Longitudinal Determinants of Bronchial Responsiveness to Inhaled Histamine*

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**Background and study objective:** The point prevalence of bronchial hyperresponsiveness (BHR) is imperfectly associated with current asthma, possibly due to changes over time in bronchial responsiveness (BR). To evaluate cross-sectional and longitudinal determinants of BR, a population sample comprising 408 children and adolescents, aged 7 to 17 years at enrollment, was examined twice, 6 years apart.

**Methods:** Case history was obtained by interview and questionnaire. BR to inhaled histamine, pulmonary function, and skin prick test reactivity were measured using standard techniques.

**Results:** The point prevalence of BHR (the concentration of histamine causing a 20% decline in FEV1 < 8 mg/mL) declined from childhood to early adulthood (25% and 6%, respectively; p<0.001); and similarly a decline in histamine dose-response slope was observed. At both surveys, prechallenge FEV1 percent predicted, asthma, and atopy, especially atopy to house dust mite (HDM), were important determinants for the degree of BR. After adjustment for prechallenge FEV1 percent predicted, no male-female difference was observed in degree of BR. Lower FEV1 percent predicted (p=0.003), asthma (p<0.001), higher degree of BR (p=0.003), and atopy to HDM (p=0.007) at enrollment predicted a higher degree of BR at the second survey (degree of BR at second survey adjusted for prechallenge FEV1). Furthermore, new asthma (p<0.001) and/or atopy to HDM (p=0.003) were associated with higher BR at the second survey. Confining the analysis to nonasthmatics showed that subjects with new or persistent atopy to HDM had significantly increased BR compared with nonatopic subjects; and, moreover, prechallenge FEV1 percent predicted was significantly correlated with BR.

**Conclusions:** BR declines from childhood to early adulthood, possibly reflecting the increase in airway caliber. The level of FEV1 and atopy, especially to HDM, are important determinants for changes over time in level of BR, also in nonasthmatic subjects.

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**Key words:** asthma; atopy; bronchial responsiveness; longitudinal evaluation; population sample

**Abbreviations:** BHR=bronchial hyperresponsiveness; BR=bronchial responsiveness; DRS=dose-response slope; HDM=house dust mite; PC20=the concentration of histamine causing a 20% decline in FEV1; %pred=percentage of predicted values; SPT=skin prick test

The close association between current asthma and bronchial hyperresponsiveness (BHR) to inhaled histamine has been clearly established based on observations in both selected groups of patients and population studies. However, the cross-sectional agreement between BHR and asthma is, although very close, less than perfect, not least in epidemiologic studies in which a substantial proportion of the subjects with BHR are asymptomatic. Therefore, in addition to symptoms of asthma, various other factors are likely to have an impact on the degree of bronchial responsiveness (BR). Both environmental and host factors may modify the individual subject’s responsiveness to inhaled agents such as histamine and methacholine, and, furthermore, changes in some of these factors may at least partly explain individual changes in the degree of airway responsiveness over time. In keeping with this, longitudinal changes in the factors underlying histamine responsiveness might be the background for the observed discrepancies between the period prevalence of asthma and the point prevalence of histamine and methacholine hyperresponsiveness.

Previous studies of both children and adults have demonstrated that lower level of FEV1, as an index of airway caliber, is associated with a higher degree of BR. Furthermore, the increase in pulmonary...
function in children depends most likely more on the increase in height than on age and gender. It therefore appears likely that changes in BR from childhood to early adulthood may be related to the individually obtained levels of pulmonary function. Atopy is strongly associated with BHR in random populations, and early-onset atopy may be a particularly strong risk factor for subsequent development of airway hyperresponsiveness. The interplay over time between changes in atopic status and level of pulmonary function may have important implications for the level of BR, and by that, possibly the risk for development of respiratory symptoms.

Asymptomatic hyperresponsiveness is a known risk factor for subsequent development of symptomatic asthma, but a substantial proportion of subjects with BHR measured at one point in time will most likely never develop symptomatic asthma. Further knowledge of mechanisms underlying BR and not least longitudinal changes in BR, might therefore be of utmost importance for future primary prevention of asthma.

To study determinants for and changes over time in BR to inhaled histamine, with special reference to asthma, airway caliber, and atopy, we have examined a population sample comprising 408 children and adolescents, aged 7 to 17 years at enrollment, twice with an interval of 6 years.

Materials and Methods

Subjects

A sample of 983 children and adolescents living in the area surrounding Rigshospitalet in the city of Copenhagen was drawn at random from the civil registration list in 1986; all subjects were born in the first week of each month with a mean age of 12 years (range, 7 to 17 years). In 1986 (first survey) and 1992 (second survey), all subjects (N=983) were invited by letter to participate in a study concerning asthma, allergy, and BHR.

Of the 983 subjects, 527 (54%) participated in the first survey and 665 (69%) participated in the second survey; 408 subjects (199 males and 209 females) participated in both surveys. Only data for the 408 subjects who participated in both surveys are included in the present analysis.

The question of nonresponder bias has been addressed in a previous article. Briefly, apart from a significantly higher number of current smokers among those subjects who only participated in the second survey, no significant differences were found between the groups (that is, “stayers,” “dropouts,” and “newcomers”) with respect to anthropometric data, pulmonary function, or prevalences of atopy, BHR, and allergic diseases, indicating that the subjects included in the present analysis are representative of the entire sample; for further details see Ulrik et al.

Exclusion Criteria

The subjects were asked to abstain from cigarette smoking for at least 2 h prior to their appointment at the laboratory. In case they were taking medication for asthma or allergy, they were asked not to use theophylline or an antihistamine for at least 24 h, astemizole for 6 weeks, an oral B2-agonist for 18 h, and an inhaled bronchodilator for 6 h before the tests; long-acting B2-agonists were not available in Denmark at the time of either of the surveys. They were allowed to continue use of any inhaled or oral corticosteroid they had been taking.

Case History

The participants, and if present, their parents, were interviewed by one person about birth weight, diseases (respiratory and nonrespiratory), active and passive smoking, use of medication, and known or suspected allergic disease and allergy. Furthermore, all participants filled in a questionnaire about asthmatic and allergic symptoms, that is, rhinitis (sneezing, runny or blocked nose not associated with a cold), and eczema (an itchy dry rash on face, arms, or legs), as related to themselves, their siblings, and their parents.

The questionnaire concerning respiratory symptoms and the definition of asthma were adopted from studies by the American Thoracic Society, Division of Lung Disease of the National Heart, Lung, and Blood Institute, Hopp et al. and Asthma was defined by questionnaire criteria on the basis of the responses to the following questions:

1. Have you ever had asthma?
2. Does your breathing ever sound wheezy or whistling?
3. Do you have attacks of shortness of breath with wheezing?
4. Do you experience wheezing, chest tightness, cough, breathlessness with any of the following: rest, with exertion, with emotional stress, with exposure to cold air, with chest infections or head cold?
5. Do you experience wheezing after exposure to dust, fumes, mold, pollen, food, pets, or drugs?
6. Have you ever been hospitalized or observed and treated by a physician for asthma?
7. Have you ever received medication for your asthma?
8. What was the medication used?
9. Did it help?
10. How many episodes of wheezing have you had during the least year?
11. Have you ever had attacks of wheezing, shortness of breath, or dry cough at night?

Asthma was defined on the basis of positive responses to questions 2, and 3, and 4, and/or 5. Current asthma was defined as symptoms within the preceding 12 months. Furthermore, all participants reported whether they were current smokers, ex-smokers, or never smokers, and for the first two categories, they reported the duration of smoking. Current and ex-smokers also reported their daily tobacco consumption, and an estimate of their lifetime tobacco exposure was calculated as pack-years (current tobacco consumption [packs per day] x duration of smoking [years]). Smoking history (daily tobacco consumption and duration of smoking) was obtained for both parents (that is, adult members of the participant’s household) and included in the analysis as an estimate of passive tobacco exposure.

Pulmonary Function Tests

The FEV1 and FVC were measured with a 7-L dry wedge spirometer (Vitalograph) that was calibrated weekly. Each measurement consisted of at least three maximal expiratory maneuvers from total lung capacity to residual volume with a variation of <5%. The highest FEV1 and FVC were used in the analyses.

Data on pulmonary function were also expressed as a percent-
age of predicted values (%pred), using prediction equations based on age, gender, and height. A standard dose of bronchodilator (salbutamol) was given at the first survey to aid recovery after the histamine challenge test and at the second survey (all subjects) also as a test for reversibility, and values obtained after administration of bronchodilator were used in the analyses (unless stated otherwise).

Skin Prick Test

Skin prick tests (SPTs) were performed on the volar surface of the forearm, using standard dilutions (100,000 BU/mL) of allergens in 50% glycerol (ALK; Horsholm, Denmark). The allergens used were birch, grass, mugwort, horse, dog, cat, house dust mite (HDM) (Dermatophagoides pteronyssinus, and at the second survey also Dermatophagoides farinae) and two molds (Alternaria tenuis and Cladosporium herbarum). Histamine hydrochloride (10 mg/mL) in 50% glycerol was used as a positive reference, and a negative reference (50% glycerol) was also included. The reactions were read after 15 to 20 min. A positive SPT was defined as a positive reaction to at least one of the allergens.17 The reaction to each of the allergens was regarded as positive if the mean wheal diameter (d1+d2) was at least 3 mm. In case of reaction to the negative reference, a positive result was recorded when the difference between the mean wheal diameter of the reaction to the allergen and to the negative reference exceeded 3 mm. Atopy was defined as a positive SPT.

Serum IgE and Blood Eosinophils

The total serum IgE level was determined by paper radioimmunosorbent test (PRIST; Pharmacia; Sweden) (at the first survey only), and the number of eosinophil leukocytes in peripheral blood was counted in a counting chamber (at the second survey only).18

Histamine Challenge Test

BR to inhaled histamine was measured using the method described by Cockcroft et al.1 Aerosols of the test solution were generated by a nebulizer (Wright; Aerosol Products Ltd; London, UK) operated to give an output of 0.14 mL/min. Each aerosol was inhaled through the mouth by tidal breathing for 2 min. The first aerosol was saline solution (0.9%), and it was followed at 4-min intervals by twofold increasing concentrations of histamine (0.075 to 8.0 mg/mL). The response was measured by the FEV1, 1 min after each inhalation. The test was terminated when a ≥20% decline in FEV1 from the postsaline solution value occurred, or at the end of the dose schedule if such a decline did not occur. For all subjects having at least 20% decline in FEV1 by the end of the dose schedule, the concentration of histamine causing a 20% fall in FEV1 (PC20) was calculated by linear interpolation from the individual log dose-response curve as follows:19

$$PC_{20} = \frac{-\log(C_1) + \log(C_2)}{\log(C_1) - \log(C_2)}(20 - R_1)/(R_2 - R_1)$$

where: $C_1$ is second to the last concentration of histamine (<20% FEV1 fall), $C_2$ is the last concentration of histamine (>20% fall), $R_1$ is percent fall FEV1 after $C_1$, and $R_2$ is percent fall FEV1 after $C_2$.

A positive test was defined as a PC20 FEV1 <8.0 mg/mL histamine.

Histamine responsiveness was also analyzed with use of an estimate of the overall slope of the dose-response relationship.20 The dose-response slope (DRS) was calculated as the decline in FEV1 from the postsaline solution value (expressed as a percentage of the postsaline solution value) after the final dose divided by the dose of histamine administered;20 a constant of 3 was added to all DRSs to eliminate negative and zero values.

Statistical Methods

Unless stated otherwise, the prevalence figures given are the cumulative prevalence rates from birth to the time of the surveys. Separate cross-sectional analyses were performed on the data from the two surveys. Differences between groups in level of bronchial responsiveness were analyzed using Student’s paired or unpaired t test, as appropriate. Changes in the proportion of subjects with a positive test/symptoms were assessed by means of McNemar’s $\chi^2$ test.

Linear regression analysis was used to assess putative risk factors at the first survey in relation to outcome at the second survey, primarily the level of BR to inhaled histamine, and nonsignificant variables were deleted by backward elimination. A p value <0.05 was considered significant.

Table 1—Characteristics of the Population Sample Comprising 408 Subjects, Aged 7 to 17 Years at Enrollment, Examined Twice 6 Years Apart*

<table>
<thead>
<tr>
<th></th>
<th>First Survey</th>
<th></th>
<th>Second Survey</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M (n=199)</td>
<td>F (n=209)</td>
<td>M (n=199)</td>
</tr>
<tr>
<td>Age, yr</td>
<td>12.1 (2.9)</td>
<td>12.5 (2.9)</td>
<td>18.1 (2.9)</td>
</tr>
<tr>
<td>Range</td>
<td>8-17</td>
<td>7-17</td>
<td>14-23</td>
</tr>
<tr>
<td>Height, cm</td>
<td>1.54 (0.18)</td>
<td>1.52 (0.14)</td>
<td>1.79 (0.09)</td>
</tr>
<tr>
<td>Smoking habits</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smokers, No.</td>
<td>189</td>
<td>188</td>
<td>143</td>
</tr>
<tr>
<td>Ex-smokers, No.</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Current smokers, No.</td>
<td>10</td>
<td>20</td>
<td>56</td>
</tr>
<tr>
<td>Pack-years</td>
<td></td>
<td></td>
<td>2.8 (2.0)</td>
</tr>
<tr>
<td>FEV1, L</td>
<td>2.6 (1.0)</td>
<td>2.4 (0.7)</td>
<td>4.4 (0.8)</td>
</tr>
<tr>
<td>%pred</td>
<td>92 (11)</td>
<td>90 (10)</td>
<td>99 (11)</td>
</tr>
<tr>
<td>Range</td>
<td>60-116</td>
<td>67-129</td>
<td>70-136</td>
</tr>
<tr>
<td>FEV1/FVC, %</td>
<td>80 (6)</td>
<td>91 (4)</td>
<td>86 (7)</td>
</tr>
<tr>
<td>Range</td>
<td>61-99</td>
<td>73-99</td>
<td>66-99</td>
</tr>
</tbody>
</table>

*Standard deviations in parentheses.
RESULTS

Complete data were available for 408 subjects, 199 male and 209 female; characteristics of the examined subjects are displayed in Table 1. The proportion of subjects with current asthma increased from 5% at the first survey to 15% at the second survey (Table 2); and likewise did the point prevalence of a positive SPT increase from 26 to 44% (Table 2).

The prevalence of a positive histamine challenge test declined from 25% (n=102) at the first survey to 6% (n=24) at the second survey, of whom 81 (20%) and 4 (1%), respectively, had asymptomatic BHR and 299 (73%) subjects were persistent nonhyperresponsive to inhaled histamine. The mean of the histamine DRS declined from 0.58 to 0.55 (p=0.02).

The cross-sectional analysis of data from the first survey showed that lower prechallenge FEV1 (p=0.007), lower age (p=0.04), a history of wheezy bronchitis (p=0.006), a positive SPT (p=0.04), and current asthma (p<0.0001) were associated with increased level of histamine DRS, whereas no significant association could be demonstrated between total serum IgE and passive smoking, and level of histamine DRS. Reanalyzing the data after inclusion of reactivity to each of the used aeroallergens as an index of atopy (instead of the overall result of the SPT showed that the presence of atopy to HDM was significantly associated with higher level of histamine DRS (p=0.003).

Table 3 shows the results of the cross-sectional regression analysis concerning the degree of histamine responsiveness at the second survey. Apart from lower prechallenge FEV1, asthma, and atopy, a higher number of blood eosinophils and need for treatment with inhaled steroids were also associated with higher degree of histamine responsiveness. Comparable to the cross-sectional findings from the first survey, repeat of the regression analysis as described above demonstrated a significant association between atopy to HDM and histamine DRS (coefficient, 0.277, [SEM 0.048]; p<0.0001).

The results of the multiple regression analysis predicting histamine DRS at the second survey as a function of variables measured at the first survey and changes in these variables during the observation period are shown in Table 4. Preliminary analyses of the data showed that atopy to HDM was associated closer with histamine responsiveness than overall skin test reactivity, and the former was therefore included in the final model. However, reintroducing the overall result of the SPT in the final model instead of HDM reactivity only reduced the overall variance in histamine DRS explained by the multiple linear regression model; and, furthermore, it did not change the overall results. Likewise, introducing change in FEV1 %pred as a further index of pulmonary function did not contribute to the model.

The substantial impact of baseline airway caliber, as assessed by the FEV1 %pred, on the degree of histamine responsiveness was confirmed in the lon-

Table 2—Point Prevalences of Asthma, Allergic Diseases, Atopy, and BHR in the Population Sample Comprising 408 Subjects*  

<table>
<thead>
<tr>
<th></th>
<th>M (n=199)</th>
<th>F (n=209)</th>
<th>M (n=199)</th>
<th>F (n=209)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma, No. (%)</td>
<td>12 (6)*</td>
<td>10 (5)*</td>
<td>30 (15)*</td>
<td>31 (15)*</td>
</tr>
<tr>
<td>Rhinitis, No. (%)</td>
<td>27 (14)*</td>
<td>31 (15)*</td>
<td>46 (23)*</td>
<td>44 (21)*</td>
</tr>
<tr>
<td>Eczema, No. (%)</td>
<td>12 (6)</td>
<td>15 (7)*</td>
<td>18 (9)</td>
<td>28 (13)*</td>
</tr>
<tr>
<td>Positive SPT, No. (%)</td>
<td>55 (28)*</td>
<td>51 (24)*</td>
<td>96 (48)*</td>
<td>82 (39)*</td>
</tr>
<tr>
<td>HDM positive, No. (%)</td>
<td>31 (16)*</td>
<td>24 (12)*</td>
<td>60 (30)*</td>
<td>47 (23)*</td>
</tr>
<tr>
<td>BHR, No. (%)</td>
<td>57 (29)*</td>
<td>45 (22)</td>
<td>10 (5)*</td>
<td>14 (7)</td>
</tr>
</tbody>
</table>

*BHR = PC20, FEV1 <8 mg/mL histamine.
*P<0.001.
*P<0.01 (first survey vs second survey in male and female subjects, respectively).

Table 3—Cross-sectional Regression Analysis of BR to Inhaled Histamine (DRS*) on Level of FEV1, Asthma Status, Number of Blood Eosinophils, Use of Inhaled Steroids, and SPT Reactivity in a Population Sample (n=408) of Adolescents and Young Adults  

<table>
<thead>
<tr>
<th></th>
<th>Coefficient</th>
<th>SEM</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prechallenge FEV1, %pred</td>
<td>-0.051</td>
<td>3.66×10⁻⁴</td>
<td>0.004</td>
</tr>
<tr>
<td>Asthma†</td>
<td>0.147</td>
<td>0.026</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Blood eosinophils, 10⁹/L</td>
<td>0.163</td>
<td>0.056</td>
<td>0.004</td>
</tr>
<tr>
<td>Inhaled steroids†</td>
<td>0.247</td>
<td>0.049</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Atopy‡</td>
<td>0.033</td>
<td>0.016</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*DRS = (percent fall in FEV1±3)/μmol histamine administered.
†Defined as the presence of current asthma, that is symptoms, within the preceding 12 months.
‡Defined as current treatment with inhaled steroids.
§Defined as a positive SPT, that is, a reaction to at least 1 of the 10 used common aeroallergens with a mean wheal diameter of at least 3 mm.

Clinical Investigations
Persistent asthma (n=345) had measured asthma/atopy (n=41) and asthma/atopy atopy, respectively, are displayed in Table 5. Subjects (n=54) who developed symptoms of rhinitis during the observation period (with or without concurrent asthma) were more responsive to histamine than asymptomatic subjects were (p=0.0003).

Subjects without current or former asthma (n=345), who had either persistent (n=24) or new (n=52) atopy to HDM, had a significantly higher degree of histamine responsiveness (p=0.01 and p=0.02, respectively) than nonatopic, nonasthmatic subjects. Furthermore, among nonasthmatic subjects (n=345), a significant correlation was found between the prechallenge level of FEV1 %pred and the level of histamine DRS (p=0.02).

**DISCUSSION**

The present study showed an overall decline in BR to inhaled histamine from childhood to early adulthood, possibly reflecting the growth-related increase in airway caliber, and furthermore, the level of FEV1 %pred, as an index of airway caliber, and atopy, especially to HDMs, are important determinants for changes over time in degree of histamine responsiveness in both asthmatic and nonasthmatic subjects.

The present population study not only confirmed that prechallenge airway caliber has a significant impact on degree of BR, but showed also that the level of FEV1 in childhood has significant impact on the degree of histamine responsiveness in early adulthood, even when BR in early adulthood was adjusted for prechallenge FEV1. These observations may have important implications. In epidemiologic studies focused on the prevalence of BHR, as an index of the proportion of individuals with asthma abnormalities, it appears reasonable to standardize measurements of BR for airway caliber, not the least

**Table 4—Longitudinal Multiple Regression Analysis Predicting BR to Inhaled Histamine (Histamine DRS) at the Second Survey as a Function of Variables Measured at the First Survey and Changes in These Variables**

<table>
<thead>
<tr>
<th></th>
<th>Coefficient</th>
<th>SEM</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prechallenge FEV1 (±10%)</td>
<td>-0.003</td>
<td>0.0008</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>First survey, %pred</td>
<td>-0.003</td>
<td>0.0003</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Histamine DRS (first survey)</td>
<td>0.196</td>
<td>0.038</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Asthma (n=345)</td>
<td>0.272</td>
<td>0.039</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>New asthma (n=345)</td>
<td>0.121</td>
<td>0.024</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HDM positive (n=345)</td>
<td>0.090</td>
<td>0.033</td>
<td>0.007</td>
</tr>
<tr>
<td>New HDM positive (n=345)</td>
<td>0.055</td>
<td>0.019</td>
<td>0.003</td>
</tr>
</tbody>
</table>

*The sample comprised 408 subjects (aged 7 to 17 years at enrollment) examined twice 6 years apart.

1Defined as current asthma/atopy to HDM at the first survey and/or persistent asthma/atopy to HDM (that is, current asthma/atopy to HDM at both surveys).

2Including subjects with former asthma (n=2) and former atopy to HDM (n=11), respectively.

3Defined as nonasthmatic/nonatopic to HDM at the first survey, but current asthma/atopy to HDM at the second survey; for further explanations, see legend to Table 3.

**Table 5—Cross-table of BR to Inhaled Histamine (DRS) vs Asthma and Atopy Status, Respectively**

<table>
<thead>
<tr>
<th>Histamine DRS</th>
<th>p Value</th>
<th>Histamine DRS</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonasthmatic (n=345)</td>
<td>0.52</td>
<td>Nonatopic (n=209)</td>
<td>0.52</td>
</tr>
<tr>
<td>Former asthma (n=2)</td>
<td>0.67</td>
<td>0.0003*</td>
<td>Former atopy (n=21)</td>
</tr>
<tr>
<td>New asthma (n=41)</td>
<td>0.70</td>
<td>&lt;0.0001*</td>
<td>New atopy (n=93)</td>
</tr>
<tr>
<td>Persistent asthma (n=20)</td>
<td>0.92</td>
<td>&lt;0.0001*</td>
<td>Persistent atopy (n=85)</td>
</tr>
</tbody>
</table>

*Compared with nonasthmatics/nonatopics.

NS=not significant.
when comparing prevalences of BHR between different age groups, eg, children vs adults, and different populations, primarily due to hereditary differences in body size. BHR is a major risk factor for ongoing and subsequent development of respiratory symptoms, but a large proportion of subjects with BHR, especially when measured at only one point in time, are and will most likely remain asymptomatic. Adjustment for airway caliber might therefore be of importance for the identification of those hyperresponsive subjects with the highest risk for respiratory morbidity, in that some subjects with borderline hyperresponsiveness, for instance due to small stature, may be excluded from the group of subjects regarded as having “abnormal” airway function. In keeping with this, longitudinal studies of BR should probably be adjusted for airway caliber to assess true differences and changes in the studied subjects’ physiologic responses, not least in studies focused on predictors and clinical implications of increased BR. The latter not least because it has been suggested that those subjects with the greatest variability over time in physiologic airway responses might be the subjects at greatest risk for later development of chronic respiratory disease.

In keeping with previous reports, the cross-sectional analyses of data from the two surveys showed a strong association between atopy to HDMs and degree of histamine responsiveness, irrespective of the presence or absence of symptomatic asthma. Furthermore, the longitudinal analysis revealed that persistent or new atopy to HDM had significant impact on the degree of histamine responsiveness in early adulthood, that is, at the second survey. The latter occurred even despite the fact that asthma, indexes of airway caliber, and degree of BR at the first survey were already in the model. The present findings therefore indicate that atopy to HDM, at least in susceptible individuals, might trigger a persistent increase in airway responsiveness, which might subsequently lead to development of obstructive lung disease.

At present, our knowledge about longitudinal variability in BR in unselected younger subjects is limited. However, a previous study by Redline et al has demonstrated considerable long-term variability in airway responsiveness to eucapnic hyperventilation with cold air in children and young adults. Furthermore, Forastiere et al have restudied a large cohort of 7- to 11-year-old children after a 3.5-year interval and reported an overall decline in BR to inhaled methacholine. These findings are confirmed in the present study of a population sample with a wider age span at enrollment and a 6-year interval between the surveys. Although random variation may partly explain the between-survey variability, the consistency of the findings indicates that the BR level also depends substantially on specific individual- and time-related factors such as airway caliber and immunologic reactivity.

Asymptomatic hyperresponsiveness to agents such as histamine and methacholine is a known risk factor for development of asthma. The proportion of subjects in the present study with a positive histamine challenge test declined substantially from childhood to early adulthood (Table 2). Most of the subjects who ever had asthma had at least one positive histamine test result, but 64 subjects (16% of the sample) had asymptomatic BHR at either one or both of the surveys. A substantial proportion of hyperresponsive subjects therefore may seem to have transient BHR of probably only minor clinical significance. BHR in some asymptomatic and only temporary symptomatic subjects may be due to an acute inflammatory reaction in the airways with reversible hyperresponsiveness (that is, acute hyperresponsiveness), whereas BHR in persistent symptomatic subjects may reflect the combination of reversible airway inflammation and permanent damage to the airways (sequelae from long-standing inflammation) (that is, chronic hyperresponsiveness). In the present study, atopic subjects, especially subjects atopic to HDM, were more likely to be hyperresponsive, irrespective of asthmatic status, and, what may be of greater clinical significance, they were more likely to retain their hyperresponsiveness (data not shown). The former observation is supported by a recent Norwegian study showing that indoor allergic sensitization, especially presence of HDM antibodies, rather than allergic sensitization per se was related to increased BR. Furthermore, Peat and coworkers have recently published a study showing a dose-response relationship between exposure to HDM allergen and sensitization to HDM, BHR, and recent wheeze. These observations combined with the present findings suggest that subjects at greatest risk for development of chronic hyperresponsiveness and respiratory symptoms are those with both hyperresponsiveness and atopy, especially in the case of atopy to HDM. These observations might have significant implications for future intervention trials focused on primary asthma prevention.

In summary, our data have demonstrated substantial long-term variability in BR to inhaled histamine between childhood and early adulthood. The observed variability can at least partially be attributed to changes in airway caliber, as assessed by the FEV₁%pred, and atopy, especially atopy to HDM, in both asthmatics and nonasthmatics. Future primary asthma prevention trials should possibly focus on
subjects with both asymptomatic increased BR and atopy, not least subjects sensitized to HDM allergen.

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