.6%. There were significantly more boys who had lifetime asthma and current wheezing and asthma, but significantly more girls who had nasal allergic symptoms and lifetime and current eczema. As expected, the cumulative prevalence of lifetime asthma and hayfever increased with age. Current asthma and allergic disorders were not age-dependent. Asthma and allied diseases were more frequent in the two southern French centres than in the two northern ones, with maximum prevalence in Bordeaux. Both severe asthma and current rhinoconjunctivitis were rare (0.2% and 0.4%, respectively).

Tobacco smoking habits

The majority of the teenagers were passive smokers (Table 1); non-smokers were intermediate in number between passive and active smokers. More teenagers were exposed to passive smoking in the two northern centres. The prevalence of passive exposure rose with age. Girls were more exposed to passive smoking than boys in all four centres, but the difference reached statistical significance only in Strasbourg and Bordeaux. There was no sex/gender-related difference with respect to active cigarette smoking. As would be expected, the percentage of active smokers increased with age. There were more active smokers in the northern centres, particularly in West Marne where significantly more boys smoked than girls. Conversely, significantly more girls smoked

than boys in Marseilles and Bordeaux. No sex-related differences were observed in Strasbourg. The average number of cigarettes smoked was higher among boys in all four centres. Overall, active boy smokers consumed 6 cigarettes a day compared with 5 for girl smokers. Among active smokers, 1.4% was not exposed at all to passive smoking.

Asthma and allied diseases related to smoking habits

Among active smokers we found the greatest percentage of asthma and allied diseases except lifetime eczema (Table 2). Relations were stronger in girls (Fig. 1). The relationships persisted after applying a logistic regression model in which asthma and allied diseases (one at a time) were included as response variables and age, sex, geographic region as well as active and passive cigarette smoking, respectively, as independent variables (Fig. 2). In particular, current asthma was also significantly associated with active smoking. Passive tobacco smoking was associated only with current wheezing, rhinoconjunctivitis or eczema. Results remained significant for both active and passive smoking after including in the model also family history of allergy (all the centres but Bordeaux) and in the case of active smoking after having excluded individuals exposed to passive smoking. According to the polychotomous logistic regression model adjusted on age and sex, adolescents exposed to both active and passive smoking presented a slight higher risk of current wheezing, current and lifetime asthma and current eczema but not of nasal allergies and lifetime eczema than smokers who were not exposed to passive smoking, passive smokers or non-smokers, respectively (Table 3). Similar ORs, although not always significant, were obtained after additional adjustment in the polychotomous model for geographic zone and familial history of allergy.

The highest rate of adolescents suffering from the comorbidity of lifetime asthma and hayfever (3.6%) was also seen in active smokers compared with passive and non-smokers (5.5% vs. 3.6% and 3.1%, respectively; $P = 0.001$). Lastly active smoking was highly related to both severe asthma (OR = 4.02; 95% confidence interval: 1.37, 11.79) and severe rhinoconjunctivitis (OR = 2.95; 1.58, 5.49). Passive smoking was associated only with severe rhinoconjunctivitis (OR = 2.84; 1.35, 5.95).

Table 1. Prevalence of asthma and allied disorders and tobacco smoking in adolescents ($n = 14\,578$)

	All	Boys ($n = 7143$)	Girls ($n = 7435$)	OR (boys vs. girls)	95% CI
Asthma and allied disorders (%)					
Current (past year) wheezing	12.4	12.7	12.0	0.94	0.85–1.04
Current asthma	5.6	6.5	4.7	0.72	0.62–0.83
Lifetime asthma	12.3	13.6	11.1	0.79	0.72–0.87
Current rhinoconjunctivitis	13.9	11.3	16.4	1.54	1.40–1.69
Lifetime hayfever	14.4	13.5	15.3	1.16	1.06–1.27
Current eczema	9.3	7.7	10.8	1.45	1.30–1.63
Lifetime eczema	22.5	20.2	24.8	1.30	1.20–1.40
Smoking (%)					
Non-smokers	40.3	42.1	38.6	1	–
Passive smokers	50.4	48.8	52.0	1.16	1.09–1.25
Active smokers	9.3	9.2	9.4	1.12	1.00–1.26

OR, odds ratio; 95% CI, 95% confidence interval.

Table 2. Relationship of asthma and allied disorders to active and passive smoking in adolescents ($n = 14\,578$)

	Non-smokers ($n = 5871$)	Passive smokers ($n = 7353$)	Active smokers ($n = 1354$)	P	P passive vs. non-smokers	P active vs. non-smokers	P active vs. passive+non-smokers
Current (past year) wheezing	11.0	12.5	17.9	0.0001	0.01	0.0001	0.0001
Current asthma	5.5	5.6	6.7	NS	NS	0.08	0.06
Lifetime asthma	11.9	12.3	14.2	0.06	NS	0.02	0.02
Current rhinoconjunctivitis	12.1	14.2	19.9	0.0001	0.001	0.0001	0.0001
Lifetime hayfever	13.3	14.3	20.0	0.0001	0.11	0.0001	0.0001
Current eczema	8.0	9.4	14.4	0.0001	0.005	0.0001	0.0001
Lifetime eczema	22.6	22.2	24.0	NS	NS	NS	NS

P , probability; NS, not significant.

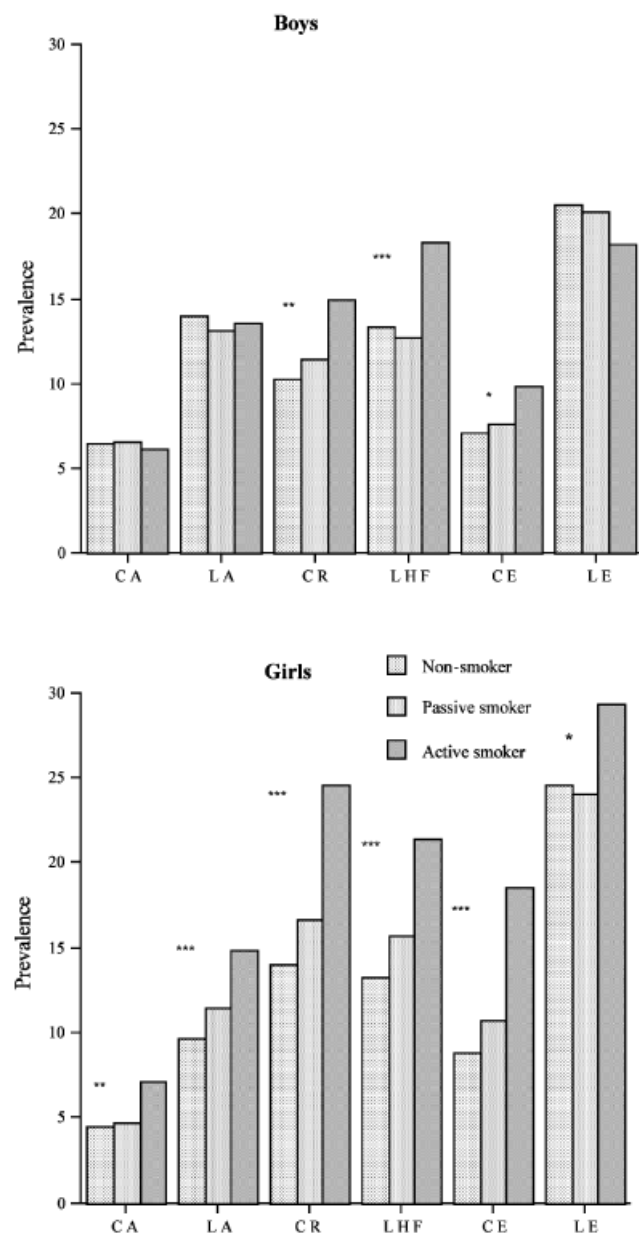


Fig. 1. Prevalence of asthma and allergies in adolescents according to smoking habits and sex in France. CA, current (past year) wheezing associated with a history of asthma; LA, lifetime asthma; CR, current (past year) rhinoconjunctivitis; LHF, lifetime hayfever; CE, current (year) eczema; LE, lifetime eczema. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

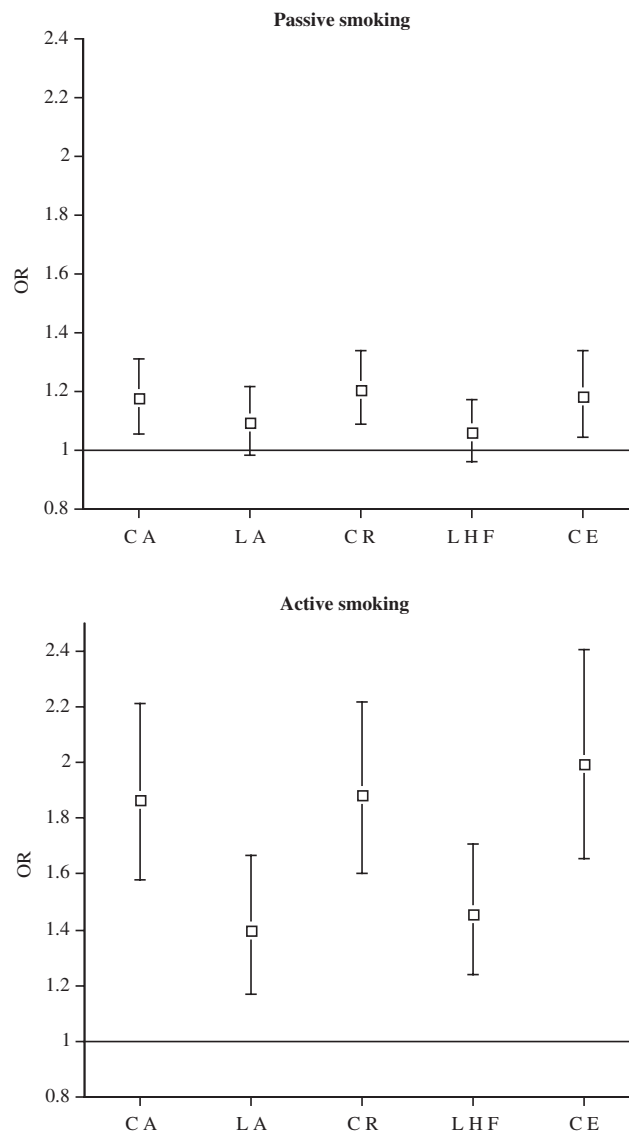


Fig. 2. Relationships of active and passive smoking to asthma and allied diseases in adolescents after adjustment for potential confounding factors in France. Figures are odds ratio (OR) obtained with logistic models. The model predicting factors associated with passive smoking was adjusted for age, sex, region, active smoking (and familial history of allergy when appropriate) whereas the model predicting factors associated with active smoking was adjusted for age, sex, region, passive smoking (and familial history of allergy when appropriate), respectively. CA, current asthma; LA, lifetime asthma; CR, current rhinoconjunctivitis; LHF, lifetime hayfever; CE, current eczema.

Table 3. Relationship of asthma and allied disorders to smoking habits by separating active smokers non-exposed to passive smoking from active smokers exposed to passive smoking in adolescents ($n = 14\,578$)

	Non smokers (reference group) ($n = 5871$)	Passive smokers ($n = 7353$)	Active smokers non-exposed to passive smoking ($n = 206$)	Active smokers exposed to passive smoking ($n = 1148$)
Current (past year) wheezing	1	1.2 (1.0–1.2)	1.7 (1.1–2.4)	1.9 (1.6–2.2)
Current asthma	1	1.0 (0.9–1.2)	1.2 (0.7–2.1)	1.2 (1.1–1.4)
Lifetime asthma	1	1.1 (0.9–1.2)	1.1 (0.69–1.6)	1.3 (1.1–1.6)
Current rhinoconjunctivitis	1	1.2 (1.1–1.3)	2.1 (1.5–2.9)	1.7 (1.5–2.0)
Lifetime hayfever	1	1.1 (0.9–1.2)	1.5 (1.1–2.2)	1.5 (1.3–1.8)
Current eczema	1	1.2 (1.0–1.2)	1.8 (1.2–2.7)	2.0 (1.7–2.5)
Lifetime eczema	1	0.9 (0.9–1.3)	1.3 (0.9–1.8)	1.1 (0.9–1.3)

Figures are odds ratio obtained using polychotomous logistic regression model (95% confidence interval) adjusted on age and sex.

Discussion

In our large population-based sample of young teenagers, asthma and allergic diseases except lifetime eczema were significantly associated with active tobacco smoking even after controlling for passive tobacco smoking, which is known to increase asthma especially in children. Although wheezing is increased along with cough and phlegm in adolescents who smoke independently of asthma, this could not explain the relationship we found between active smoking and chest wheezing or whistling over the previous 12 months associated with a history of asthma at some point in life (current asthma) in the adolescents.

The role of active cigarette smoking as a potential risk factor, a selection factor ('healthy smoker effect') or a modifier (with respect to their severity) of asthma and allied diseases is still discussed [3, 12]. Various studies [13–20], but not all those having examined the relationship [21–25] have suggested that active cigarette smoking could be a risk factor for asthma overall among adolescents. However, only longitudinal studies [15–17, 22] can contribute to establish the causality between smoking and asthma. Interestingly, the present study completed previous population-based observations according to which both allergic rhinitis and eczema are more commonly reported by current smokers among adolescents [26] and by former smokers among adults [27, 28], respectively. Active smoking has also been linked to the severity of asthma in both adolescents [19] and adults [29], which was confirmed in the present study where active smoking was highly associated not only with severe asthma but also with severe rhinoconjunctivitis. The relationship of active smoking to asthma and allied disease we found is consistent with the fact that tobacco consumption is a known risk factor for elevated total IgE levels and bronchial and nasal hyper-responsiveness, which constitute intermediate phenotypes of IgE-mediated allergy. However, such consistence does not allow assessing that tobacco smoking is a risk factor for asthma and allied diseases in the absence of prospective data.

Isolating active from passive smoking in the investigation of the relationship between tobacco and asthma and allied diseases was necessary because of the known effects of passive tobacco smoking in terms of allergic and respiratory diseases, and represents one of the added features of our study. Another supplementary characteristic of our study is provided by the taking into account of the additive effect of active and passive smoking. A slight higher risk of current wheezing,

current and lifetime asthma as well as current eczema was seen in smokers who were exposed to passive smoking of parents and peers compared with smokers not exposed to passive smoking, true passive smokers or non-smokers, respectively. A cumulative effect of active and passive smoking had already been hypothesized in respiratory diseases other than allergy, but without any quantification. Finally, our study allowed exploring the effects of active smoking on the comorbidity between asthma and rhinitis, which was lacking [30].

It has been shown that the major period of risk for becoming a cigarette smoker is adolescence, a time of life that is characterized by various developmental changes. Yet, the important question of whether the effects of tobacco smoking in adolescence may be more harmful than at other periods of life has not been addressed so far. *Stricto sensu*, this cannot be settled by a cross-sectional study like ours. However, our data provide two epidemiological arguments in favour of a higher effect of active smoking in the youth than in adulthood. The relationship (1) was observed among teenagers in spite of the small number of cigarettes smoked, so suggesting the existence of a lower sensitivity threshold in adolescence than later; and (2) existed for various clinical manifestations of allergy among adolescents whereas only for asthma among adults, so putting forward the hypothesis of a wider spectre of action of active smoking in adolescence. From the biological point of view, this could be due to factors encountered in puberty such as hormones, which are inter-related to individual susceptibility to nicotine [31], although genetic factors certainly play a role [32]. Nevertheless, longitudinal studies would be necessary to substantiate the hypothesis that adolescence may influence the relationship between active tobacco smoking and allergic disorders in a more harmful way than later in life.

In the absence of longitudinal data, the hypothesis can be raised that active smoking could act as a factor influencing the persistence of the disease, since it is extremely likely that in the class of age considered in the study the onset of asthma comes before the start of the exposure to active smoking. Data on the age of asthma onset were not available in the study but in one centre (West Marne) where most adolescents (90%) had their first asthma attack before the age of 12 years (mean and median age of asthma onset: 7.5 and 9 years, respectively) and thus before their starting of smoking. That asthma onset likely precedes active smoking is also confirmed by its natural history with the highest prevalence and incidence rates for asthma observed before puberty (the so-called Allergy March) when active smoking starts. Thereafter, the

figures for asthma decrease. We had previously shown that different phenotypes of asthma exist according to the timing of smoking onset [33]: asthma that developed before smoking and asthma without smoking were both significantly related to nasal allergy, parental asthma and atopy (as assessed by skin prick test positivity and increased total and specific IgE levels) whereas only a lower FEV₁ level was significantly associated with asthma that initiated after beginning smoking. There exists also epidemiological evidence that the effects of active smoking on asthma seen in adolescence persist through life. In various industrialized countries (except one [23]), the relationship of tobacco smoking to either the prevalence or the severity of asthma in adolescence is paralleled by a relation to asthma severity in adulthood, like if there were continuity in the action of tobacco.

Our finding that passive smoking might act also on allergic rhinitis contrasts with previous investigations conducted in population-based samples [34, 35]. However, it is consistent with experimental and clinical data according to which passive smoking can trigger nasal symptoms [36], and participate in the enhancement of total IgE production, especially among women [37], and allergic mediators in nasal mucosa [38].

Our findings acquire relevance from the public health point of view in the light of the non-negligible prevalence of active and passive smoking in adolescence. Although direct comparisons of smoking habits among adolescents are difficult because active smoking is often occasional in adolescence, various studies have shown that in average one out of ten adolescents already smoke in industrialized countries (the present study 9%, Italy 9%, USA 12%, UK 12%, Europe 10%, respectively). Passive smoking exposure in adolescence, for which data are less available in the literature, seems even more prevalent; one out of two adolescents being exposed to passive tobacco smoking in industrialized countries. Therefore, the effects of active and passive smoking are potentially noxious in terms of allergic and respiratory health even in adolescence.

From the methodological point of view, large population-based studies using suitable statistical methods allowing for potential confounders are especially valuable in public health because it has been shown that inferences from such observations are highly reliable. Among the confounders, familial history of allergy was taken into account in our study, thus avoiding differential reporting of exposure and diseases among the children of allergic parents. Furthermore, recall bias was avoided in our study, as active smoking was associated with both current allergic diseases and lifetime disorders. The validity of assessing active and passive smoking by questionnaire has been extensively proven [39]. It would have been interesting to take into account parental smoking history over the children's lifetime, but such data were not available in the entire sample. However, the validity of such assessment is questionable, as recall bias cannot be excluded in the reporting of lifetime exposure to smoking overall among parents of allergic and asthmatic children.

In the light of our results, being allergic does not seem to act as a deterrent towards starting active tobacco smoking or continuing to smoke in adolescence but rather as an incentive to stop smoking later in life due to the severity of the disease that smoking induces. That active smoking might be responsible for smoking cessation in adults with severe asthma is

supported by various studies having observed a higher prevalence of asthmatics among former smokers [3].

In conclusion, our results suggest the need to (1) adopt preventive measures concerning smoking in adolescence in order to protect young teenagers from development and exacerbation of allergic manifestations and (2) take into account the individual allergic status in programming health educational activities aimed at reducing smoking among adolescents. Such measures would appear all the more justified because active cigarette smoking typically begins during adolescence.

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References

- 1 Group publication. Evidence for an increase in atopic disease and possible causes. *Clin Exp Allergy* 1993; 23:484–92.
- 2 Strachan D, Cook D. Passive smoking. *Rev Thorax* 1997; 12:1–32.
- 3 Viegi G, Annesi-Maesano I, Matteoli G. Epidemiology of asthma. In: Chung F, Fabbri LM, eds. *Asthma European Respiratory Monograph*. Sheffield 2003; 23:1–25.
- 4 ISAAC manual December 1993; 2nd Edn. Auckland (NZ) Munster (FRG).
- 5 Charpin D, Annesi-Maesano I, Godard PH et al. Présentation générale de l'étude ISAAC. *Rev Mal Respir* 1997; 14:4S7–14.
- 6 Jenksin MA, Clarke JR, Carlin JB et al. Validation of questionnaire and bronchial hyperresponsiveness against respiratory physician assessment in the diagnosis of asthma. *Int J Epidemiol* 1996; 25:609–16.
- 7 Sibbald B, Rink E. Epidemiology of seasonal and perennial rhinitis: clinical presentation and medical history. *Thorax* 1991; 46:895–901.
- 8 Sibbald B, Rink E. Labelling of rhinitis and hay fever by doctors. *Thorax* 1991; 46:378–81.
- 9 Williams HC, Burney PGJ on behalf of the UK diagnostic criteria for atopic dermatitis working party. Validation of the UK diagnostic criteria for atopic dermatitis in a population setting. *Br J Dermatol* 1996; 135:12–7.
- 10 Snedecor GW, Cochran WG. *Statistical methods*. Ames: The Iowa State University Press, 1967.
- 11 Lee ET. *Statistical methods for survival data analysis*. Belmont, CA: Belmont Lifetime Learning, 1980.
- 12 Flodin U, Jönsson P, Ziegler J, Axelson O. An epidemiological study of bronchial asthma and smoking. *Epidemiology* 1995; 6:503–5.
- 13 Larsson L. Incidence of asthma in Swedish teenagers: relation to sex and smoking habits. *Thorax* 1994; 50:260–4.
- 14 Dodge RR, Burrows B. The prevalence and incidence of asthma and asthma-like symptoms in a general population sample. *Am Rev Respir Dis* 1980; 122:567–75.
- 15 Vesterinen E, Kaprio J, Koskenvuo M. Prospective study of asthma in relation to smoking habits among 14729 adults. *Thorax* 1988; 43:534–9.
- 16 Viegi G, Baldacci S, Vellutini M et al. Prevalence rates of diagnosis of asthma in general population samples of northern and central Italy. *Monaldi Arch Chest Dis* 1994; 49:191–6.

- 17 Strachan DP, Butland BK, Anderson HR. Incidence and prognosis of asthma and wheezing illness from early childhood to age 33 in a national British cohort. *BMJ* 1996; 312:1195–9.
- 18 Bodner CH, Ross S, Little J et al. Risk factors for adult onset wheeze: a case control study. *Am J Respir Crit Care Med* 1998; 157:35–42.
- 19 Moreau D, Ledoux S, Choquet M, Annesi-Maesano I. Prevalence and severity of asthma in adolescents in France. Cross-sectional and retrospective analyses of a large population-based sample. *Int J Tuberc Lung Dis* 2000; 4:1–10.
- 20 Higgins MW, Keller JB, Metzner HL. Smoking, socioeconomic status and chronic respiratory disease. *Am Rev Respir Dis* 1977; 116:403–10.
- 21 Troisi R, Speizer FE, Rosner B et al. Cigarette smoking and incidence of chronic bronchitis and asthma in women. *Chest* 1995; 108:1557–61.
- 22 Wakefield M, Ruffin R, Campbell D, Roberts L, Wilson D. Smoking-related beliefs and behaviour among adults with asthma in a representative population sample. *Aust NZ Med* 1995; 25: 12–7.
- 23 Ulrik CS, Backer V, Hesse B, Dirksen A. Risk factors for development of asthma in children and adolescents: findings from a longitudinal population study. *Respir Med* 1996; 90: 623–30.
- 24 Viegi G, Paoletti P, Prediletto R et al. Prevalence of respiratory symptoms in an unpolluted area of northern Italy. *Eur Respir J* 1988; 1:311–8.
- 25 Rasmussen F, Siersted HC, Lambrechtsen J, Hansen HS, Hansen NG. Impact of airway lability, atopy, and tobacco smoking on the development of asthma-like symptoms in asymptomatic teenagers. The Odense Schoolchild Study. *Chest* 2000; 117:1330–5.
- 26 Duhme H, Weiland SK, Rudolph P, Wienke A, Kramer A, Keil U. Asthma and allergies among children in West and East Germany: a comparison between Munster and Greifswald using the ISAAC phase I protocol. *International Study of Asthma and Allergies in Childhood*. *Eur Respir J* 1998; 11:840–7.
- 27 Annesi-Maesano I, Oryszczyn MP, Neukirch F, Kauffmann F. Relationship of upper airway disease to tobacco smoking and allergic markers: a cohort study of men followed up for 5 years. *Int Arch Allergy Immunol* 1997; 114:193–201.
- 28 Bakke P, Gulsvik A, Eide G. Hay fever, eczema and urticaria in southwest Norway. Lifetime prevalences and association with sex, age, smoking habits, occupational airborne exposures and respiratory symptoms. *Allergy* 1990; 45:515–2.
- 29 Siroux V, Pin I, Oryszczyn MP, Le Moual N, Kauffmann F. Relationships of active smoking to asthma and asthma severity in the EGEA study. *Epidemiological study on the Genetics and Environment of Asthma*. *Eur Respir J* 2000; 15:470–7.
- 30 Annesi-Maesano I. Epidemiological evidence of the occurrence of rhinitis and sinusitis in asthmatics. *Allergy* 1999; 54 (Suppl. 57):7–13.
- 31 Kolasa E, Hulanicka B, Waliszko A. Does exposure to cigarette smoke influence girls maturation. *Przegl Epidemiol* 1998; 52:339–50.
- 32 Swan GE. Implications of genetic epidemiology for the prevention of tobacco use. *Nicotine Tob Res* 1999; S49–56.
- 33 Raherison C, Baldi I, Tunon-De-Lara JM, Taytard A, Annesi-Maesano I. Asthma phenotypes according to the timing of smoking onset in young adults. *Int J Tuberc Lung Dis* 2003; 7:84–92.
- 34 Upton MN, McConnachie A, McSharry C et al. Intergenerational 20 year trends in the prevalence of asthma and hay fever in adults: the Midspan family study surveys of parents and offspring. *BMJ* 2000; 8:88–92.
- 35 Wuthrich B, Schindler C, Medici TC, Zellweger JP, Leuenberger P. IgE levels, atopy markers and hay fever in relation to age, sex and smoking status in a normal adult Swiss population. SAPALDIA (Swiss Study on Air Pollution and Lung Diseases in Adults) Team. *Int Arch Allergy Immunol* 1996; 111:396–402.
- 36 Benninger MS. The impact of cigarette smoking and environmental tobacco smoke on nasal and sinus disease: a review of the literature. *Am J Rhinol* 1999; 13:435–8.
- 37 Oryszczyn MP, Annesi-Maesano I, Charpin D, Paty E, Maccario J, Kauffmann F. Relationships of active and passive smoking to total IgE in adults of the Epidemiological Study of the Genetics and Environment of Asthma, Bronchial Hyperresponsiveness, and Atopy (EGEA). *Am J Respir Crit Care Med* 2000; 161:1241–6.
- 38 Vinke JG, KleinJan A, Severijnen LW, Fokkens WJ. Passive smoking causes an 'allergic' cell infiltrate in the nasal mucosa of non-atopic children. *Int J Pediatr Otorhinolaryngol* 1999; 51:73–81.
- 39 Forastiere F, Agabiti N, Dell'Orco V et al. Questionnaire data as predictors of urinary cotinine levels among nonsmoking adolescents. *Arch Environ Health* 1993; 48:230–4.