

Risk factors of new-onset asthma in adults: a population-based international cohort study

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Abstract

Background: The occurrence of new-onset asthma during adulthood is common, but there is insufficient understanding of its determinants including the role of atopy.

Objective: To assess the risk factors for the development of new-onset asthma in middle-aged adults and to compare them according to atopy.

Methods: A longitudinal analysis of 9175 young adults who participated in two surveys of the European Community Respiratory Health Survey (ECRHS) conducted 9 years apart.

Findings: We observed 179 cases of new-onset asthma among 4588 participants who were free of asthma and reported at the beginning of the follow-up that they had never had asthma (4.5 per 1000 person-years). In a logistic regression, the following risk factors were found to increase the risk of new-onset asthma: female gender (OR: 1.97; 95% confidence interval (CI): 1.38,2.81), bronchial hyperresponsiveness (3.25; 2.19,4.83), atopy (1.55;1.08,2.21), FEV₁ < 100 % predicted (1.87;1.34,2.62), nasal allergy (1.98;1.39,2.84) and maternal asthma (1.91;1.13;3.21). Obesity, respiratory infections in early life and high-risk occupations increased the risk of new-onset asthma although we had limited power to confirm their role. Among the atopics, total IgE and sensitization to cat were independently related to the risk of new-onset asthma. The proportion of new-onset asthma attributable to atopy varied from 12% to 21%.

Conclusion: Adults reporting that they had never had asthma were at a substantial risk of new-onset asthma as a result of multiple independent risk factors including lung function. Atopy explains a small proportion of new-onset adult asthma.

After several decades of epidemic growth, asthma has become a common disease during adulthood. It is now well established that adult asthma commonly begins in childhood. However, the occurrence of new-onset asthma during adulthood is substantial (1). Birth cohorts and prospective studies of children in schools have provided valuable

information about the determinants of the development of asthma (2) but there are few longitudinal studies recording new-onset asthma in adulthood. The few available studies have shown that among adults, prior respiratory symptoms, smoking, atopy, BMI, hayfever/eczema and exposure to moulds are associated with an increased risk of new-onset

asthma (3–5). Whereas allergic factors have been reported as commonly associated with childhood asthma (2–6), a major controversy remains about the role of atopy and the occurrence of extrinsic (atopic) asthma during adulthood (7). The European Community Respiratory Health Survey (ECRHS) is the largest international longitudinal study of asthma in adults, covering a wide geographical area and including information on a wide range of host and environmental risk factors on new-onset asthma and previous publications have focused on particular risks (8–12). Here, we provide an aetiological model of new-onset adult asthma, with special emphasis on the role of atopy.

Methods

Design, population and methods

Participants were recruited at ECRHS I when they were 20–44 years of age (1990–95) and were randomly selected from the local populations of 27 centres in 13 countries (including 25 centres in 12 European countries). Those included in the ECRHS I were invited to take part in the ECRHS II follow-up survey (1998–2003). Information about design and methods of ECRHS II has been reported elsewhere (13). Ethical approval was obtained from the appropriate institutional ethics committees and written consent was obtained from each participant.

To identify the population at risk of new-onset asthma, those who reported a history of asthma or respiratory symptoms (wheezing or whistling without a cold, ever having had asthma and/or having been woken by an attack of shortness of breath in the past 12 months) in ECRHS I were excluded. Among those included, new-onset asthma was defined as an affirmative response to the question 'have you ever had asthma' in ECRHS II. In a sensitivity analysis, asthma was alternatively defined as having had an attack of asthma in the last 12 months and/or receiving medication for asthma.

We considered as potential determinants of new-onset asthma those host and environmental factors included in the list of risk factors influencing the development and expression of asthma reported by the Global Initiative for Asthma (GINA) (14) for which we had information available for the complete ECRHS I and II samples: gender, parental asthma, atopy, bronchial hyperresponsiveness (BHR), obesity, maternal and current smoking, older siblings, respiratory infections during childhood and occupational exposures. We also included the following as potential risk factors: age, lung function, hay fever and level of education. Parental asthma, smoking, siblings, respiratory infections during childhood, hay fever and education were self-reported according to the ECRHS questionnaire (13). For occupational exposures, status during the entire follow-up period was considered (13). As in a previous study (8), we assessed occupational exposures with a list of occupations that potentially have high risk of asthma. Participants who worked exclusively in professional, clerical, or administrative jobs between surveys were classified as having low-risk occupations and were the reference group.

Procedures and equipment for clinical testing were identical at both surveys. Standardized spirometry was performed to obtain the forced expiratory volume in the first second (FEV₁), the ECSC prediction equations being used to estimate the predicted values of FEV₁. (13) An abnormal FEV₁ was defined as any level below 100% predicted, which corresponded to the 25 percentile in our population. BHR was assessed using the methacholine challenge, which was carried out with a dosimeter (Mefar, Brescia, Italy). The presence of BHR was defined as a fall of at least 20% in FEV₁ associated with a methacholine dose of 1 mg or less. Serum levels of total and specific IgE against four common environmental aeroallergens (house dust mite, cat, timothy grass and *Cladosporium herbarum*) were determined using the Pharmacia CAP system (Pharmacia Diagnostics, Uppsala, Sweden). Atopy was defined as a specific IgE level greater than 0.35 kU/l to at least one out of the four allergens. Alternatively, atopy was defined as any positive response to the skin prick test to seven allergens (15). High-risk occupations for asthma were defined according to previous literature (8).

Statistical analysis

We calculated the person-years of follow-up for those free of symptoms at baseline to estimate the incidence of new-onset asthma. Odds ratios for new-onset asthma were computed with logistic regression models with centre as a random effect. Models were stratified by atopic status at baseline. The final multivariable models included all risk factors that showed a *P*-value smaller than 0.1 in at least one of the three univariate analyses (overall, nonatopics, atopics). The population attributable fractions were estimated from the logistic model (16). Sensitivity analyses were performed to test the robustness of our results when using different exclusion criteria, asthma definitions and statistical models (see Supporting information). To analyse asthma as a time to event variable, age at the onset of asthma was fitted into a Cox proportional hazards regression survival model with clustering by centre. We assessed the effect of missing data using multiple imputation methods for multivariate categorical data (17). Analyses were carried out using STATA, version 10 (StataCorp. 2007, Stata Statistical Software: Release 10. College Station, TX, USA: StataCorp LP).

Role of the funding source

None of the study sponsors had any role on study design, data collection, data analysis, data interpretation or writing of the report. The corresponding author had full access to all the data in the study and had full responsibility for the decision to submit for publication.

Results

Among 15716 people who participated in the ECRHS I, 9175 participated in the ECRHS-II. Nonparticipants were slightly more likely to have BHR (14.9% vs 12.2%), atopy (33.4% vs 30.4%), FEV₁ less than 100% predicted (35.4% vs 32%), be

current smokers (41.2% vs 34%) and to have a lower BMI (BMI < 20: 14.2% vs 11.3%) at ECRHS I (all *P*-values ≤ 0.001). Median follow-up was 8.9 years. Of the participants, 1703 were excluded because they reported symptoms of asthma at ECRHS I and 63 because of having missing data on asthma at ECRHS I, leaving 7409 participants free of symptoms at baseline. Of those, 2821 were excluded from the analysis because of incomplete data, restricting the final analysis to 4588 participants free of asthma symptoms, who never had asthma and had complete data in both surveys. All those with incomplete data (2821) were included in the sensitivity analysis which included all 7409 participants free of asthma symptoms at baseline.

The total follow-up included 39 535 person-years, ranging between centres from 491 to 2578 person-years with a median of 1339. We observed 179 (3.9%) cases of new-onset asthma, corresponding to an incidence rate of 4.5 per 1000 person-years (95% confidence interval (CI): 3.8–5.1). Incidence rates varied with different definitions of the baseline population (Table 1). Among host factors, female gender, BHR, total and specific IgE, FEV₁ (% predicted), nasal allergy and maternal asthma were all positively associated with new-onset asthma. Among the environmental factors, respiratory infection before the age of 5 and high-risk occupation were also associated with new-onset asthma although the latter was only marginally significant (*P* < 0.10) (Table 2). After stratification by atopy, variables associated (*P*-values < 0.05) with both atopics and nonatopics were as follows: male gender, BHR, nasal allergy and maternal asthma; in addition, respiratory infection before the age of 5 was associated with new-onset asthma only in the nonatopics whereas reduced lung function, high-risk occupation, total IgE and specific IgEs against cat and timothy grass did so only among the atopics (Supporting Information).

In a multivariate model adjusted for centre (Table 3), the variables that showed positive and statistically significant associations with new-onset asthma were gender (female), BHR, atopy, reduced FEV₁, nasal allergy and maternal asthma. In addition, obesity, serious respiratory infection before the age of five and high-risk occupations were associated with asthma without reaching statistical significance. We tested the interactions between atopy and BHR and between obesity and gender, but only the latter approached significance (*P*-value for the interaction: 0.06) showing that women with obesity were at an increased risk. The attributable fractions of new-onset asthma to the main associated causal factors were as follows: atopy 12.1% (95% CI: 0.7–22.2), BHR 17% (10–24), FEV₁ < 100% predicted 19% (8–29), nasal allergy 19% (9–28) and maternal asthma 5% (0–9). By defining atopy as any positive response to the skin prick test to seven allergens (model 8 in Fig. 1), its attributable fraction increased up to 21% (8–29).

After stratification by the presence of atopy at baseline, there were statistically significant associations with gender (female), BHR and reported nasal allergies in both nonatopic and atopic subjects, whereas the association with reduced FEV₁ became stronger and remained significant only in the nonatopic group (Table 3). Among the remaining risk

factors, the association with respiratory infection during infancy appeared stronger in the group without atopy at baseline as did the association with occupation. Maternal asthma remained significant with a similar association in both groups. Smoking showed a different pattern in atopics and nonatopics (global *P*-value for interaction: 0.01) with current smokers being at lower risk, among nonatopics, but higher risk among atopics. A third level stratification between lung function, atopy and smoking showed that among never smokers, a predicted FEV₁ < 100% was associated with asthma in both nonatopic (2.80; 1.47–5.32) and atopic subjects (2.33; 1.05–5.15). Among the atopics, a serum level of total IgE > 100 kU/l and specific IgE against cat greater than 0.35 kU/l was associated with new-onset asthma. Among the nonatopics, there was no association between a high level of total IgE and asthma even when the latter was categorized with a lower cut-off (30 kU/l).

The variance of the random effects associated with centre was statistically significant in the final model, indicating the presence of heterogeneity of the factors associated with incidence rates among centres. In addition, with centres grouped into three geographical regions (North, Central and South), all *P*-values for heterogeneity of effects were greater than 0.3 except for high-risk occupations, which showed an effect only in the South (*P*-value: 0.04), and cat allergen sensitization, which showed an effect only in the Central region (*P*-value: 0.08).

The results of the sensitivity analysis showed that most of the associations remained stable across the different models. A similar pattern of stability was observed when the alternative models were obtained for both those with and without atopy at baseline (Figs S1 and S2 in the Supporting Information).

Discussion

We have shown that close to 4% of the baseline population developed asthma over the follow-up period of 8.9 years indicating that onset of asthma during adulthood is a common event. Occurrence of new cases was more common in women and those with BHR, atopy, reduced lung function, reporting nasal allergy or maternal asthma. About 60% of

Table 1 New-onset asthma incidence (incidence rate per 1000 person-years and 95% confidence interval (CI)) by baseline status according to bronchial hyperresponsiveness (BHR) and atopy. Participants with asthma symptoms at baseline (ever asthma, wheezing without a cold and/or woken by an attack of shortness of breath) were excluded (*N* = 4588)

Baseline				
BHR	Atopy	N	Cases	Incidence rate (95% CI)
No	No	3179	85	3.0 (2.5, 3.8)
No	Yes	1063	47	5.1 (3.8, 6.7)
Yes	No	211	23	12.5 (8.3, 18.8)
Yes	Yes	135	24	20.8 (13.9, 31.0)
All	All	4588	179	4.5 (3.8, 5.1)

Table 2 Characteristics of the population and their associations with new-onset asthma. Participants with asthma symptoms at baseline (ever asthma, wheezing without a cold and/or woken by an attack of shortness of breath) were excluded ($N = 4588$)

	<i>N</i> (%)	New-onset asthma <i>n</i> (%)	<i>P</i> -value for chi-square test
Sex			
Male	2326 (50.7%)	62 (2.7%)	<0.001
Female	2262 (49.3%)	117 (5.2%)	
Age			
<30	1428 (31.1%)	60 (4.2%)	0.47
30–40	1930 (42.1%)	78 (4%)	
≥40	1230 (26.8%)	41 (3.3%)	
Bronchial hyperresponsiveness			
No	4242 (92.5%)	132 (3.1%)	<0.001
Yes	346 (7.5%)	47 (13.6%)	
Atopy			
No	3390 (73.9%)	108 (3.2%)	<0.001
Yes	1198 (26.1%)	71 (5.9%)	
Total IgE (kU/l)			
<100	3650 (79.6%)	119 (3.3%)	<0.001
≥100	938 (20.4%)	30 (6.4%)	
Specific IgE (kU/l)			
House dust mite			
<0.35	3942 (85.9%)	137 (3.5%)	<0.001
≥0.35	646 (14.1%)	42 (6.5%)	
Cat			
<0.35	4292 (93.6%)	149 (3.5%)	<0.001
≥0.35	296 (6.5%)	30 (10.1%)	
Timothy grass			
<0.35	3881 (84.6%)	129 (3.3%)	<0.001
≥0.35	707 (15.4%)	50 (7.1%)	
<i>Cladosporium herbarum</i>			
<0.35	4492 (97.9%)	175 (3.9%)	0.89
≥0.35	96 (2.1%)	4 (4.2%)	
FEV ₁ (% predicted)			
<100%	1265 (27.6%)	79 (6.2%)	<0.001
≥100%	3323 (72.4%)	100 (3%)	
BMI			
<20	517 (11.3%)	23 (4.4%)	0.30
20–25	2673 (58.3%)	95 (3.6%)	
25–30	1177 (25.7%)	48 (4.1%)	
≥30	221 (4.8%)	13 (5.9%)	
Reported nasal allergies			
No	3622 (78.9%)	110 (3%)	<0.001
Yes	966 (21.1%)	69 (7.1%)	
Maternal asthma			
No	4330 (94.5%)	160 (3.7%)	0.002
Yes	252 (5.5%)	19 (7.5%)	
Paternal asthma			
No	4325 (94.5%)	164 (3.8%)	0.15
Yes	250 (5.5%)	14 (5.6%)	
Smoking			
Never	1960 (42.7%)	79 (4%)	0.57
Ex	1131 (24.7%)	50 (4.4%)	
New/re-starters	163 (3.6%)	7 (4.3%)	
Current	969 (21.1%)	33 (3.4%)	
Discordant data	365 (8%)	10 (2.7%)	

Table 2 (Continued)

	<i>N</i> (%)	New-onset asthma <i>n</i> (%)	<i>P</i> -value for chi-square test
Maternal smoking during pregnancy			
No	3509 (77%)	136 (3.9%)	0.80
Yes	1046 (23%)	43 (4.1%)	
Respiratory infections before 5 years			
No	4195 (91.4%)	155 (3.7%)	0.03
Yes	393 (8.6%)	24 (6.1%)	
High-risk occupation			
No	3469 (80.2%)	125 (3.6%)	0.07
Yes	855 (19.8%)	43 (5%)	
Mould inside the home			
No	3600 (82.9%)	145 (4%)	0.20
Yes	743 (17.1%)	22 (3%)	
Firstborn			
No	2718 (59.3%)	100 (3.7%)	0.39
Yes	1869 (40.7%)	79 (4.2%)	
Low education level			
No	3514 (82.4%)	133 (3.8%)	0.24
Yes	753 (17.6%)	36 (4.8%)	

cases occurred among nonatopics, and the attributable fraction of asthma to atopy was 12%.

It has been suggested that the importance of atopy in asthma has been overemphasized and that less than half of asthma is attributable to atopy (7). This view was in disagreement with previous reports (18) suggesting that most of asthma could have an allergic background and the issue continues unresolved. Several of our findings are to be highlighted. First, about two-thirds of new-onset asthma cases occurred in nonatopics. In the 1995–96 Health Survey for England, the proportion of recent wheezing attributable to atopy was 30% in those aged 30–49 (19). In a review of how much asthma is attributable to atopy (7), the lowest attributable fractions reported were those for new-onset wheeze in both older adults (8%) (20) and young adults (18%) (21). These low proportions could have resulted from considering wheeze instead of asthma. In our study, the attributable fraction of new-onset asthma to atopy varied from 12% to 21%, suggesting that only a relatively small part of new-onset asthma in adults is linked to atopy and that the investigation of causal factors that operate through non-IgE mechanisms should be actively considered. Second, our finding that among nonatopics there was no association between new-onset asthma and total IgE does not agree with previous studies (6, 18, 22), which showed that the prevalence of asthma was closely related to total IgE irrespective of atopy. These studies were cross-sectional, and it could be that among nonatopics total IgE is associated with persistence and relapse rather than with the development of asthma. Third, we have found remarkable similarities in the effect of some risk factor among atopics and nonatopics. This is consistent with previous studies regarding rhinitis (12, 23) and BHR (24). For these risk factors, similar associations with new-onset asthma in both atopics and nonatopics were consistently replicated in the

Table 3 Risk factors for new-onset asthma, adjusted for centre and time of follow-up. Participants with symptoms at baseline (ever asthma, wheezing without a cold and/or woken by an attack of shortness of breath) were excluded. Models include all risk factors in Table 2 with a *P*-value <0.10 in any of the three models (overall, nonatopics and atopics)

	All N = 4588 Asthma = 179 (3.9%)	Nonatopics N = 3390 Asthma = 108 (3.2%)	Atopics N = 1198 Asthma = 71 (5.9%)
Odds Ratio (95% confidence interval)			
Female	1.97 (1.38, 2.81)	2.04 (1.28, 3.25)	1.94 (1.11, 3.38)
Bronchial hyperresponsiveness	3.33 (2.24, 4.94)	3.23 (1.86, 5.60)	4.19 (2.32, 7.58)
Atopy	1.59 (1.11, 2.27)	–	–
Predicted FEV ₁ < 100%	1.88 (1.35, 2.63)	2.23 (1.46, 3.41)	1.46 (0.84, 2.53)
BMI (reference: 20–25, normal)			
<20 (underweight)	1.01 (0.62, 1.66)	1.39 (0.78, 2.48)	0.47 (0.17, 1.28)
25–30 (overweight)	1.20 (0.81, 1.78)	1.15 (0.69, 1.92)	1.23 (0.65, 2.31)
≥30 (obese)	1.69 (0.90, 3.15)	1.38 (0.61, 3.08)	2.53 (0.90, 7.10)
Reported nasal allergies	1.96 (1.37, 2.81)	2.05 (1.26, 3.34)	1.84 (1.08, 3.14)
Maternal asthma	1.92 (1.14, 3.24)	1.96 (1.00, 3.83)	1.91 (0.81, 4.51)
Smoking at baseline (reference: never)			
Ex-smoking	1.32 (0.90, 1.95)	1.59 (1.00, 2.54)	0.78 (0.36, 1.65)
Current smoking	0.93 (0.63, 1.38)	0.67 (0.40, 1.15)	1.45 (0.81, 2.61)
Infections before age five	1.41 (0.87, 2.29)	1.60 (0.92, 2.78)	0.84 (0.28, 2.47)
High-risk occupation	1.25 (0.86, 1.81)	1.00 (0.61, 1.63)	1.78 (0.99, 3.20)
Odds ratios when total IgE and sensitization to specific allergens were used instead of atopy*			
Total IgE > 100 kU/l	1.77 (1.23, 2.56)	1.05 (0.54, 2.06)	2.52 (1.42, 4.47)
Sensitization to cat allergen	1.88 (1.16, 3.04)		1.83 (1.06, 3.17)

*Odds ratios obtained from different models. These models included all variables in Table 3 except for atopy, which was substituted for total IgE > 100 and sensitization to specific allergies. Because of the high collinearity between sensitization to the four different allergens (house dust mite, cat, timothy grass and *Cladosporium herbarum*), only sensitization to cat allergen, the only one that remained significant in a model with the four sensitization variables was left in the model.

sensitivity analysis. So, our results challenge the concept that asthma is almost always associated with some type of IgE-related reaction and therefore has an allergic basis as suggested two decades ago (18) and supports recent claims that the role of atopy on asthma has been overemphasized (7). The latter does not preclude the importance of allergic airways inflammation in the asthmatics without atopy which can result from several non-IgE mechanisms (25).

As far as we know, this is the first longitudinal study to clearly show that reduced lung function in adulthood is associated with new-onset asthma, an association that was stronger and statistically significant in nonatopics. Dodge and Burrows reported that subjects with asthma developing after the age of 40 had spirometric abnormalities and no atopy. However, their analysis included subjects with previous respiratory symptoms (26). Reduced lung function at birth has been found to be associated with an increased risk of asthma by the age of 10 years (27) and with a low respiratory function at the age of 22 (28). Thus, it seems reasonable to suggest that lung function decrements at birth or soon after, may persist carrying an increased risk of new-onset asthma into adulthood. The lack of association between FEV₁ and asthma in atopics could be because of the influence of smoking because among never smokers this association was positive, strong and statistically significant in both nonatopics and atopics. The role of smoking could

result from a self-selection bias or be a true biological effect. Thus, overall, the association between FEV₁ and new-onset adult asthma in our study was strong, independent of all the other risk factors and remained in all the sensitivity models, supporting the view that lung function impairment has a genuine role in the development of asthma. As in a previous retrospective analysis in our population (29), we found that reports of respiratory infection during infancy were associated with new-onset asthma among the nonatopic subjects, and there was evidence that this association was independent of lung function. Our finding is in agreement with a study showing that hospitalization during infancy because of a respiratory syncytial virus bronchiolitis was associated with the development of asthma up to age of 13 (30).

The environmental risk factors included in our study apparently had a smaller role in the occurrence of new-onset asthma than host factors. Whether atopic and nonatopic subjects respond differently to environmental factors is of interest (19). We found current smoking negatively associated with asthma in the nonatopics and positively in the atopics with a significant interaction between smoking and atopy in the overall model (*P*-value for the interaction 0.007), this pattern of associations being consistently replicated by the sensitivity analysis (Figs S1 and S2 in the Supporting Information). The later included a model, which excluded

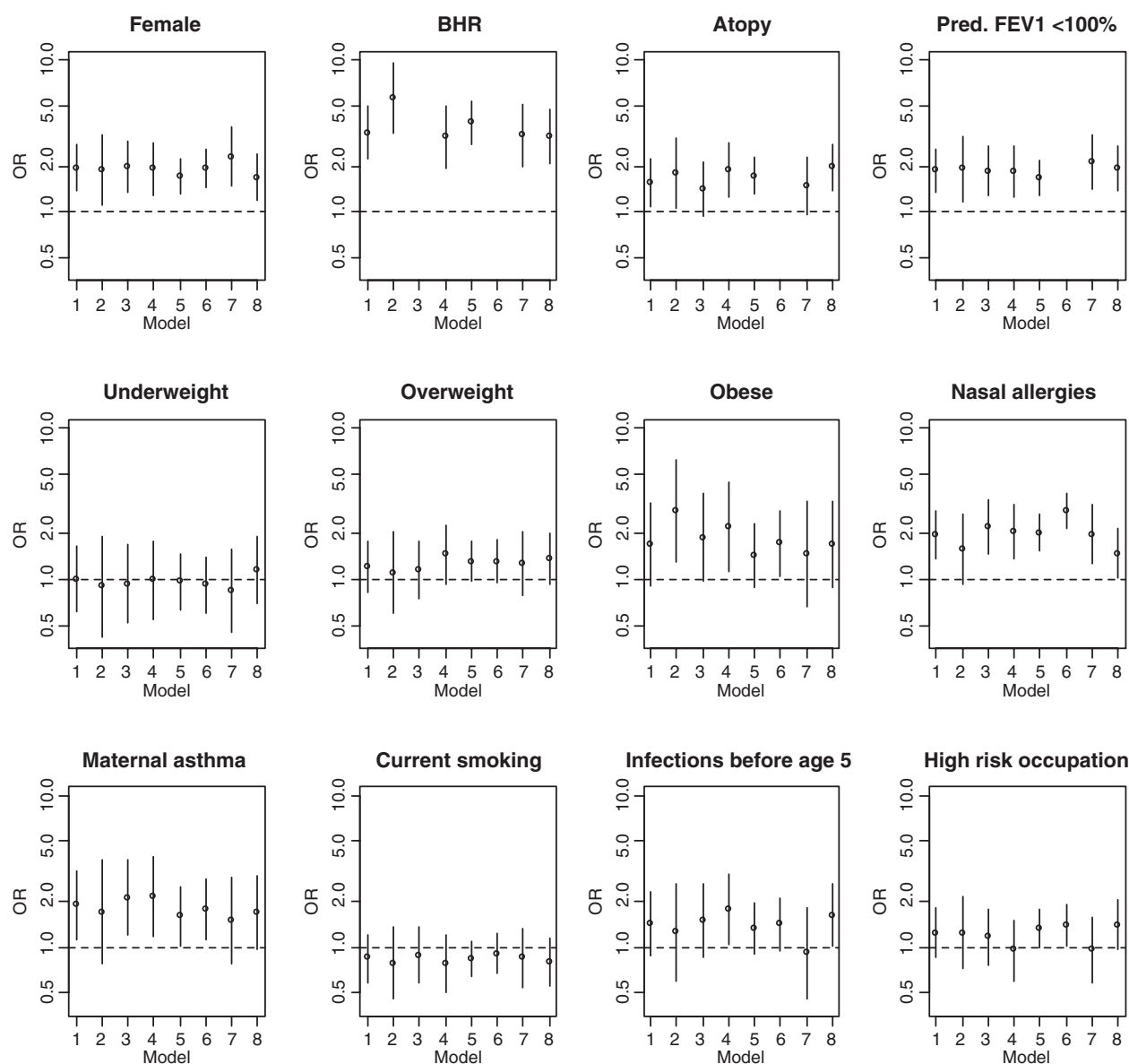


Figure 1 Sensitivity analysis results. Odds ratios (OR) and 95% confidence intervals for the risk factors in Table 3 under different modelling strategies. Unstratified results. Models indicate the following: (1) results from Table 3 ($N = 4588$); (2) defining asthma as having had an attack of asthma in the last 12 months and/or receiving medication for asthma ($N = 4588$); (3) excluding those with BHR at baseline (assuming that its presence could indicate the presence of preclinical asthma) ($N = 4242$); (4) excluding those participants who had any of the six respiratory symptoms plus ever asthma and medication because of respiratory symptoms used to the define an asthma score (14) ($N = 3873$); (5) using multiple

imputation to treat missing values in the risk factors and then using the complete dataset to estimate the associations while accounting for the additional uncertainty because of missing data ($N = 7409$); (6) model not including any of the variable that can be considered part of the disease in the model, i.e. not including BHR, atopy and reduced FEV₁ as predictors ($N = 5829$); (7) Using Cox proportional hazards model and using age of onset of asthma (Hazards Ratios are reported instead of Odds Ratios) ($N = 4588$); (8) measuring atopy by means of the skin prick test as any positive response to seven common allergens (15) ($N = 4567$). The Y-axis is on logarithmic scale.

lung function, suggesting that the negative association between smoking and asthma among nonatopics was not because of the influence of lung function as an intermediate variable (model 6 in Fig. S2). This finding, which is in con-

flict with previous studies showing an opposite trend (19–21), could more likely reflect the presence of a smoking-related bias of different origins or alternatively be a true effect of smoking mediated by atopy. We have previously reported in

the same population that occupational exposures (8) are an important risk factor for new-onset adult asthma, in particular among atopy subjects although in the present analysis, we found a weaker association. The latter was most likely because of differences in asthma definition and exclusion of subjects with incomplete data as the role of occupation was confirmed in the sensitivity analysis both in the overall population (model 5 in Fig. 1) and among the atopy subjects (models 2, 5 and 6 in Fig. S2). For other environmental factors like indoor allergens, information was only available for a subsample and was not included in the present analysis. So, for allergens, we could only assess the role of specific IgE showing that sensitization to cat allergen increases the risk of new-onset asthma among atopy subjects, consistently with previous studies in older (31) and young adults (32). In a previous study carried out in a subsample of our population, we reported that common use of household cleaning sprays could be an important risk factor of adult asthma (9). Similarly, it has been recently reported in our study population that exposure to outdoor NO₂ (11) and occupational exposures (8) are associated with an increased risk of new-onset asthma. In some of these studies (9–11), we found no difference between atopy subjects and nonatopy subjects in the reported associations.

The incidence rate of new-onset asthma in our study (4.5 per 1000 person-years) was higher than the 1.1 reported by Torén et al. in a 16- to 50-year-old Swedish general population (33) but slightly lower than the 5.5 per 1000 person-years reported in a 12- to 41-year-old population ascertained from the Danish Twin Register (3). Unfortunately, the different definitions of asthma and different methods used in the available studies make the comparison of the different incidence rates difficult.

As with most of cohort studies among general urban populations, we had a substantial proportion of nonresponders. However, our response rates are similar to those of other recent population-based studies (34, 35). Those not followed had greater BHR and atopy at ECRHS I than participants and were more likely to be smokers. It can be argued that those not followed up could include a group at a higher risk of developing new-onset asthma and that our incidence rates were underestimated. Accordingly, we may still have underestimated the incidence of new-onset asthma. Obviously, we cannot exclude the possibility that some of our estimates of associations between risk factors and new-onset asthma might be biased because of nonresponders.

In addition, we were concerned with other methodological limitations that have persistently hampered the epidemiological investigation of asthma and approached them in the sensitivity analysis. The results of the seven alternative models were very consistent with those from the original model. The results of model 5, which included 7409 participants, provided reasonable confidence that our results were not biased by missing data. Our interpretation about the role of atopy is conditional to the assumption that our measure of atopy was a valid one. We included a sensitivity model with a definition of atopy based on the prick test to 7 allergens and showed almost identical results (model 8 in Figs 1, E1 and E2). However, as has been reported in soybean epidemic asthma (36)

and more recently in patients with obstructive airways disease (37), even nonatopy subjects can react to inhaled environmental particles through an IgE-mediated mechanism. The latter may be explained if an IgE-dependent mechanisms locally operating at the target organ can develop allergic inflammation and organ dysfunction even in nonatopy subjects with a low serum level of total IgE (38). Several potentially important causal factors of asthma like genes and gender-related factors were not included in our analysis. For few of them, including TNF gene and menstrual irregularity results have been reported elsewhere (38, 39). Finally, as in all previous studies among adults, we cannot exclude that those adults who reported to be asthma free at ages 20–44 may have had asthma during childhood. To circumvent this difficulty, we have included a sensitivity model based on the age of onset as retrospectively assessed. Retrospective assessment of age of onset has been found to increase the reliability of longitudinal asthma assessment (40, 41). Even if a degree of misclassification exists, the fraction of asthma attributable to atopy would be even less than the one reported, as atopy is strongly related to asthma in childhood.

In summary, the results of the present study have shown that during adulthood the occurrence of new-onset asthma is a relatively common event, which is related to the independent role of relevant host and environmental factors: female gender, lung function, BHR, atopy, nasal allergy, obesity, parental asthma, respiratory infections in early life and high-risk occupations. Our finding that only one in five cases of new-onset asthma are attributable to atopy supports the concern that the role of atopy on the development of asthma has been overemphasized and that other aetiological paradigms should be actively considered. Lung function impairment seems to have a genuine role in the development of a new-onset adult asthma which understanding requires further investigation.

Contributors

Josep M Antó, Jordi Sunyer, Isa Cerveri, Roberto de Marco, Joachim Heinrich, Christer Janson, Deborah Jarvis, Nino Kuenzli, Benedicte Leynaert, Cecile Svanes, Matthias Wjst and Peter Burney are members of the steering committee of the ECRHS II and have contributed to all the steps of the study. Josep M Antó, Jordi Sunyer, Xavier Basagaña and Peter Burney planned the analysis. Xavier Basagaña and Raquel Garcia-Esteban conducted the analysis. Josep M Antó wrote the manuscript. All authors have read, contributed and approved the manuscript.

Conflict of interest statement

We declare that we have no conflict of interest.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Online data supplement.

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Online data supplement

The causes of new-onset asthma in adults: a population-based international cohort study.

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Methods

Study centers

The following centers were included in the analyses: South Antwerp, Antwerp city (Belgium); Hamburg, Erfurt (Germany); Barcelona, Galdakao, Albacete, Oviedo, Huelva (Spain); Bordeaux, Grenoble, Montpellier, Paris (France); Pavia, Turin, Verona (Italy); Geleen (Netherlands); Ipswich, Norwich (UK); Reykjavik (Iceland); Bergen (Norway); Goteborg, Umea, Uppsala (Sweden); Basel (Switzerland); Portland (USA); Melbourne (Australia). To study the geographical variation centers were grouped into three groups in the following way: North (Iceland, Norway, Sweden); Central (Belgium, Germany, Netherlands, UK, USA); South (Australia, France, Italy, Spain, Switzerland).

Respiratory Symptoms

In one of the sensitivity analyses, we excluded all participants with any of the eight respiratory symptoms that were part of an asthma score (E1) in the baseline questionnaire. These eight symptoms are: Wheeze and breathless during any time in the last 12 months; Feeling of chest tightness any time in the last 12 months; Attack of shortness of breath at rest any time in the last 12 months; Attack of shortness of breath after exercise any time in the last 12 months; Woken by attack of shortness of breath any time in the last 12 months; Ever asthma; Attack of asthma any time in the last 12 months; and Currently taking medication for asthma.

Lung function

Spirometric methods are described in detail in the ECRHS protocol (available at www.ecrhs.org). Briefly, baseline FVC (forced vital capacity) and FEV₁ (maximal one-second forced expiratory volume) were measured in all eligible subjects who agreed to these tests. Subjects were permitted nine attempts to provide at least two technically acceptable maneuvers. Quality controls were performed at different levels. All field-workers involved in the study received identical training, a quality control visit was made by investigators of the ECRHS, and equipment quality controls were also performed.

Methacholine challenge

Methacholine challenge methods have been reported elsewhere (E02). Methacholine was delivered via a Mefar dosimeter (Mefar, Bobezzo, Italy), using two methods of challenge, a long and short schedule of doses, with a maximum cumulative dose of 1 mg. Bronchial responsiveness (BHR) was defined as any subject with a $\geq 20\%$ fall in FEV₁, with respect to the highest post-diluent FEV₁ during the methacholine challenge with a maximum cumulative dose of 5.117 μmol of methacholine.

Total and specific IgE

Serum total IgE and specific IgE to cat, house dust mite (*D. pteronyssinus*), *Cladosporium* and Timothy grass were measured using the Pharmacia CAP System (Pharmacia Diagnostics AB, Uppsala, Sweden). The measurement range for total IgE was 2 to 2000 kU/L, and 0.35 to 100 kUA/L for specific IgE. Specific IgE In ECRHS I measurements were made by the Pharmacia laboratory.

Sensitization and skin prick tests

In the present study, the allergen-coated Phazet ® was used, including seven selected allergens that allow the identification of almost all sensitized subjects in epidemiologic studies: *Dermatophagoides pteronyssinus*, cat, Timothy grass pollen, birch, *Olea europea* (olive) pollen, *Alternaria alternata* and *Cladosporium herbarum* (E03). A histamine positive control and a negative control were also tested. A skin prick test was considered to be positive if the mean wheal diameter was found to be over 0mm. Subjects were excluded if they had a positive negative control or had a mean wheal diameter of over 30mm for at least one allergen as this would lead to a practical difficulty in assessing the reaction to other allergens. Subjects with at least one positive SPT were considered to be sensitized.

Geographical variations

The variation of the incidence rates by centre was assessed by testing whether the variance of the random effects was greater than zero. The adjusted incidence rates and the odds ratios of the risk factors by three geographical regions were calculated by including a categorical variable (North/Central/South) in the models.

Results

Sensitivity analysis

The sensitivity analysis that was performed for the overall population in the paper (Figure 1) is repeated here for the atopics and non-atopics. We fitted eight different models using different definitions of asthma and different adjustments. In particular, the eight models indicate: 1) results from Table 3; 2) defining asthma as having had an attack of asthma in the last 12 months and/or receiving medication for asthma; 3) excluding those with BHR at baseline (assuming that its presence could indicate the presence of pre-clinical asthma); 4) excluding those participants that had any of the eight respiratory symptoms used to define an asthma score (E01); 5) using multiple imputation to treat missing values in the risk factors and then using the complete dataset (N=5,464 for non-atopics, N=1,945 for atopics) to estimate the associations while accounting for the additional uncertainty due to missing data; 6) model not including any of the variable that can be considered part of the disease in the model, i.e. not including BHR and reduced FEV₁ as predictors; 7) Using Cox proportional hazards model and using age of onset of asthma (Hazard Ratios are reported instead of Odds Ratios); 8) measuring atopy by means of the skin prick test as any positive response to seven common allergens (E03). Results from non-atopic subjects are shown in Figure E1 and for atopic subjects in Figure E2.

Geographical variations

The variance of the random effects associated with centre was statistically significant in the final model, indicating the presence of heterogeneity of the incidence rates among

centres. Figure E3 shows the adjusted asthma incidence for the three geographical regions (North, Central and South). Figure E4 shows the effect of the risk factors by the same geographical, and the p-values for interaction. None of the effects were different by region, except for high risk occupations, which showed an effect only in the South (p-value: 0.04), and cat allergen sensitization, which showed an effect only in the Central region (p-value: 0.08).

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Figure E1. Odds ratios (OR) and 95% confidence intervals for the risk factors in table 3 under different modelling strategies for non-atopics.

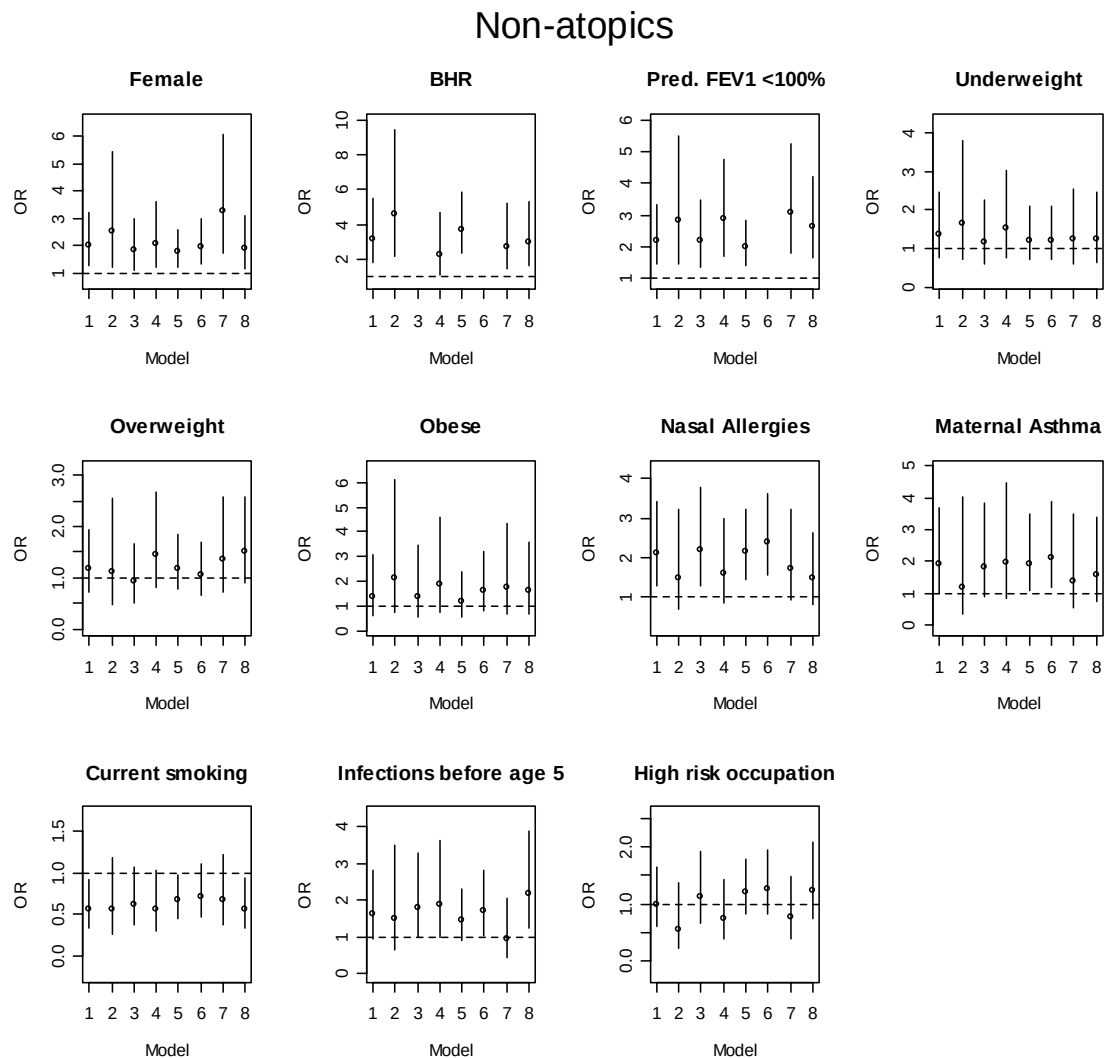


Figure 2 displays 12 subplots showing Odds Ratios (OR) for each model (1 to 8) for various variables. The variables are arranged in a 4x3 grid. Each plot includes a dashed horizontal line at OR = 1.0. The y-axis scale varies by plot to accommodate the range of OR values.

- Female:** OR ranges from 0 to 5. Model 3 has the highest OR (~2.5), while Model 4 has the lowest (~1.5).
- BHR:** OR ranges from 0 to 20. Model 2 has the highest OR (~10), while Model 1 has the lowest (~4).
- Pred. FEV1 <100%:** OR ranges from 0.0 to 3.0. Model 1 has the highest OR (~1.5), while Model 5 has the lowest (~1.0).
- Underweight:** OR ranges from -0.5 to 2.5. Model 1 has the highest OR (~1.0), while Model 7 has the lowest (~0.5).
- Overweight:** OR ranges from 0 to 3. Model 3 has the highest OR (~2.5), while Model 1 has the lowest (~1.2).
- Obese:** OR ranges from 0 to 15. Model 2 has the highest OR (~10), while Model 7 has the lowest (~1).
- Nasal Allergies:** OR ranges from 1 to 5. Model 4 has the highest OR (~4.5), while Model 1 has the lowest (~1.8).
- Maternal Asthma:** OR ranges from 0 to 8. Model 2 has the highest OR (~7.5), while Model 5 has the lowest (~1.5).
- Current smoking:** OR ranges from 0 to 4. Model 3 has the highest OR (~3.5), while Model 4 has the lowest (~1.2).
- Infections before age 5:** OR ranges from 0 to 5. Model 2 has the highest OR (~4.5), while Model 3 has the lowest (~0.8).
- High risk occupation:** OR ranges from 0 to 8. Model 2 has the highest OR (~3.5), while Model 3 has the lowest (~1.2).

Figure E3. Adjusted asthma incidence per 1,000 person year and 95% confidence intervals by geographical regions (North/Central/South).

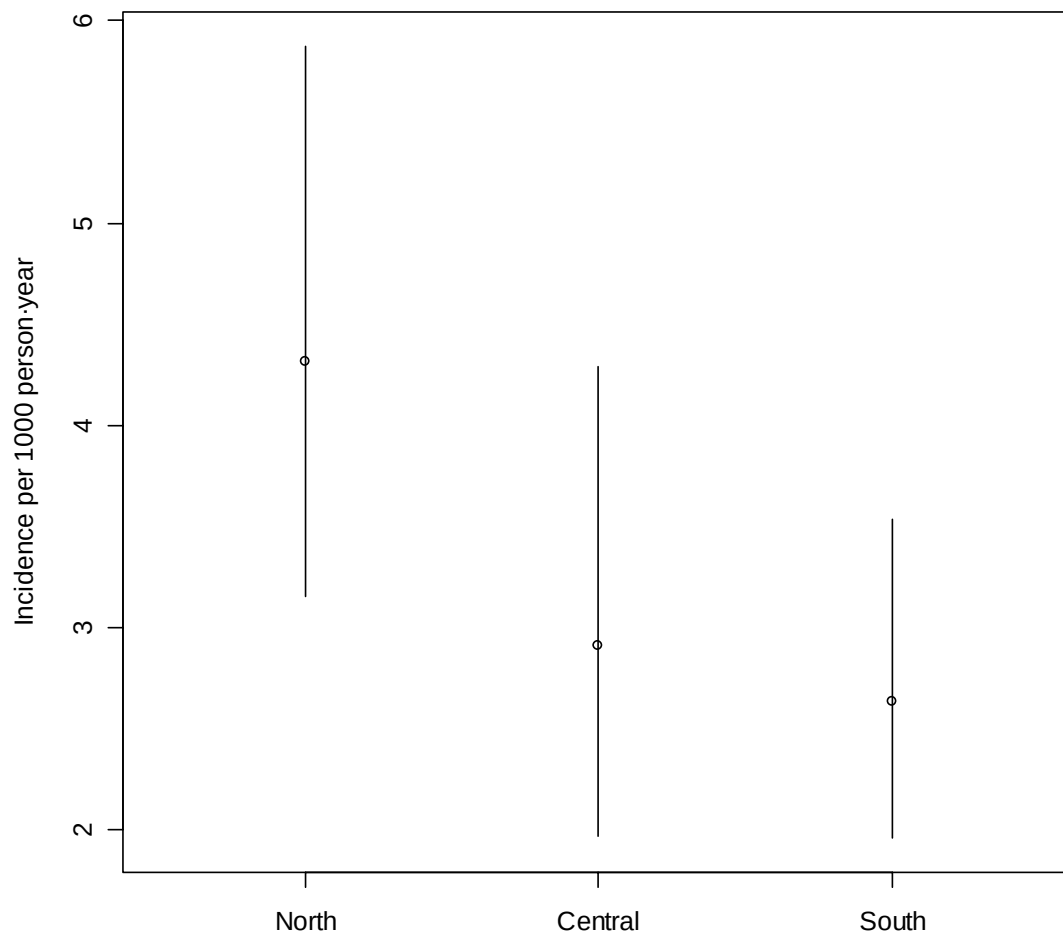


Figure E4. Effect of risk factors (odds ratio and 95% confidence intervals) by geographical regions (North/Central/South).

