SMOKING, AND AIRWAY HYPERRESPONSIVENESS ESPECIALLY IN THE PRESENCE OF BLOOD EOSINOPHILIA INCREASE THE RISK TO DEVELOP RESPIRATORY SYMPTOMS

A 25 year follow-up study in the general adult population

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Abstract

Airway hyperresponsiveness (AHR) constitutes a risk for development of respiratory symptoms. We assessed whether blood eosinophilia (>275 eosinophils/μl), skin test positivity (sumscore >3), and cigarette smoking (never, ex-smoker, 1-14 cig/d, 15-24 cig/d, >25 cig/d) at the first of two successive surveys are related to the development of respiratory symptoms (chronic cough or phlegm, bronchitis, persistent wheeze, dyspnea, and asthma) at the second survey, and whether these relations are the same in subjects with (PC10 <8 mg/ml histamine) and without AHR. We analyzed data of the longitudinal Vlagtwedde-Vlaardingen Study (1965 to 1990) using logistic regression analyses with paired observations, taking multiple measurements within a person into account.

In total, 995 men and 792 women contributed 4,403 paired observations. Eosinophilia in hyperresponsive subjects significantly increased the risk to develop one or more respiratory symptoms (Odds ratio [OR]=3.67, 95% confidence interval [CI]=1.79 to 7.52), wheeze (OR=5.06, 95% CI=2.11 to 12.13), and dyspnea (OR=2.73, 95% CI=1.13 to 6.60), independent of smoking, age, sex, area of residence, and time between two successive surveys. Smoking at the first of two successive surveys increased the risk to develop symptoms in a dose-dependent relation. Subjects with positive skin tests in the past were less likely to develop one or more respiratory symptoms (OR=0.64, 95% CI=0.46 to 0.88) and chronic phlegm (OR=0.65, 95% CI=0.42 to 1.00), independent of AHR. This longitudinal study in the general adult population shows that cigarette smoking and hyperresponsive subjects are at increased risk to develop respiratory symptoms, and especially so when eosinophilia is present in hyperresponsive persons.

Introduction

Risk factors for the development of respiratory symptoms in the general adult population are not well known. A recent study on the development of respiratory symptoms in adults showed that subjects with airway hyperresponsiveness (AHR) were more likely to develop respiratory symptoms than were subjects without AHR (1). Prior to this report, the only other known risk factor important for the development of respiratory symptoms in adults was cigarette smoking (2). Cross-sectional studies have shown that both skin test positivity and peripheral blood eosinophilia are associated with the presence of respiratory symptoms and AHR (3-10). Although no longitudinal data are available in adults, a few studies in children have suggested that skin test positivity in young childhood is predictive of respiratory symptoms in late childhood and young adulthood (11-13). Therefore, these factors might, just as is AHR, be associated with the development of respiratory symptoms.

Using methodology similar to that of Xu and colleagues (1), we determined whether peripheral blood eosinophilia and skin test positivity at the first of two successive surveys are related to the development of respiratory symptoms at the second
survey. Furthermore, we assessed whether these factors influenced the increased risk to develop respiratory symptoms, especially in persons with AHR. Finally, we assessed whether the previously reported risk of smoking was present in a dose dependent manner.

Methods

We used data from the longitudinal Vlagtwedde-Vlaardingen Study of 1965 to 1990. The study was originally designed to determine risk factors for chronic obstructive lung diseases. The selection of the study population has been described previously (9,14). In brief, baseline measurements were carried out in 1965 and 1967 in Vlagtwedde and in 1965 and 1969 in Vlaardingen. In 1965, a random sample of subjects from the general population 40 to 64 yr of age was studied, and in 1967 and 1969, subjects 15 to 39 yr of age were studied. Follow-up surveys were organized in 1970, 1973, 1976, 1979, 1982, 1985, and 1989 at Vlagtwedde and in 1972, 1975, 1978, 1981, 1984, 1987, and 1990 at Vlaardingen, all during the month of October. At each survey, information was collected by a questionnaire, a blood sample was taken, and spirometry and a histamine provocation test were performed. Skin prick tests were performed at the baseline surveys and at the first follow-up survey only. The study protocol was approved by the local medical ethics committee, and all participants gave their informed consent at each survey.

Information on respiratory symptoms, smoking status, age, and sex was collected by the Dutch version of the British Medical Research Council standardized questionnaire (15,16). Subjects were considered symptomatic if they reported one or more of the following chronic respiratory symptoms: cough or phlegm production on most days or nights for as long as 3 consecutive months each year during winter (referred to as chronic cough/chronic phlegm), a period of at least 3 wk during the previous 3 yr with (increased) cough and phlegm (bronchitis episodes), shortness of breath when walking with other persons of the same age on level ground (dyspnea ≥ Grade 3), a wheezing or whistling sound in the chest on most days or nights (persistent wheeze), or attacks of shortness of breath in the previous 3 yr (asthma attacks). We excluded the observations of subjects who participated in the baseline survey in 1965 at Vlagtwedde and reported ever having asthma attacks because no information was available when the last asthma attack was experienced. Subjects were categorized as current smokers (defined as smoking at least one cigarette per day at the first of two successive surveys), ex-smokers (defined as those who had quit smoking at least 1 month before the first of two successive surveys), and never-smokers (no smoking history at the first of two successive surveys). Current smoking was categorized as 1-14, 15-24, and ≥ 25 cigarettes per day. Pipe and cigar smokers were excluded.

Pulmonary function measurements were performed with a water-sealed spirometer (Lode Spirograph D53, Lode Instruments, Groningen, The Netherlands).
Measurement of inspiratory vital capacity (IVC) after a deep expiration was followed by measurement of FEV$_1$. The higher of the values obtained in two technically satisfactory tracings was taken as the baseline measurement as long as the difference between the two IVC values was less than 150 ml and that between the two FEV$_1$ values was less than 100 ml. All values were recorded at ATPS.

Airway responsiveness to histamine was assessed by the method of Tiffeneau as modified by de Vries and coworkers (17), which meets standardization guidelines (18). After baseline measurements of pulmonary function, subjects inhaled nebulized distilled water from a Wiesbaden Doppel inhalator (Lode Instruments, Groningen, The Netherlands). The test was terminated when the IVC or the FEV$_1$ decreased by 10% or more. After pretesting, aerosols of histamine biphosphate were inhaled for 30 s in concentrations of 1, 4, 8, 16, and 32 mg/ml. After each challenge, two IVC and FEV$_1$ maneuvers were performed. The concentration at which the IVC or the FEV$_1$ value persistently declined by 10% or more, was considered the threshold value (PC$_{10}$). AHR was defined as a PC$_{10}$ <8 mg/ml histamine. Subjects with excessively low levels of pulmonary function (FEV$_1$ <1.5 L) and those who could not perform a forced expiration were not tested. Subjects suffering from heart disease, hypertension, or acute respiratory infections were also excluded from challenge.

Atopy was assessed by skin prick tests in the surveys of 1965, 1967/1969, and 1970/1972. Four inhalant allergens were tested: house dust mite, mixed pollen, mixed epidermal products, and mixed molds (Diephuis, Groningen, The Netherlands). The solvent for the allergens served as a negative control, and histamine served as a positive control. The wheal diameter for each allergen was measured to the nearest half millimeter and the diameter of the negative control was subtracted. The measurements were coded on a 6 point scale: 0 = 0-5 mm, 1 = >5-7.5 mm, 2 = >7.5-10 mm, 3 = >10-12.5 mm, 4 = >12.5-15 mm, 5 = >15 mm. Subjects were considered to be skin test positive if they had a total score of the four allergens of at least 3 (sumscore > 3) (10). Once subjects were skin test positive they were considered to be skin test positive throughout the longitudinal study. Eosinophils were counted in a 1:10 dilution using a Bürker counting chamber and expressed in cells/l. Eosinophilia was defined as >275 cells/l (10). Blood samples were taken, before spirometry and skin prick tests were performed.

Statistical analyses
The longitudinal analyses included all data collected during the surveys from 1965 to 1990. Information of two successive surveys was compared to study the development of respiratory symptoms. The paired observation had a minimum interval of 3 yr. Subjects could contribute more than one paired observation to the analyses, with a maximum of seven pairs. Eighty-two percent of all paired observations had an interval of 3 yr. The incidence (development) of respiratory symptoms was calculated as the percentage of subjects without a symptom at the first of two successive surveys who had developed the symptom at the nearest
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follow-up survey.
The risk estimates of peripheral blood eosinophilia, skin test positivity, AHR, and cigarette smoking on the development of respiratory symptoms were assessed by multiple logistic regression analyses using SAS version 6.12. We used the GEE macro for longitudinal data analyses, which uses the Generalized Estimation Equation approach of Liang and Zeger (19). This method takes into account the dependence of multiple measurements within a person. Odds ratios (OR) and 95% confidence intervals (CI) are calculated from the logistic regression model with the robust variance estimates. Respiratory symptoms (yes/no) at the last of two successive surveys were taken as the dependent variable, and AHR, cigarette smoking, and eosinophilia or skin test positivity at the first of two successive surveys were used as independent variables. To determine whether peripheral blood eosinophilia or skin test positivity influenced the relationship between AHR and the development of respiratory symptoms, interaction terms of AHR and eosinophilia, and AHR and skin test positivity were included in the analyses. All analyses were adjusted for age, sex, area of residence, and number of years between two successive surveys. After we assessed the separate risk estimates of eosinophilia, skin test positivity, AHR, and their interaction, we determined the risk estimates for the different combinations of peripheral blood eosinophilia with AHR (EO—AHR—, EO+AHR—, EO—AHR+, EO+AHR+) and skin test positivity with AHR (ST—AHR—, ST+AHR—, ST—AHR+, ST+AHR+) for interpretation purposes. The analyses were performed for the development of any respiratory symptom and for each respiratory symptom separately. The analyses on the specific symptoms were repeated, with additional adjustment for the presence of that specific symptom in the survey before the first of two successive surveys. Further, the analyses on the development of a specific symptom (e.g., chronic cough) concerned subjects without that specific symptom (e.g., chronic cough) at the first of two successive surveys but they may have had other symptoms (e.g., phlegm or dyspnea). Therefore, we also repeated the analyses with additional adjustment for the presence of other symptoms than the respiratory symptom that is studied, including one composite variable.
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Results

In total, 995 men and 792 women without chronic cough or phlegm, bronchitis episodes, persistent wheeze, dyspnea, or asthma attacks at the first of two successive surveys contributed 4,403 paired observations (Table 1).

Table 1. Characteristics at the first of two successive surveys for all paired observations

<table>
<thead>
<tr>
<th>Total number</th>
<th>4,403</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, %</td>
<td>57</td>
</tr>
<tr>
<td>Age, yr (mean ± SD)</td>
<td>42 ± 12</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td></td>
</tr>
<tr>
<td>Never-smokers</td>
<td>1,301 (30)</td>
</tr>
<tr>
<td>Ex-smokers</td>
<td>980 (22)</td>
</tr>
<tr>
<td>1-14 cigarettes/day</td>
<td>1,001 (23)</td>
</tr>
<tr>
<td>15-24 cigarettes/day</td>
<td>695 (16)</td>
</tr>
<tr>
<td>≥25 cigarettes/day</td>
<td>425 (10)</td>
</tr>
<tr>
<td>Urban area of residence, n (%)</td>
<td>2,068 (47)</td>
</tr>
<tr>
<td>FEV\textsubscript{1}, % pred. (mean ± SD)</td>
<td>104 ± 15</td>
</tr>
<tr>
<td>PC\textsubscript{10} ≤8 mg/ml histamine, n (%)</td>
<td>578 (13)</td>
</tr>
<tr>
<td>Eosinophilia, n (%)</td>
<td>426 (10)</td>
</tr>
<tr>
<td>Skin test positive, n (%)</td>
<td>1,005 (23)</td>
</tr>
</tbody>
</table>

Peripheral blood eosinophilia and the development of respiratory symptoms

Descriptive analyses showed that more subjects with both peripheral blood eosinophilia and AHR (EO+AHR+) developed respiratory symptoms than did subjects with either peripheral blood eosinophilia (EO+AHR—) or AHR (EO—AHR+) alone and also more than subjects with neither peripheral blood eosinophilia nor AHR (EO—AHR—) (Figure1). EO+AHR+ subjects more frequently developed dyspnea (p=0.05), wheeze (p=0.02), and asthma attacks (p=0.0007) than did EO—AHR+ subjects. The number of subjects who developed symptoms was not significantly different between EO—AHR— subjects and EO+AHR— subjects.
Multivariate logistic regression analyses (Table 2) showed that the independent relationship between peripheral blood eosinophilia and the development of respiratory symptoms differed significantly between AHR— and AHR+ subjects (tested by the interaction term “eosinophilia by AHR’’). The risk of developing one or more respiratory symptoms was only significantly increased in EO+AHR+ subjects, borderline significantly increased in EO—AHR+ subjects, and not different between EO+AHR— subjects and EO—AHR— subjects. Subjects with both peripheral blood eosinophilia and AHR were more likely to develop one or more respiratory symptoms than were subjects with either peripheral blood eosinophilia (OR=4.41 95% CI=1.91 to 10.14) or with AHR (OR= 2.85, 95% CI= 1.29 to 6.30). Peripheral blood eosinophilia increased the risk of developing wheeze or dyspnea in hyperresponsive subjects only (OR=5.06, 95% CI= 2.11 to 12.13 and OR=2.73, 95% CI=1.13 to 6.60, respectively, compared with EO—AHR— subjects). EO+AHR+ subjects had an increased risk of developing wheeze or dyspnea compared with EO-AHR+ subjects (OR=2.36, 95% CI=0.96 to 5.78 and OR=2.48, 95%CI=0.99 to 6.21, respectively) and to EO+AHR— subjects (OR=11.29, 95% CI=3.15 to 40.44 and OR= 5.38, 95% CI=1.72 to 16.85, respectively). The number of subjects with peripheral blood eosinophilia who developed asthma attacks was too small to assess the difference in risk in subjects with and without AHR. When peripheral blood eosinophilia was included in the analyses as a continuous variable (In-transformed), the risk to develop asthma attacks was significantly increased in subjects with higher numbers of peripheral blood eosinophils and AHR, and not in subjects with either
high eosinophil counts or AHR. Peripheral blood eosinophilia did not significantly increase the risk to develop chronic cough, phlegm, or bronchitis in hyperresponsive subjects after adjustment for age, sex, area of residence, and the number of years between the two successive surveys.

Table 2. Risk of eosinophilia, AHR, and smoking for the development of respiratory symptoms, adjusted for age, sex, area of residence, and the number of years between two successive surveys (interval)

<table>
<thead>
<tr>
<th>Development of symptoms</th>
<th>n</th>
<th>Odds Ratio</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>EO—AHR—</td>
<td>3416</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>EO+AHR—</td>
<td>353</td>
<td>0.83</td>
<td>0.54-1.27</td>
</tr>
<tr>
<td>EO—AHR+</td>
<td>497</td>
<td>1.29</td>
<td>0.91-1.82</td>
</tr>
<tr>
<td>EO+AHR+</td>
<td>73</td>
<td>3.67*</td>
<td>1.75-7.67</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td></td>
<td>1.21</td>
<td>0.85-1.74</td>
</tr>
<tr>
<td>1-14 cig/d</td>
<td></td>
<td>1.89*</td>
<td>1.37-2.60</td>
</tr>
<tr>
<td>15-24 cig/d</td>
<td></td>
<td>2.98*</td>
<td>2.07-4.29</td>
</tr>
<tr>
<td>≥ 25 cig/d</td>
<td></td>
<td>3.57*</td>
<td>2.32-5.48</td>
</tr>
</tbody>
</table>

Adjusting factors

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>1.00</td>
<td>0.99-1.01</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.03</td>
<td>0.80-1.33</td>
</tr>
<tr>
<td>Urban area of residence</td>
<td>1.55*</td>
<td>1.22-1.97</td>
</tr>
<tr>
<td>Interval, yr</td>
<td>1.11*</td>
<td>1.06-1.16</td>
</tr>
</tbody>
</table>

Definition of abbreviations: AHR=airway hyperresponsiveness; CI=confidence interval; EO=peripheral blood eosinophilia; OR=odds ratio. * p < 0.001

Cigarette smokers had an increased risk to develop respiratory symptoms compared with never-smokers, ranging from 1.89 (95% CI= 1.37 to 2.60) for those who smoked 1-14 cig/d to 3.57 (95% CI= 2.32 to 5.48) for those who smoked 25 or more cig/d (Table 2). No interaction was observed between the effect of cigarette smoking, peripheral blood eosinophilia, and AHR, i.e., the risks for the development of respiratory symptoms in subjects with and without peripheral blood eosinophilia and AHR are similar in current smokers, ex-smokers, and never smokers. Other factors increasing the risk to develop any respiratory symptom were living in the urban area Vlaardingen, and a longer interval between two successive surveys.
Skin test positivity and the development of respiratory symptoms

More subjects with negative skin tests (ST-) developed symptoms than did subjects with positive skin tests (ST+), independent of the presence of AHR (Figure 2). This was observed for all symptoms, except for the development of asthma attacks. The risk for the latter symptom was highest in ST+AHR+ subjects.

The adjusted risk estimates of skin test positivity on the development of respiratory symptoms are shown in Table 3. We have not presented the risk estimates of the confounding factors smoking, age, sex, urban area of residence, and the number of years between two successive surveys because they are similar to those presented in Table 2. ST+AHR— subjects had a decreased risk to develop respiratory symptoms, whereas ST—AHR+ subjects had an increased risk to develop respiratory symptoms compared with ST—AHR— subjects. The opposite risks counterbalance each other in ST+AHR+ subjects, in whom the risk to develop any respiratory symptom is not significantly different from that of ST—AHR— subjects. Skin test positivity decreased the risk to develop any of the specific respiratory symptoms but this was only significant for the development of chronic phlegm (OR=0.65, 95% CI=0.42 to 1.00) in subjects with and without AHR.

The results did not change when peripheral blood eosinophilia and skin test positivity were adjusted for each other. This was also the case when the risks were adjusted for pack-years (OR=1.02, 95% CI=1.01 to 1.03) instead of the number of cigarettes smoked per day at the first of two successive surveys.
Table 3. Risk of skin test positivity and AHR for the development of “any” respiratory symptom, adjusted for smoking, age, sex, area of residence, and number of years between two successive surveys

<table>
<thead>
<tr>
<th>Development of symptoms</th>
<th>n</th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>ST—AHR—</td>
<td>2,833</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>ST+AHR—</td>
<td>873</td>
<td>0.64*</td>
<td>0.47-0.87</td>
</tr>
<tr>
<td>ST—AHR+</td>
<td>433</td>
<td>1.65*</td>
<td>1.17-2.33</td>
</tr>
<tr>
<td>ST+AHR+</td>
<td>132</td>
<td>0.74</td>
<td>0.35-1.56</td>
</tr>
</tbody>
</table>

Definition of abbreviations: AHR=airway hyperresponsiveness; CI=confidence interval; OR=odds ratio; ST=skin test positivity. * p<0.01

Similar risks were observed when the analyses were repeated with five specific interval periods ((a) 3 or 4 years; (b) 5, 6, or 7 years; (c) 8, 9, or 10 years; (d) 12 or 13 years; and (e) 15 or 16 years). All analyses were repeated with additional adjustment for FEV1. Further, in the analyses on the specific respiratory symptoms additional adjustments were made for the presence of that specific symptom in the survey before the first of two successive surveys, and for the presence of other respiratory symptoms at the first of two successive surveys. These additional adjustments did not change any of the observed relationships.

Discussion

The results of this longitudinal study in a general adult population showed that the risk to develop respiratory symptoms is increased in subjects who smoke cigarettes in a dose-dependent way. In subjects with airway hyperresponsiveness (AHR) the risk is increased as well, and especially in the presence of peripheral blood eosinophilia, whereas the risk is decreased in subjects with skin test positivity.

This is the first longitudinal study that has shown a dose-dependent relation between cigarette smoking and an increased risk to develop respiratory symptoms. Xu and colleagues (1) had already shown that the risk of smoking for the development of respiratory symptoms was the same for AHR+ and AHR— subjects. Thus, AHR+ subjects who smoked were not more susceptible to develop respiratory symptoms than AHR— subjects who smoked. Earlier, Krzyzanowski and Lebowitz (2) showed that subjects who continued to smoke during the 11 to 13 yr of follow-up had a two to three times higher risk to develop chronic cough, chronic phlegm, dyspnea, wheeze, attacks of breathlessness, and a doctor’s-diagnosed asthma compared with never smokers. Although our study assessed the risk on a relatively short time span (82% of all observations had an interval of 3 yr) and we took into account the smoking habit at the first of two successive surveys, we found similar risks. More specific
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information on the change in smoking habits during the period of follow-up (smokers who quit smoking and “persistent” smokers) and a longer follow-up period will probably result in higher risk estimates.

Development of wheeze and dyspnea appears to occur especially in subjects with both AHR and peripheral blood eosinophilia. Until now, only results of cross-sectional studies are available that show an association between higher peripheral blood eosinophil counts and the presence (4) and severity (5) of respiratory symptoms. The association between higher peripheral blood eosinophil counts and AHR was found in some studies (7,8), whereas other studies found no association (20,21).

In asthma, the number of eosinophils are increased in the bronchial submucosa (22-25). Further, the degree of airway responsiveness is associated with the number of eosinophils in airway wall biopsies (23,25-27). Thus, eosinophils in the airways play a role in the presence of respiratory symptoms as well as the presence of AHR. Our results showed an increased risk to develop wheeze and dyspnea only when both peripheral blood eosinophilia and AHR are present. A common underlying mechanism may be responsible for this to occur; for example, increased levels of interleukin-5 released by T-lymphocytes. This may cause both peripheral blood eosinophilia and AHR, or peripheral blood eosinophilia that indirectly induces AHR. Possibly, the presence of both peripheral blood eosinophilia and AHR indicates a more activated immunologic process in the airways. Peripheral blood eosinophilia may reflect higher numbers of eosinophils in the bronchial mucosa, which may be activated by certain stimuli, and subsequently cause respiratory symptoms. This suggests that AHR+ subjects whose wheeze and dyspnea symptoms are in remission are likely to develop recurrent symptoms, especially when peripheral blood eosinophilia is present. Whether therapeutic intervention may alter this trail of events is a subject for further study.

In our study, skin test positivity was not associated with the development of wheeze, dyspnea, and asthma attacks. In other studies, skin test positivity in childhood was predictive of wheeze and asthma at adolescence (11,13). We expected this to occur in adults as well, as some epidemiologic studies showed that skin test positivity is associated with an increased decline in FEV, (28,29), which in turn is associated with respiratory symptoms (30). The definition of skin test positivity in our study was based on the skin prick tests performed at the baseline measurements in 1965, 1967, and 1969 or at the first follow-up surveys in 1970 and 1972. As skin test positivity wanes with increasing age, misclassification of ST— subjects as ST+ subjects may have occurred. Further, the allergens used for the skin tests performed more than 25 yr previously were less standardized than those used for skin tests nowadays. Allergic subjects may not have been identified in our baseline surveys (1965, 1967/1969) or in the first follow-up survey (1970/1972). These misclassification possibilities will underestimate a possible association of skin test positivity. Besides possible misclassification, age may be an important factor, in that skin test positivity may be a more important factor for the development of respiratory symptoms in children rather than in adults. Further, skin test positivity may be associated with the development of respiratory symptoms only for specific allergens. In our study, no association was found between skin test positivity and the development of asthma.
attacks. The study of Ulrik and coworkers (13) showed an increased risk of 2.6 in children with positive skin tests for house dust mites compared with children without positive skin tests, whereas no increased risks were found in children with positive skin tests for pollen, animals, or moulds. Another study showed that AHR+ students who developed asthma were not more atopic than AHR+ students who remained asymptomatic (31). In the latter and our study, atopy was based on positive skin tests for house dust mite, pollen, animals, and/or moulds. Ulrik and coworkers (13) found only atopy to house dust mite and not atopy to other allergens to be predictive for the development of asthma. The low numbers of subjects with skin test positivity for house dust mite and other specific allergens prevented further analyses, which may explain a lack of association between skin test positivity and the development of asthma symptoms in our study. No explanation was found for the decreased risk of the development of chronic phlegm in skin test positive subjects.

In conclusion, this longitudinal study in the general adult population showed that smoking is associated with the development of respiratory symptoms in a dose-dependent way. Furthermore, peripheral blood eosinophilia increases the risk to develop dyspnea or wheeze, especially in subjects with AHR. Skin test positivity in the past decreases the risk to develop respiratory symptoms, especially for chronic phlegm, which was similar in AHR— and AHR+ subjects. Hyperresponsive subjects whose symptoms are in remission are likely to develop recurrent symptoms, especially when peripheral blood eosinophilia is present. Therefore, future studies have to show whether therapeutic intervention in these subjects focused on symptoms and airway hyperresponsiveness may lower the risk of recurrence of respiratory symptoms.

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References

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