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The Course of Persistent Airflow Limitation in Subjects with and without Asthma

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Abstract

Rationale—Most patients who develop persistent airflow limitation do so either as a manifestation of chronic obstructive pulmonary disease that is largely related to smoking or as a consequence of persistent asthma. We sought to compare the natural course of lung function associated with persistent airflow limitation in subjects with and without asthma from early to late adult life.

Methods—We studied 2552 participants aged 25 or more who had multiple questionnaire and lung function data from the long-term prospective population-based Tucson Epidemiological Study of Airway Obstructive Disease. Persistent airflow limitation was defined as FEV1/FVC ratio consistently < 70% in all completed surveys subsequent to the first survey with airflow limitation. Participants were divided into nine groups based on the combination of their physician-confirmed asthma status (never, onset ≤ 25 years, or onset > 25 years) and the presence of airflow limitation during the study follow-up (never, inconsistent, or persistent).

Results—Among subjects with an asthma onset ≤ 25 years, blood eosinophilia increased significantly the odds of developing persistent airflow limitation (adjOR: 3.7, 1.4–9.5), whereas cigarette smoking was the strongest risk factor for persistent airflow limitation among non-asthmatics and among subjects with asthma onset after age 25 years. Among subjects with persistent airflow limitation, the natural course of lung function differed between subjects with asthma onset ≤ 25 years and non-asthmatics, with the former having lower FEV1 levels at age 25 (predicted value for a 175-cm tall male of 3,400 versus 4,090 ml, respectively; p<0.001) and the latter having greater FEV1 loss between age 25 and 75 (1,590 versus 2,140 ml; p=0.003).

Conclusion—In subjects who have asthma onset before 25 years of age and persistent airflow limitation in adult life, the bulk of the FEV1 deficit is already established before age 25 years.

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Conflict of Interest Statement

SG, DLS, MK-S, CV, MH, and SFQ have no conflicts of interest to disclose in relation to this manuscript. FDM has served on the Merck Advisory Board and as a consultant for GlaxoSmithKline, Pfizer and Genentech. In the last three years he has also received lecture fees from speaking at the invitation of Merck and Genentech. In each of the last three years he has been selected as the Pfizer Visiting Scholar, a program meant to increase opportunities for scientific exchange and education at medical schools, teaching hospitals and other organizations. Values of each service are determined by quantity of time and effort required.

Keywords

asthma; COPD; eosinophilia; airflow limitation

Introduction

Airflow limitation that is variable and reversible either spontaneously or with treatment is a defining feature of asthma[1, 2]. Yet, subgroups of patients with long-term persistent asthma may develop irreversible airflow limitation[3–5], which has been associated with markers of disease severity[5] and overall mortality risk[6]. The possible progression of persistent asthma into chronic airflow limitation is consistent with observations showing that, at the population level, co-existing diagnoses of asthma, chronic bronchitis and emphysema are frequently reported by the same patient[7, 8] and that active asthma increases substantially the risk of acquiring a subsequent diagnosis of chronic obstructive pulmonary disease (COPD)[9]. Indeed, in the presence of irreversible airflow limitation, a differential diagnosis between asthma and COPD can be quite difficult using the physiologic tests that are routinely utilized in the clinical setting[10–12].

Understanding the natural course of lung function and the patterns of risk factors for development of persistent airflow limitation among asthmatics, as contrasted with those of subjects with classical smoking-related COPD, is essential to determine whether, how, and when prevention and treatment strategies can be implemented to reduce the long-term *sequelae* of this disease. However, population-based long-term prospective studies on persistent airflow limitation in subjects with asthma are scant. Seminal work by Burrows and colleagues[1] assessed the course and prognosis of chronic airway obstruction in 27 asthmatics who already had moderate to severe airflow limitation at their enrollment in the Tucson Epidemiological Study of Airway Obstructive Disease (TESAOD). They found that subjects with asthma had a slower FEV1 decline than did subjects with smoking-related emphysema, but they did not study how the natural course of lung function from young to late adult life differed in these two groups. The large cohort of the TESAOD study has now covered a sufficiently long period with prospective follow-up of well-characterized respiratory phenotypes and repeated lung function tests over a substantial proportion of adult life for most of the participants, to address this issue. The goal of the present study was to determine risk factors and natural course of lung function associated with persistent airflow limitation in subjects with and without asthma in the TESAOD study.

Methods

Study Population

TESAOD is a population-based prospective cohort study initiated in Tucson, AZ in 1972. Details of the enrollment process have been previously reported[13]. During the follow-up, new enrollees were added by marriages and births for a final total of 5,377 white participants.

TESAOD is composed of surveys that took place approximately every two years between 1972 and 1996. All participants were eligible to take part in the first 12 surveys, whereas survey 13 was conducted on selected subgroups based on previous reports of respiratory symptoms/ disease or residence in Arizona. During each survey, participants completed a standardized questionnaire and, with the exception of survey 4, performed spirometric lung function tests with a pneumotachygraph device, which was calibrated daily, according to ATS guidelines[14]. In survey 13, spirometric tests were repeated 15 minutes after inhalation of 180 μg of albuterol *via* a pressured metered-dose inhaler and a valved holding chamber.

For the present study, we used data from 2,552 participants who completed questionnaire and lung function tests in at least two TESAOD surveys in which they were 25 years or older. Only lung function data from surveys completed at or after age 25 were used to minimize potential confounding by individual variation in onset and length of the plateau phase of lung function growth. Of the 2,552 participants, 515 (20%) were 25 years or younger at the time of enrollment into TESAOD.

Definitions and Measurements

Participants were considered to have physician-confirmed asthma if they reported to have ever had asthma and to have been seen, diagnosed, or treated for asthma by a doctor at any completed survey. Participants with asthma were classified into two mutually exclusive groups based on whether they had disease onset at / before age 25 years or after age 25 years. We selected this age cut-off to be consistent with the above mentioned age cut-off that was chosen as initial point for analyses on lung function. Asthma onset ≤ 25 years was defined as having asthma (as described above) at any survey before age 25 or, for subjects enrolled after age 25, as having asthma at enrollment into the study and reporting being ≤ 25 years at first asthma attack or having had 'respiratory trouble' before age 16[15]. Asthma onset > 25 years was defined as either having no asthma at enrollment and having new asthma at any subsequent survey after age 25 or as having asthma at enrollment into the study after age 25 and reporting age at first asthma attack > 25 years and no 'respiratory trouble' before age 16.

Airflow limitation was defined as FEV1/FVC ratio < 70%. Airflow limitation was defined as *"persistent"* if the subject had FEV1/FVC values < 70% in all completed lung function tests subsequent to the first survey with airflow limitation. Otherwise, it was coded as *"inconsistent"*. The categories of no, inconsistent, and persistent airflow limitation were created based on available observations and missing observations were assumed to be at random in the statistical analyses. Both subjects with prevalent airflow limitation and subjects with incident airflow limitation were included in this study to avoid selective removal of subjects with early onset of airflow limitation. Because the FEV1/FVC ratio declines significantly with aging, analyses on lung function were also repeated after defining airflow limitation based on lower limit of normal equations for FEV1/FVC[16].

We categorized subjects as ever smokers if they had smoked at least 1 pack-year by the time they completed their last survey.

A detailed description of assessment methods for skin prick tests, IgE, eosinophil measurements, and other clinical variables is included in Table E1 in the online appendix.

Study Design and Statistical Analyses

The 2,552 study subjects were divided into nine mutually exclusive groups based on the combination of their physician-confirmed asthma status (no asthma, asthma onset ≤ 25 years, or asthma onset > 25 years) and the presence of airflow limitation during the study follow-up (never, inconsistent, or persistent). The study design is summarized in Figure 1.

Multinomial logistic regression was used to determine factors associated with persistent and inconsistent airflow limitation, as compared with no airflow limitation, in the total population and separately for subjects with no asthma, asthma onset ≤ 25 years, and asthma onset > 25 years. Robust variance estimates were used to minimize the effects of correlation within households. In order to compare FEV1 trends over time across the groups with persistent airflow limitation while adjusting for the intra-subject serial correlation of repeated observations and reducing the impact of missing observations[17], we used random coefficients models that included as fix covariates a categorical indicator of study groups, sex, height, length

of follow-up, age, age squared, an interaction term between study groups and age, and an interaction term between study groups and age squared. Because FEV1 is part of the defining criteria of persistent airflow limitation, FEV1 trends were compared using linear contrasts only between pairs of groups with persistent airflow limitation. In addition, the slope of FEV1 was computed for each subject with at least three lung function tests ≥ 25 years of age by regressing FEV1 against age. Two multivariate logistic regression models were then used to determine factors associated with being in the fastest tertile and being in the fastest quintile of FEV1 decline (i.e., having an FEV1 slope of at least 33 ml per year or at least 45 ml per year, respectively). Statistical analyses were completed using the statistical packages SPSS version 15.0 and Stata version 9.0.

The study was approved by the Human Subjects Committee at the University of Arizona and all participants provided informed consent.

Results

Of the 2,552 subjects included in this study, 1,778 (70%) had no airflow limitation, 460 (18%) inconsistent airflow limitation, and 314 (12%) persistent airflow limitation. Figure 2 shows the frequency of persistent and inconsistent airflow limitation among subjects with no asthma, asthma onset ≤ 25 years, and asthma onset > 25 years. Subjects in either asthma group were at increased risk of inconsistent and persistent airflow limitation as compared with subjects with no asthma. When analyses were stratified by smoking, the associations between asthma and airflow limitation were significant both among non-smokers and smokers.

Factors Associated with Airflow Limitation

Table I shows the characteristics of the subjects in the nine study groups (see methods). Factors potentially associated with inconsistent and persistent airflow limitation were tested in multinomial logistic regression models for the total population and separately for subjects with no asthma, asthma onset ≤ 25 years, and asthma onset > 25 years (Table II). Male sex, age, pack-years, elevated IgE, eosinophilia, and asthma status were significantly associated with persistent airflow limitation in the total population. The risk for persistent airflow limitation was 8 times higher for subjects with asthma onset ≤ 25 years than subjects with no asthma. The corresponding RR was lower (4.9) but still highly significant for subjects with asthma onset > 25 years. Age and smoking were significantly associated with persistent airflow limitation in all models stratified by asthma status. However, the RRs for the association between pack-years and persistent airflow limitation were substantially higher among subjects with no asthma or asthma onset > 25 years than among subjects with asthma onset ≤ 25 years. In contrast, eosinophilia was associated with an almost 4-fold increased risk of developing persistent airflow limitation only among subjects with asthma onset ≤ 25 years. Of note, in this group the RR for persistent airflow limitation associated with eosinophilia was particularly high among never smokers (6.8; 1.6–28.9). Table E2 in the online data supplement shows multinomial logistic regression models for inconsistent and persistent airflow limitation separately for males and females. The increased risk for persistent airflow limitation associated with eosinophilia appeared stronger among females than males, with the corresponding RRs being 2.1 (1.3–3.5) and 1.5 (0.9–2.5), respectively. This trend was particularly evident among subjects with asthma onset ≤ 25 years. In this group, eosinophilia was associated with a RR of 6.8 (1.6–28.4) among females and a RR of 1.9 (0.5–7.3) among males, although the interaction term between eosinophilia and sex was not significant (data not shown).

Lung Function

FEV1 levels during adult age were assessed in the study groups based on lung function tests completed over age 25 (see Figure E1 for distribution of available observations by age). Figure

3 shows that, inherent in the classification, the groups with persistent airflow limitation had lower FEV1 values as compared with controls, but the natural history of their lung function differed based on the presence and time of onset of asthma. As compared with controls with no asthma and no airflow limitation, subjects with no asthma and persistent airflow limitation had only moderate deficits of FEV1 at age 25 (mean deficit, 95% CI: 213, 16–410 ml), but they had 874 (665–1,084) ml excess loss of FEV1 between age 25 and 75. In contrast, subjects with asthma onset ≤ 25 years and persistent airflow limitation had larger deficits of FEV1 at age 25 (904, 637–1,171 ml) and a moderate excess loss of FEV1 between age 25 and 75 (322, 15–630 ml). Subjects with asthma onset > 25 years and persistent airflow limitation had a mean 524 (145–904) ml deficit of FEV1 at age 25 and a 763 (372–1,154) ml excess loss of FEV1 between age 25 and 75. Linear contrasts indicated that, as compared with subjects with no asthma and persistent airflow limitation, subjects with asthma onset ≤ 25 years and persistent airflow limitation had significantly lower FEV1 levels at age 25 (predicted values for a 175-cm tall male: 4,090 versus 3,400 ml, respectively; $p<0.001$) and a significantly smaller FEV1 loss between age 25 and 75 (2,140 versus 1,590 ml, respectively; $p=0.003$). Predicted FEV1 values and FEV1 loss are shown for each of the study groups in Figure 3. In the online data supplement, Figure E2a–d shows predicted FEV1 values from the best-fitting random coefficients models stratified by sex and smoking.

In order to estimate slopes of FEV1 decline for each of the groups with persistent airflow limitation, random coefficients models were re-run after excluding the age squared term. The expected FEV1 decline in controls with no asthma and no airflow limitation was 26 ml per year. Subjects with no asthma and persistent airflow limitation had a significantly faster FEV1 decline than did subjects with asthma onset ≤ 25 years and persistent airflow limitation or subjects with asthma onset > 25 years and persistent airflow limitation (43 [95% CI: 40–46] ml per year, 30 [24–36] ml per year, and 35 [29–40] ml per year; respectively).

We used multivariate logistic regression models to identify factors associated with being in the fastest tertile of FEV1 decline (i.e., having an FEV1 slope of at least 33 ml per year). Only male sex and packyears, but not IgE levels or eosinophilia, were associated with increased odds of being in the fastest tertile of FEV1 decline (adjusted ORs: 1.98, 1.63–2.41, for male sex; and 1.09, 1.05–1.13, for a 10-packyears increase). Similarly, male sex and packyears were the only significant risk factors for being in the fastest quintile of FEV1 decline (i.e., having an FEV1 slope of at least 45 ml per year), with the corresponding adjusted ORs being 2.24, 1.77–2.84; and 1.10, 1.05–1.15; respectively.

Sensitivity Analyses

To evaluate potential loss-to-follow-up bias, analyses were repeated and results confirmed after selecting for the 1,149 subjects who had ≥ 6 lung function tests (Figure E3) and after removing observations from survey 13, in which only subgroups of participants were eligible to participate (Figure E4). Results were also unchanged when persistent airflow limitation was defined as FEV1/FVC ratio consistently < 70% plus FEV1 % predicted < 80% during or after the first survey with FEV1/FVC < 70% (Figure E5). Random coefficients models including only observations over age 40 years returned very similar trends across the study groups (Figure E6).

Because the ratio FEV1/FVC declines significantly with aging in the general population, random coefficients models for lung function were also repeated after defining the study groups based on airflow limitation as assessed by an FEV1/FVC ratio below the lower limit of normal[16] (Figure E7). The main differences in the natural course of lung function associated with persistent airflow limitation between subjects with asthma onset ≤ 25 years and non-asthmatics were confirmed, with the former having lower FEV1 levels at age 25 and the latter having greater FEV1 loss between age 25 and 75. In these models, the natural course of lung

function of subjects with persistent airflow limitation was similar between the groups with asthma onset ≤ 25 years and asthma onset > 25 years.

Finally, using data from a subgroup of 418 adult subjects who completed pulmonary function tests before and after albuterol in survey 13, we found that 70% (23/33) of subjects with persistent airflow limitation had GOLD-defined COPD (FEV1/FVC < 70% after bronchodilator) in survey 13. This proportion was 60% (9/15) and 78% (14/18) among subjects with and without asthma, respectively.

Discussion

Using a population-based long-term prospective cohort, we identified subjects who had persistent airflow limitation during the study and compared risk factors and natural course of their disease based on the presence and age at onset of asthma. Findings of this study provide novel evidence that: 1) subjects with asthma account for a significant proportion of persistent airflow limitation in the general population; 2) the profile of risk factors for developing persistent airflow limitation is dependent upon the presence and the age at onset of asthma, with blood eosinophilia being the strongest risk factor among subjects with asthma onset before age 25 years; 3) among patients who have asthma before age 25, development of persistent airflow limitation in adult age is mainly associated with deficits that are already established by the time these subjects reach the growth plateau of their lung function.

Factors Associated with Persistent Airflow Limitation

Consistent with the well-known inverse relationship between the ratio FEV1/FVC and age[18, 19], aging was strongly associated with airflow limitation both among subjects with and without asthma. However, lifetime exposure to cigarette smoking was associated with an increased risk for persistent airflow limitation that was almost twice as high among subjects with no asthma or asthma onset > 25 years than among subjects with asthma onset ≤ 25 years. In contrast, among subjects with asthma onset ≤ 25 years, eosinophilia was the strongest risk factor for persistent airflow limitation. Eosinophilia is a known risk factor for the development of respiratory symptoms[20, 21] and, among asthmatics, is associated with lung function impairment[22, 23] and mortality risk[24, 25]. In a cross-sectional study of 132 nonsmoking outpatients with severe asthma, sputum eosinophils ≥ 2% were associated with an almost 8-fold increase in the odds of having postbronchodilator FEV1 or FEV1/FVC < 75% predicted[22]. Similarly, among children with asthma in the Childhood Asthma Management Program cohort levels of sputum and circulating eosinophils were higher in subjects with at least 1% per year loss in FEV1 % predicted than in subjects with non-significant FEV1 loss[23]. However, the present study is the first population-based study showing that eosinophilia predicts development of persistent airflow limitation among adults who had asthma onset in their first 25 years of life. Our findings support a major role for eosinophilia in the smoking-independent component of the phenotypic overlap between asthma and COPD, as suggested by the particularly strong association between eosinophilia and persistent airflow limitation among non-smoker asthmatics.

Natural History of Lung Function

Because FEV1 represents the numerator of the ratio ‘FEV1/FVC’, levels of FEV1 are expected to be reduced in most patients with airflow limitation. However, in adults these FEV1 deficits can be the result of any combination between lower FEV1 levels at the beginning of adult age or an accelerated FEV1 decline during adulthood[26]. One of the major findings of our study is that, among subjects who had asthma onset ≤ 25 years, persistent airflow limitation in adult age was strongly associated with FEV1 deficits that were already established by young adulthood. Whether these deficits are related to early airway remodeling or impaired lung

development, or both, remains to be determined. These findings are consistent with those of several other prospective studies – including the Dunedin Multidisciplinary Health and Development Study[18], the Melbourne Asthma Study[27], and the British 1958 Birth Cohort[28] – in which persistent childhood asthma was associated with lung function deficits that are present before adult life begins and track over time from childhood to mid-adult life. In the European Community Respiratory Health Survey, percent predicted FEV1 values at age 20 – 44 years were strong predictors of asthma severity and persistence during the follow-up period[29]. In addition, in the birth cohort of the Children's Respiratory Study our group has previously found that children who start life with low levels of lung function have lower expiratory flows throughout childhood[30] as well as lower FEV1/FVC levels at age 22[31] as compared with their peers, suggesting that early exposures and/or genetic factors also play a role in determining levels of lung function that will be attained before entering adult life. In our study, the impact of asthma on early deficits of lung function appeared stronger among males (Figure E2a), who are known to be at increased risk for severe and/or persistent childhood asthma as compared with females, and among non-smokers (Figure E2c).

Conversely, subjects with no asthma developed persistent airflow limitation mainly in response to cigarette smoking and, thus, they showed only mild FEV1 deficits at age 25 but steeper FEV1 decline over adult life. The natural course of lung function of subjects who had asthma onset after age 25 years included both moderate FEV1 deficits in young adulthood and accelerated FEV1 decline thereafter, although these results should be interpreted with caution because of the possibility of reverse causality (i.e., acquiring a diagnosis of adult-onset asthma might be the consequence rather than the cause of the steep decline of lung function) and the small number of observations before age 40 in this group.

The different natural history of lung function between subjects who developed persistent airflow limitation with or without asthma is consistent with the observation that eosinophilia, the strongest risk factor for persistent airflow limitation among subjects with asthma onset ≤ 25 years, was not associated with FEV1 decline. This observation suggests that eosinophilia influences lung function among subjects with childhood asthma mainly by affecting FEV1 levels that are attained before young adult age rather than by accelerating FEV1 decline in adult life.

Within our study design, we were unable to study potential effects of anti-inflammatory treatments[32] on asthma progression. In addition, the small sample size of some of our study groups suggests the importance of other studies to replicate these findings. As with most large epidemiological studies, post-bronchodilator lung function tests were not available for the vast majority of TESAOD participants. Thus, to what extent persistent airflow limitation can be used as a surrogate of GOLD-defined COPD is not known, although sensitivity analyses from a sub-group of 418 TESAOD participants suggested acceptable correlations between these two phenotypes. We also acknowledge that, although a maximum 24-year follow-up was possible in TESAOD, subjects enrolled in this study were followed on average for 11 years. Thus, we studied the natural course of the disease over adult life by combining information from multiple sub-cohorts of subjects who differed in age at enrollment into the study and length of follow-up. However, this is an unavoidable limitation of most large prospective studies in adults. The relatively homogeneous distribution of available observations over the entire span of adult life (Figure E1) and the use of statistical techniques that are specifically designed for analysis of unbalanced longitudinal data[17] should have minimized the impact of this limitation in our study.

Conclusions

In summary, development of persistent airflow limitation in adult patients with asthma is a common event and accounts for a significant proportion of the public health burden of

obstructive lung disease. We showed that blood eosinophilia is the strongest risk factor for the development of persistent airflow limitation among patients with asthma onset ≤ 25 years and that, among these patients, the bulk of lung function impairment is already established by young adulthood. Therefore, future prevention programs will need to identify and target these patients before they enter adult life.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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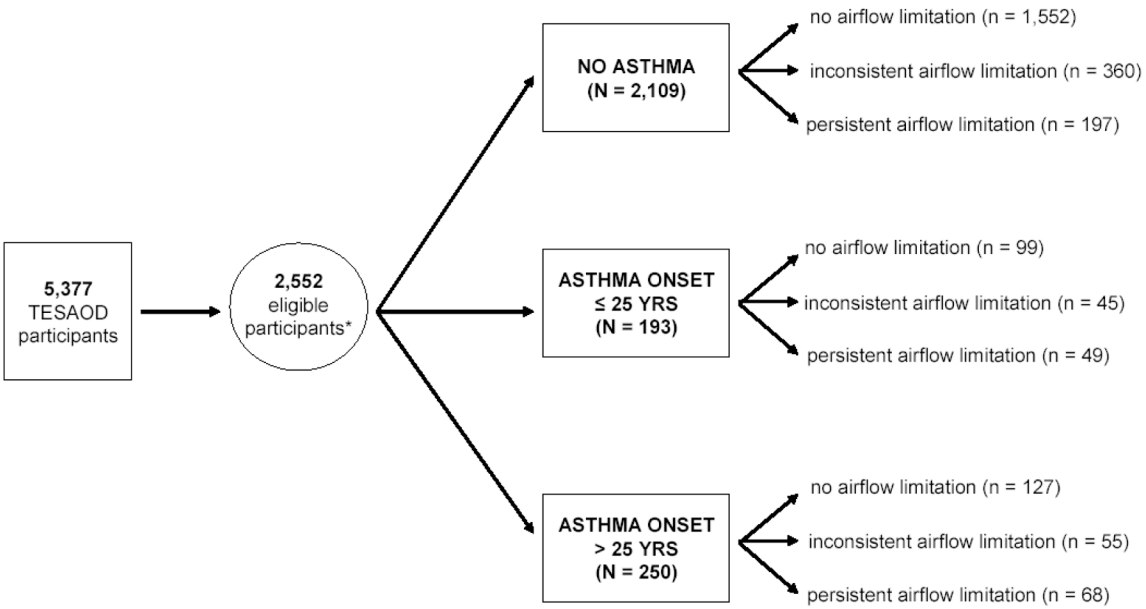

Figure 1.

Summary of study design. The nine study groups were created based on the combination of physician-confirmed asthma status (no asthma, asthma onset ≤ 25 years, or asthma onset > 25 years) and the presence of airflow limitation during the study follow-up (never, inconsistent, or persistent).

* Only participants who completed questionnaire and lung function tests in at least two surveys in which they were ≥ 25 years or older were eligible for the current study.

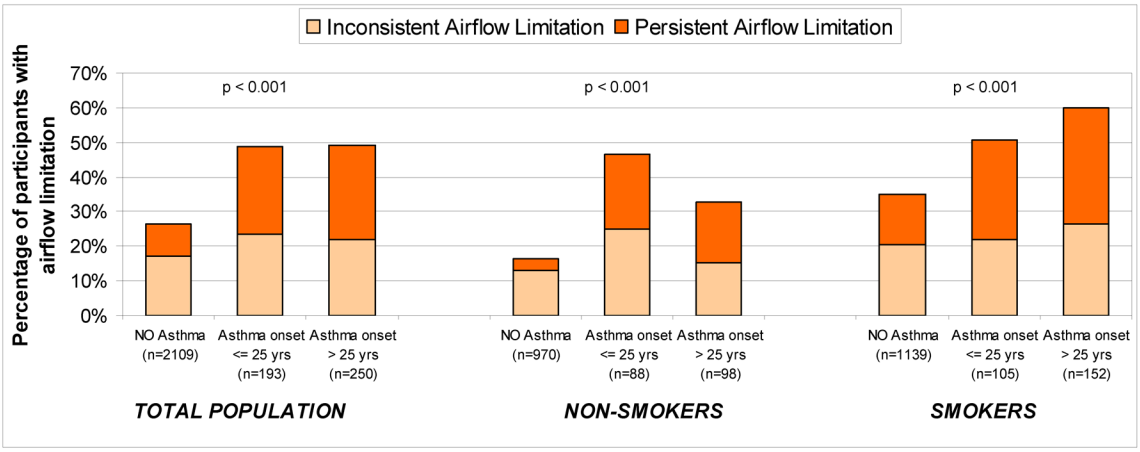

Figure 2.

Proportion of subjects with inconsistent and persistent airflow limitation in the groups with no asthma, asthma onset ≤ 25 years, and asthma onset > 25 years. Data are presented for the total population as well as stratified by the groups of non-smokers and smokers.

P values refer to the comparison of proportion of any airflow limitation among subjects with no asthma, asthma onset ≤ 25 years, and asthma onset > 25 years.

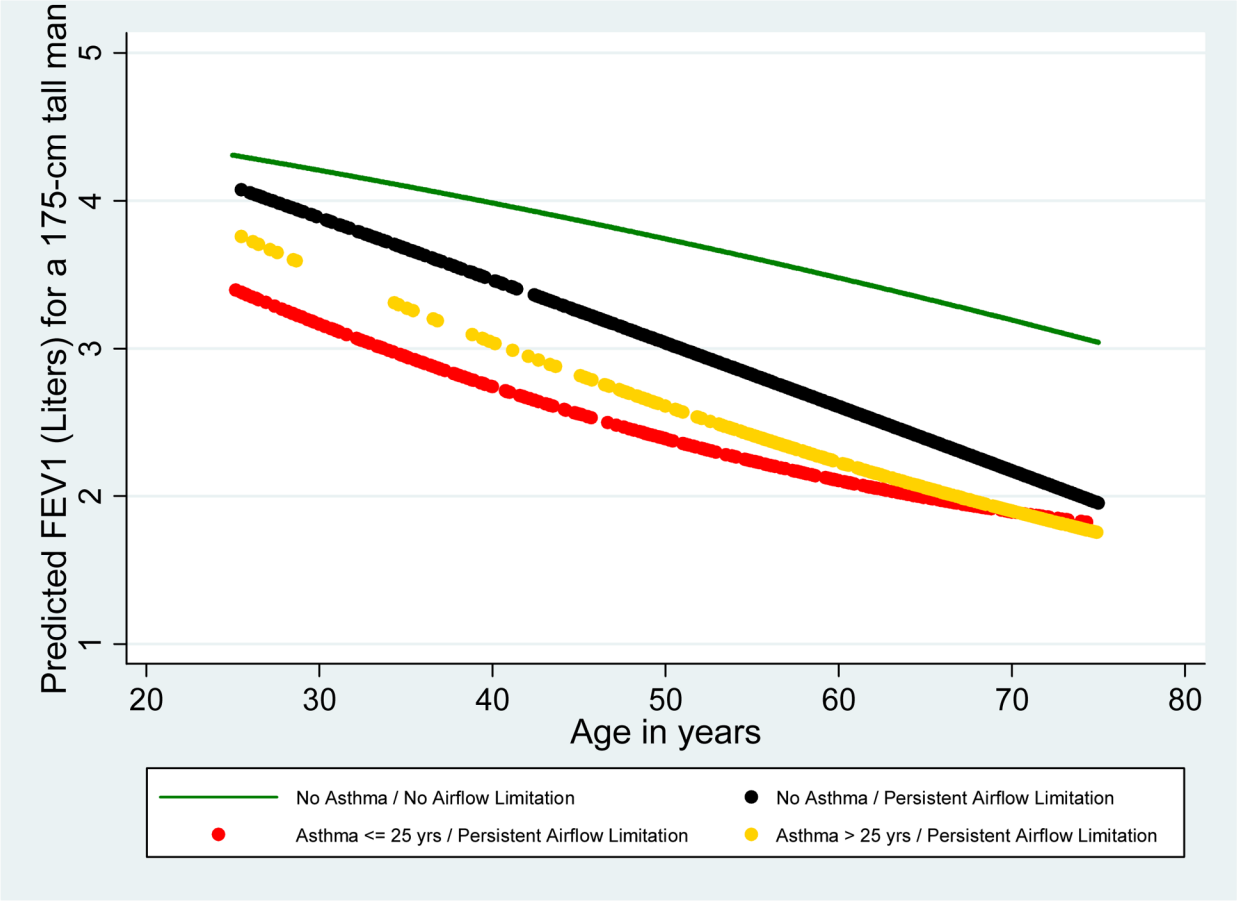

Figure 3.

Levels and decline of FEV1 during adult age for the study groups of subjects with no asthma and persistent airflow limitation (black line; number of subjects = 197; number of observations = 1,159), subjects with asthma onset ≤ 25 years and persistent airflow limitation (red line; number of subjects = 49; number of observations = 313), and subjects with asthma onset > 25 years and persistent airflow limitation (gold line; number of subjects = 68; number of observations = 385). Predicted values for subjects with no asthma and no airflow limitation (green line; number of subjects = 1,552; number of observations = 8,433) are also reported for comparison. Depicted values represent predicted values for a 175-cms tall male from the best-fitting random coefficients model.

Statistical comparisons were conducted only between pairs of groups with persistent airflow limitation (see methods) and are reported below.

	Subjects with no asthma / no airflow limitation	Subjects with no asthma / persistent airflow limitation	Subjects with asthma onset ≤ 25 yrs / persistent airflow limitation	Subjects with asthma onset > 25 yrs / persistent airflow limitation
Predicted FEV1 values (95% CI) in Liters at age 25	4.31 (4.26–4.35)	**4.09 (3.90–4.29)**	**3.40 (3.14–3.67)***	**3.78 (3.40–4.16)**
Predicted FEV1 loss (95% CI) in Liters between age 25 and 75	1.26 (1.21–1.32)	**2.14 (1.94–2.34)**	**1.59 (1.29–1.89)****	**2.03 (1.64–2.42)**

* significantly lower than subjects with no asthma / persistent airflow limitation ($p < .001$)

** significantly lower than subjects with no asthma / persistent airflow limitation ($p = .003$) and borderline lower than subjects with asthma onset > 25 years / persistent airflow limitation ($p = .08$)

wise specified.

	Asthma onset ≤ 25 years (n = 193)			Asthma onset > 25 years (n = 250)			Overall p value*
tation	No Airflow Limitation	Inconsistent Airflow Limitation	Persistent Airflow Limitation	No Airflow Limitation	Inconsistent Airflow Limitation	Persistent Airflow Limitation	
	99	45	49	127	55	68	N/A
	53.5	62.2	46.9	73.2	58.2	47.1	< 0.001
	35 ± 14	43 ± 14	48 ± 16	43 ± 17	56 ± 14	60 ± 13	< 0.001
	5.4 ± 3	7.4 ± 3	6.4 ± 3	5.3 ± 3	6.9 ± 3	5.7 ± 3	< 0.001
	10.5 ± 6	14.8 ± 6	11.6 ± 7	11.5 ± 6	13.2 ± 6	9.8 ± 7	< 0.001
	61.1	54.5	58.3	59.7	41.8	23.5	< 0.001
	76.8 12.1 11.1	53.3 33.3 13.3	28.6 26.5 44.9	67.7 21.3 11.0	56.4 25.5 18.2	29.4 27.9 42.6	< 0.001
	61.6 23.2 14.1	46.7 35.6 17.8	34.7 22.4 42.9	52.8 22.8 24.4	45.5 27.3 27.3	16.2 22.1 61.8	< 0.001
	4.0	13.3	42.9	8.7	25.5	51.5	< 0.001
	47.5 27.3 22.2 3.0	48.9 8.9 24.4 17.8	38.8 12.2 26.5 22.4	52.0 25.2 17.3 5.5	27.3 20.0 38.2 14.5	25.0 11.8 22.1 41.2	< 0.001
	80.2	87.8	68.1	70.1	65.5	42.4	< 0.001
	27.2	45.0	46.5	24.5	51.0	27.9	< 0.001

	Asthma onset ≤ 25 years (n = 193)			Asthma onset > 25 years (n = 250)			
tation	No Airflow Limitation	Inconsistent Airflow Limitation	Persistent Airflow Limitation	No Airflow Limitation	Inconsistent Airflow Limitation	Persistent Airflow Limitation	Overall p value*
	23.4	30.0	41.9	24.8	25.5	31.6	< 0.001

he measurements performed during the stdy[34]. For example, this would

surements performed during the study. For example, this would correspond

Respir Med. Author manuscript; available in PMC 2009 October 1.

Table II

consistent and persistent airflow limitation in the total population and separately for subjects
d asthma onset > 25 years. Sex, age, pack-years, skin tests, IgE, eosinophilia, and asthma
ent variables. All models were also adjusted for duration of follow-up. Factors that were
odels.

2552) ation) Limitation	MODEL 2: NO ASTHMA (n = 2109) (reference group = subjects with no asthma and no airflow limitation) Inconsistent Airflow Limitation *RR (95% CI)*	 Persistent Airflow Limitation *RR (95% CI)*	MODEL 3: ASTHMA onset ≤ 25 yrs (n = 193) (reference group = subjects with asthma onset ≤ 25 yrs and no airflow limitation) Inconsistent Airflow Limitation *RR (95% CI)*	 Persistent Airflow Limitation *RR (95% CI)*	MODEL 4: ASTHMA onset > 25 yrs (n = 250) (reference group = subjects with asthma onset > 25 yrs and no airflow limitation) Inconsistent Airflow Limitation *RR (95% CI)*	 Persistent Airflow Limitation *RR (95% CI)*
	1.10 (0.84–1.43)	**1.82 (1.29–2.58)**	0.79 (0.31–2.02)	1.17 (0.50–2.72)	**2.21 (1.00–4.88)**	**2.49 (1.17–5.26)**
	1.67 (1.53–1.82)	**1.59 (1.42–1.78)**	**1.56 (1.17–2.09)**	**1.91 (1.43–2.55)**	**1.85 (1.45–2.35)**	**1.98 (1.54–2.54)**
	1.20 (1.14–1.26)	**1.35 (1.27–1.44)**	**1.23 (1.03–1.46)**	**1.22 (1.05–1.43)**	**1.28 (1.06–1.53)**	**1.43 (1.19–1.73)**
	1.05 (0.72–1.53)	1.44 (0.90–2.32)	1.87 (0.77–4.56)	2.23 (0.92–5.41)	**3.36 (1.52–7.46)**	1.45 (0.61–3.45)
	1.29 (0.92–1.83)	1.36 (0.84–2.20)	1.72 (0.62–4.72)	**3.66 (1.41–9.54)**	1.01 (0.40–2.53)	2.16 (0.84–5.51)
	N/A -	N/A -	N/A -	N/A -	N/A -	N/A -

's sex- and age-specific category in any of the measurements performed during the study[34]

than the sex-specific mean in any of the measurements performed during the study