Abstract

Rationale: The contribution by asthma to the development of fixed airflow obstruction and the nature of its effect combined with active smoking and atopy remain unclear.

Objectives: To investigate the prevalence and relative influence of lifetime asthma, active smoking and atopy on fixed airflow obstruction in middle-age.

Methods: The population-based Tasmanian Longitudinal Health Study cohort born in 1961 (n=8,583) and studied with pre-bronchodilator spirometry in 1968 was retraced (n=7,312) and resurveyed (n=5,729 responses) from 2002-2005. A sample enriched for asthma and chronic bronchitis underwent a further questionnaire, pre- and post-bronchodilator spirometry (n=1,389), skin prick testing, lung volumes and diffusing capacity measurements. Prevalence estimates were re-weighted for sampling fractions. Multiple linear and logistic regression were used to assess the relevant associations.

Measurements: Main effects and interactions between lifetime asthma, active smoking and atopy on fixed airflow obstruction.

Main Results: The prevalence of fixed airflow obstruction was 6.0% (95% confidence interval 4.5%-7.5%). Its association with early-onset current clinical asthma was equivalent to a 33 pack-year history of smoking (odds ratio 3.7 [1.5-9.3] p=0.005), compared to a 24 pack-year history for late-onset current clinical asthma (odds ratio 2.6 [1.03-6.5] p=0.042). An interaction (multiplicative effect) was present between asthma and active smoking on the ratio of post-bronchodilator forced
expiratory volume in one second/ forced vital capacity (FEV₁/FVC), but only among those with atopic sensitization.

**Conclusions:** Active smoking and current clinical asthma both contribute substantially to fixed airflow obstruction in middle-age, especially among those with atopy. The interaction between these factors provides another compelling reason for atopic, current asthmatics who smoke to quit.

*Keywords* = fixed airflow obstruction, population cohort, prevalence, lifetime asthma, active smoking, atopy, interaction

**MeSH terms**

Asthma/ outcome/ epidemiology  
Smoking/ adverse effects/ epidemiology  
Atopy/ outcome/ epidemiology  
Fixed airflow obstruction/ epidemiology  
Complex lung function/ epidemiology

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Introduction

Obstructive lung diseases are major global health problems, with asthma and chronic obstructive pulmonary disease (COPD) being the two main contributors. COPD that is characterised by fixed post-bronchodilator airflow obstruction, is currently the fourth leading cause of death worldwide (1). Asthma is not a major cause of death, but contributes substantially to morbidity and health care expenditure (2, 3). Prevalence estimates for asthma (4) and COPD (5, 6) have varied considerably between countries, where accurate estimates for COPD are important in anticipating its future disease burden.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has previously considered asthma to be a differential diagnosis of COPD and currently asserts that evidence for a causative role is not conclusive (7, 8). Nevertheless, physician-diagnosed asthma with current symptoms at age 22 years has been linked to reduced post-bronchodilator FEV₁/FVC levels in early adulthood. This link was only seen for those whose asthma was first diagnosed after the age of 16 years, or for earlier diagnosed asthmatics who used prescription medication during the previous year (9). In another asthma cohort aged 13 to 44 years and followed for 26 years, around one in six developed a reduced pre-bronchodilator FEV₁ that improved by less than 9% predicted following bronchodilator (10). Conversely, active cigarette smoking is well known for its role in the development of COPD in susceptible individuals, and can predispose those with asthma to poorer symptom control (11).
Some studies have investigated the impact of two-way interactions between asthma and active smoking as well as atopy on longitudinal and cross-sectional measures of lung function. An interaction between airway hyper-responsiveness and smoking status on the decline of post-bronchodilator FEV$_1$ has been described (12). However, this multiplicative effect was not seen when measures such as self-reported asthma and pre-bronchodilator FEV$_1$ were used (13, 14). The European Community Respiratory Health Survey (ECRHS) has reported an interaction between atopy and smoking on pre-bronchodilator FEV$_1$ levels independent of asthma status (15). On the other hand, the ECRHS has also reported an interaction between atopy and current asthma on FEV$_1$ and FEV$_1$/FVC levels while adjusting for smoking status (16). These results raise the possibility of a three-way interaction between current asthma, smoking and atopy on adult lung function. However, these interactions may have been confounded by pre-existing reduced lung function (17-19), in addition to the misclassification of “forgotten” childhood asthma (20).

We aimed firstly to determine the prevalence of abnormal lung function measures and phenotypes of fixed airflow obstruction in a middle-aged population; and secondly, to investigate the relative contributions and any potential interactions between lifelong asthma, active smoking and atopy on these measures and phenotypes, whilst adjusting for childhood lung function. Some of the results of these analyses have been previously reported in the form of conference abstracts (21-24).
Materials and Methods

Study design and population

The study participants were those attending the laboratory study of the 5th decade follow-up of the Tasmanian Longitudinal Health Study (TAHS), details of which have been published elsewhere (25-28). This is summarized in Figure 1. Briefly, the cohort of children born in 1961 (n=8,583) and schooling in Tasmania in 1968 were studied with surveys and pre-bronchodilator spirometry. This cohort was retraced and resurveyed from 2002-2005. A sample of respondents enriched for asthma and chronic bronchitis participated in a laboratory study from 2006-2008, that included a questionnaire, pre- and post-bronchodilator spirometry, skin prick testing, lung volumes and diffusing capacity measurements (Method E1 and Table E1 in the online data supplement).

Data collection methods

Lung function tests, including pre- and post-bronchodilator (BD) spirometry, single breath diffusing capacity (DLco) and lung volume measurements were conducted according to the joint American Thoracic Society (ATS) and European Respiratory Society (ERS) criteria (29-31). The predicted values for spirometry, DLco and lung volumes as well as spirometry from 1968 were derived from the reference equations by Hankinson et al (32), Thompson et al (33), Quanjer et al (34) and Stanojevic et al (35) respectively. Skin prick testing (SPT) to eight aeroallergens was also performed. Additional details are outlined in Methods E1 and E2 of the online supplement.
Clinical Definitions

Early-onset asthma was defined as the presence of asthma or “wheezy breathing” reported at the 1968 and/or 1974 surveys, where the parental answer was used preferentially to the answer provided by the participants in the 2004 and 2006 surveys. Late-onset asthma was defined as a participant-recalled asthma history starting after 20 years of age. Current clinical asthma was defined by asthma-related symptoms and/or healthcare access for asthma within the last 12 months. Atopy was defined by positive skin sensitivity to ≥ 1 of eight allergen extracts, where positivity equaled a wheal size ≥ 3mm than the negative control.

Abnormal lung function categories, such as low D_LCO and high total lung capacity (TLC), were defined using the statistical upper and lower limits of normal of nominated reference equations (29-31). Fixed airflow obstruction, or airflow obstruction (AO) that was not fully reversible, was defined as post-BD FEV₁/FVC < lower limit of normal, regardless of bronchodilator-reversibility. Fixed small AO was defined as post-BD forced expiratory flow between 25% and 75% of the FVC (FEF_{25-75%}) < lower limit of normal plus normal FVC but without fixed AO.

Statistical Analysis

Prevalence was calculated using the survey design for dataset function. Prevalence and 95% confidence intervals (CI) of the entire TAHS population was extrapolated back from the observed prevalence by re-weighting the known sampling fractions derived from the 1968, 1974 and 2004 surveys.
Multiple Linear and Logistic Regression was used to evaluate the relative and combined associations between active smoking, asthma and atopy on lung function measures (continuous data) and phenotypes of fixed AO (categorical data), respectively. A linear relationship between pack-years and lung function was confirmed (Method E3, online data supplement). Pre-BD FEV₁ percent predicted at age seven that was expressed as a continuous variable, atopy, sampling weights, gender, current occupation, passive smoking and family history of obstructive lung disease were included in the models as a priori confounders. Education, heating, and cooking were only retained if their inclusion changed the estimates by more than 10%.

All analyses were carried out using the statistical software Stata (release 11, Stata Corporation, College Station, Texas, USA). A conventional cut-off of p < 0.05 was used to determine statistical significance.

Ethics

The study was approved by the Human Ethics Review Committees at The Universities of Melbourne, Tasmania and New South Wales, the Alfred Hospital, and Royal Brisbane & Women’s Hospital Health Service District. Written informed consent was obtained from all participants.
Results

Demographic, clinical and lung function features

The clinical and lung function data of the 1,389 who participated in the laboratory study are summarized in Table 1.

Nine hundred and twenty-five (67%) participants reported ever having asthma, of whom 335 (36%) had current clinical asthma. Among those with current clinical asthma, 218 (65%) and 117 (35%) had early-onset and late-onset asthma respectively. The median [interquartile range] asthma duration for the corresponding groups was 42 [39-43] years for early-onset and 14 [6.2-21] years for late-onset current clinical asthmatics. There was a female predominance in the late-onset group. Atopy was present in 82% of those with early-onset and 47-54% with late-onset current clinical asthma (Tables E2 and E3, online data supplement).

Over half (57%) of those attending were ever-smokers, and 9.5% (n = 130) had a smoking history of at least 30 pack-years. Almost half (48%, n = 89) of the ever-smokers with current clinical asthma were current smokers.

Technically acceptable post-BD spirometry was obtained from 1,330 (96%) participants. Of these, 131 (10%) had fixed airflow obstruction for whom the mean (standard deviation, sd) FEV₁/FVC was 0.64 (0.06), and the mean FEV₁ was 80.8 (14.2) percent of the normal predicted value (% predicted). A total of 1,021 (73%)
participants had complete lung function and skin prick test data. The majority (n = 1,148 (83%)) had valid pre-bronchodilator FEV\textsubscript{1} values from 1968.

**Re-weighted population prevalence**

The prevalence of fixed AO adjusted for the entire TAHS cohort was 6.0% (95% confidence interval 4.5-7.5), with no significant difference by gender (figure 2, Table E4 in the online data supplement). When adopting the GOLD criteria definition for COPD stages II to IV that specify an FEV\textsubscript{1} less than 80% of the predicted value (5), the prevalence for fixed AO was significantly less [1.8% (95%CI 0.9-2.6)], again with no difference by gender.

**Fixed airflow obstruction measures**

We observed a two-way interaction (multiplicative association) between active smoking and asthma on post-BD FEV\textsubscript{1}/FVC levels, but only for those with atopic sensitization (p-value for 3-way interaction = 0.0495) (Table 2). In other words, current clinical asthmatics with atopy who smoked more than the median value had reductions in post-BD FEV\textsubscript{1}/FVC levels that were greater than the individual smoking and asthma associations combined, such that the difference was attributable to the asthma-smoking interaction itself. The combined effect was additive among those without atopy.

A similar asthma-smoking interaction was seen in the atopic subgroup for both post-BD FEF\textsubscript{25-75%} (p = 0.003) and post-BD FEV\textsubscript{1} levels (p = 0.007), but not BD-reversibility (p = 0.090), D\textsubscript{L}co (p = 0.060) or TLC levels (p = 0.904).
**Fixed airflow obstruction phenotypes**

Fixed AO was independently associated with active smoking and current clinical asthma, but not with atopy itself. Table 3 (Model 1) shows the estimate for the association between early-onset current clinical asthma and fixed AO, unadjusted for atopy and pre-BD FEV₁ at age seven. When atopy was added to the model, this estimate was reduced by 22%, and was further reduced by 14% when pre-BD FEV₁ at age seven was added subsequently. This fully adjusted estimate for early-onset current clinical asthma was equivalent a lifetime smoking history of 33 (95%CI 26-40) pack-years. The association between late-onset current clinical asthma and fixed AO was equivalent to a lifetime smoking history of 24 (95%CI 15-33) pack-years.

To compare the strengths of association for early-onset and late-onset current clinical asthma while taking the duration of the diseases into account, these pack-year equivalents were divided by the median asthma duration for each group. For early-onset current clinical asthma, this was equivalent to smoking 0.8 packets of cigarettes daily, in contrast to smoking 1.7 packets daily for the late-onset group. The pack-year equivalents increased when the data were re-analyzed using a cross-sectional or retrospective study design, that is, the participant-recalled asthma history from the present survey was used preferentially to the parental answer obtained from the 1968 and 1974 surveys. For those with current asthmatic symptoms who in middle-age recalled a childhood asthma history, the equivalent association with fixed AO was 42 (32-52) pack-years (Table E5, online data supplement).
Significant relationships were seen between active smoking and fixed AO, as well as fixed AO in the presence of co-existent low D\textsubscript{L}co or high TLC (Table 4). When using categorical (unlike with continuous lung function data observed before), an interaction between smoking, asthma and atopy was not present among the 10% of participants who fulfilled the formal criteria for fixed AO.

**Discussion**

This is the first longitudinal population-based study to integrate lifetime histories of active smoking and asthma, objective measures of atopic sensitization and comprehensively documented lung function phenotypes using spirometry, D\textsubscript{L}co and lung volumes in middle-age. The association between current clinical asthma and having fixed AO in middle-age was found to be equivalent to a smoking history of 33 and 24 pack-years for early-onset and late-onset current clinical asthmatics respectively. We also identified novel interactions between lifetime active smoking and asthma on multiple measures of fixed AO, but only among those with atopic sensitization.

Using the lower limit of normal for the post-BD FEV\textsubscript{1}/FVC ratio, we estimated the prevalence of fixed AO to be 6.0%. For subjects aged in their forties and of average height, this cut-off closely approximated the FEV\textsubscript{1}/FVC ratio of <0.70 used by the GOLD guidelines to define COPD (8, 35). Using the GOLD definition, the prevalence of fixed AO described in the Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO) study was generally higher, most likely
because the PLATINO study included older individuals (6). Conversely, The Burden of Lung Disease (BOLD) Initiative reported age and gender-specific estimates for twelve international sites using the GOLD stages II to IV definition in which the FEV₁ was specified to be less than 80% of the predicted value (5). Using this exact BOLD definition, our prevalence estimates were comparable with those for the 40-49 year age group in the BOLD study in most sites.

The association between childhood-onset asthma continuing into adulthood and fixed AO was reported to confer a similar risk to a smoking history equivalent to 62 pack-years by a recent cross-sectional study from New Zealand (36), whereas our estimate for that association was less at 33 (95%CI 26-40) pack-years. Three main reasons may explain the difference. Firstly, our study was able to adjust for the confounding effects of atopy and childhood lung function. Secondly, cross-sectional studies use retrospective self-assessment of childhood asthma, and we have previously shown that adults with milder remitted disease commonly misclassify themselves to be in either the control or late-onset group (20), thereby self-selecting participants with more severe current asthma to be in the active group. Thirdly, older participants took part in the New Zealand study, with 89% of those with COPD being over 50 years of age.

Whilst our study has estimated the association between lifetime asthma and lung function in middle-age, we did not have the information to determine when during the course of the asthma history the loss in lung function occurred. Our findings on the association between childhood asthma and reduced post-bronchodilator lung function in adulthood being largely related to the presence of "current clinical asthma" as opposed to remitted asthma, are consistent with the Tucson Children’s Respiratory
Study (9). This would imply that having asthma per-se in childhood is not as important for adult lung function as the persistence of active asthma. A similar observation was seen for those with current asthma symptoms but with an asthma diagnosis after 20 years of age in our study. While the strength of the association between late-onset current clinical asthma and fixed AO was lower than for early-onset current clinical asthmatics, the higher daily pack-year equivalent since age of diagnosis was consistent with other data that has shown late-onset asthmatics having worse lung function despite a shorter duration of disease (37).

Asthmatic smokers have increased asthma symptoms compared to asthmatic non-smokers (11). This may be because smoking further increases bronchial hyper-reactivity (38) and/or because it decreases the efficacy of inhaled corticosteroids (39). Consistent with this biological plausibility, we detected a 2-way asthma-smoking interaction on multiple measures of fixed AO, where the combined effect of asthma and active smoking differed with the presence of atopy. This 3-way interaction is a novel finding. In essence, this indicates that an atopic middle-aged smoker with current asthma who decided to quit smoking would not only benefit from ending the smoking effect, but also from any future effect derived from the asthma-smoking interaction. This specific interplay between asthma, smoking and atopy on post-BD FEV₁/FVC levels may in part explain the considerable variation seen in the natural course of COPD (40).

Atopy and airway hyper-reactivity may be considered as host factors that are individually expressed through their interaction with specific lifetime environmental stimuli that can vary from one generation to the next (41, 42). These environmental
exposures include allergens, active and passive smoking, and suppurative lung infections. In contrast to cross-sectional studies, prospective cohort studies measuring these factors at multiple appropriate time points can effectively examine the time sequence of asthma onset and lung function decline.

Reduced (pre-bronchodilator) lung function and increased bronchial hyperresponsiveness that is detected shortly after birth have been linked to the subsequent expression of clinical asthma in children (43, 44). This observation highlights the possibility of reverse causation of the association between childhood onset asthma and adult fixed obstructive lung disease observed in our study. We were able to adjust for childhood pre-bronchodilator FEV₁ levels when aged seven, which is relevant to asthmatics whose lung function levels have been shown to be largely established by the age of six years (17, 45, 46). However, we do not have information on post-bronchodilator FEV₁ levels in childhood, which is the more relevant confounder of the association between childhood asthma and fixed airflow obstruction in middle-age. Thus, our study cannot provide a definitive answer to the time sequence relating childhood asthma to the development of fixed airflow obstruction in later life.

However, our prospective study design has enabled a more accurate classification of early-onset and late-onset asthma than studies that used retrospective recall or self-reported history in adulthood (13-16, 36). We have previously shown that young adults are frequently inaccurate when recalling their childhood asthma history, and this recall bias was particularly relevant to females (20). This may in part explain the associations between female gender, low FEV₁ and new adult-onset asthma described
by Antó and colleagues (47), where the recurrence of “forgotten childhood asthma/wheezy breathing” as a clinical disease in adulthood may have been a confounder.

Our use of $D_{Lco}$ and lung volume measurements provided some important findings. Almost 20% of our cases with fixed AO had co-existent low $D_{Lco}$, where the combination suggests the presence of emphysema. In a population setting, the use of high-resolution computerized tomography lung density measurements, in isolation, has not been shown to be useful in detecting clinical emphysema (48), thereby supporting the need for a physiological definition in population-based studies.

There are three main strengths of our study. Firstly, the use of sampling weights allowed the calculation of prevalence estimates of each of the lung function phenotypes for the entire TAHS population. Secondly, the prospective documentation of asthma from 1968 when study subjects were aged seven years, minimized recall bias and reduced asthma misclassification (20). This also facilitated the calculation of asthma duration to determine the estimate size per year since asthma diagnosis. Thirdly, adult smokers with asthma were by design well-represented, permitting us to examine interactions between the associations of active smoking and asthma on lung function.

In terms of limitations, the present study was designed to investigate the role of lifetime asthma and lifetime smoking on having the phenotypes of fixed airflow obstruction at an age when COPD was starting to emerge, rather than addressing causation of disease. As discussed above, the progression of fixed airflow obstruction, that is COPD, could not be adequately assessed due to the absence of
post-bronchodilator measurements in childhood. The participation rate in our laboratory study was modest, though the 59% of invited survey respondents who underwent spirometry with 43% completing all lung function tests compares well with the Australian BOLD study in which only 33% of those who were contacted and eligible participated (5). Our laboratory attendees, enriched for asthma and symptomatic chronic bronchitis, had similar clinical profiles regardless of completion of all lung function testing and comparable proportions of smokers to laboratory non-attendees (Table E1, online data supplement). Additionally, while linear regression analysed continuous data from all participants, logistic regression analysed categorical data that compared normal and abnormal lung function. As a result, the reduced power for the relatively small numbers of cases outside the limits of normality may have precluded the detection of some associations or interactions.

It is important to note that while inhaled corticosteroids have been proven useful in the treatment of asthma since the early 1970s, their widespread addition to oral corticosteroid use in clinical practice occurred some years later (49). Similar to other studies (10, 17), our risk estimates for the TAHS cohort born in 1961 therefore reflect in part, a period prior to the widespread availability of inhaled corticosteroids. Given that the study participants were almost exclusively European in ethnicity, and the high asthma prevalence (4) and mortality rates of Australia and New Zealand by international standards (50), these factors may potentially limit the generalizability of our data to other populations.

Summary
This prospective cohort study has used comprehensive clinical details and lung function measurements to determine the phenotype prevalence of fixed airflow obstruction in a large population-based cohort. Active smoking, early-onset and late-onset current clinical asthma were each found to contribute substantially to having fixed airflow obstruction in middle-age. There was no independent association between atopy and fixed airflow obstruction, but we demonstrated a synergistic effect between active smoking and asthma that varied with atopic status. Evidence of this three-way interaction was manifest as an extra source of fixed airflow obstruction in atopic smokers with current clinical asthma, where reduced post-bronchodilator FEV₁/FVC levels are integral to the definition of COPD. For atopic, current asthmatics who smoke, these findings provide another compelling reason to quit, warranting greater emphasis in public health campaigns and clinical practice guidelines.
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42. Orie NG. The dutch hypothesis. *Chest* 2000;117:299S.


### TABLE 1. CLINICAL CHARACTERISTICS AND LUNG FUNCTION DATA FROM THE LABORATORY STUDY (2006-2008)

<table>
<thead>
<tr>
<th></th>
<th>Males (N=709)</th>
<th>Females (N=680)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>44.8 (0.8)</td>
<td>44.9 (0.8)</td>
</tr>
<tr>
<td><strong>BMI (kg/m(^2))</strong></td>
<td>28 (4.3)</td>
<td>28 (6.5)</td>
</tr>
<tr>
<td>Smoking history (n(%), pack-year median [IQR])</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>302 (43)</td>
<td>284 (42)</td>
</tr>
<tr>
<td>Former</td>
<td>198 (28)</td>
<td>203 (30)</td>
</tr>
<tr>
<td>Pack-years</td>
<td>9.3 [2.1,19]</td>
<td>5.5 [1.8,14]</td>
</tr>
<tr>
<td>Current</td>
<td>203 (29)</td>
<td>172 (25)</td>
</tr>
<tr>
<td>Pack-years</td>
<td>25 [14.35]</td>
<td>18 [8.6, 26]</td>
</tr>
<tr>
<td><strong>Lifetime asthma (n(%))</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>231 (33)</td>
<td>210 (31)</td>
</tr>
<tr>
<td>Remitted</td>
<td>322 (45)</td>
<td>268 (39)</td>
</tr>
<tr>
<td><strong>Current clinical</strong></td>
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<td></td>
</tr>
<tr>
<td>Early-onset</td>
<td>108 (15)</td>
<td>110 (16)</td>
</tr>
<tr>
<td>Late-onset</td>
<td>33 (5)</td>
<td>84 (12)</td>
</tr>
<tr>
<td>Previous ICS use</td>
<td>64 (9)</td>
<td>87 (13)</td>
</tr>
<tr>
<td>Current ICS use</td>
<td>33 (5)</td>
<td>54 (9)</td>
</tr>
<tr>
<td><strong>Family history</strong></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>400 (57)</td>
<td>476 (70)</td>
</tr>
<tr>
<td><strong>Atopy (n(%))</strong></td>
<td>416 (59)</td>
<td>352 (52)</td>
</tr>
<tr>
<td><strong>Post-BD spirometry</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%)</td>
<td>685 (97)</td>
<td>645 (95)</td>
</tr>
<tr>
<td>FEV(_1) (L)</td>
<td>3.9 (0.6)</td>
<td>2.9 (0.5)</td>
</tr>
<tr>
<td>% predicted</td>
<td>97 (13)</td>
<td>98 (14)</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>5.0 (0.7)</td>
<td>3.7 (0.5)</td>
</tr>
<tr>
<td>% predicted</td>
<td>98 (12)</td>
<td>99 (12)</td>
</tr>
<tr>
<td>FEF(_{25-75}%) (L/s)</td>
<td>3.6 (1.1)</td>
<td>2.9 (0.9)</td>
</tr>
<tr>
<td>% predicted</td>
<td>98 (29)</td>
<td>98 (30)</td>
</tr>
<tr>
<td>FEV(_1)/FVC</td>
<td>0.78 (0.07)</td>
<td>0.79 (0.07)</td>
</tr>
<tr>
<td>% predicted</td>
<td>99 (8.6)</td>
<td>98 (8.6)</td>
</tr>
<tr>
<td>Predicted LLN(^\dagger)</td>
<td>0.69 (0.002)</td>
<td>0.71 (0.002)</td>
</tr>
<tr>
<td><strong>FEV(_1) BD-reversibility</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%)</td>
<td>671 (95)</td>
<td>645 (95)</td>
</tr>
<tr>
<td>Δ ml</td>
<td>143 (182)</td>
<td>104 (126)</td>
</tr>
<tr>
<td>% Δ from baseline</td>
<td>4.2 (6.1)</td>
<td>4.1 (5.7)</td>
</tr>
<tr>
<td><strong>Single breath DL(_{co})^\dagger</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%)</td>
<td>570 (80)</td>
<td>554 (81)</td>
</tr>
<tr>
<td>mmol/min/kPa</td>
<td>10.4 (1.8)</td>
<td>7.9 (1.5)</td>
</tr>
<tr>
<td>ml/min/mmHg</td>
<td>31.0 (5.5)</td>
<td>23.6 (4.5)</td>
</tr>
<tr>
<td>% predicted</td>
<td>104 (17)</td>
<td>102 (18)</td>
</tr>
</tbody>
</table>

Lung volumes
<table>
<thead>
<tr>
<th></th>
<th>Smoking</th>
<th>Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n (%)</strong></td>
<td>629 (89)</td>
<td>592 (87)</td>
</tr>
<tr>
<td><strong>Total lung capacity (L)</strong></td>
<td>7.3 (1.1)</td>
<td>5.5 (0.8)</td>
</tr>
<tr>
<td>% predicted</td>
<td>105 (13)</td>
<td>110 (13)</td>
</tr>
<tr>
<td><strong>Residual volume (L)</strong></td>
<td>2.1 (0.7)</td>
<td>1.8 (0.5)</td>
</tr>
<tr>
<td>% predicted</td>
<td>102 (33)</td>
<td>105 (29)</td>
</tr>
<tr>
<td><strong>RV/TLC ratio (%)</strong></td>
<td>28 (6.9)</td>
<td>31 (7.2)</td>
</tr>
</tbody>
</table>

**Definition of abbreviations:** Δ, change in; BMI, body mass index; DLco, diffusing capacity of the lung for carbon monoxide; FEF25-75%, forced expiratory flow between 25% and 75% of the FVC; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; ICS, inhaled corticosteroid; IQR, interquartile range; L, liters; L/s, liters/second; LLN, lower limit of normal; post-BD, post-bronchodilator; RV/TLC, residual volume/total lung capacity; SD, standard deviation; SPT, skin prick tests.

Data are expressed as mean (SD) unless otherwise indicated.

* Complete data was obtained in 1,362 (98%) for smoking; 1,366 (98%) for asthma; 1,384 (100%) for atopy; 1,273 (92%) for current ICS use. Numbers with technically acceptable lung function results are indicated in italics.

† The LLN represents the 5th percentile or 1.645 SD below the predicted mean of values derived from reference equations (32).

‡ Values were adjusted to a standard hemoglobin concentration and corrected for the presence of carboxyhemoglobin.
TABLE 2. INTERACTION BETWEEN ASTHMA AND SMOKING ON POST-BRONCHODILATOR FEV₁/FVC LEVELS, STRATIFIED BY ATOPY†

<table>
<thead>
<tr>
<th>Asthma pattern</th>
<th>Active smoking‡</th>
<th>Atopy status (N = 1,009)</th>
<th></th>
<th></th>
<th>Atopic (N = 566)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>Post-BD FEV₁/FVC % predicted [95%CI]††</td>
<td>n (%)</td>
<td>Post-BD FEV₁/FVC % predicted [95%CI]††</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No asthma</td>
<td>&lt; 0.91 py</td>
<td>97 (22) 96 [92 to 100]</td>
<td>72 (13) 97 [92 to 101]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 0.91 py</td>
<td>97 (22) -1.4 [-2.3 to -0.5]**</td>
<td>64 (11) + 0.4 [-0.6 to +1.4]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remitted asthma (any age of onset)</td>
<td>&lt; 0.91 py</td>
<td>79 (18) + 0.3 [-1.9 to +2.5]</td>
<td>143 (25) - 0.2 [-2.8 to +2.4]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 0.91 py</td>
<td>96 (22) - 0.6 [-3.0 to +1.8]</td>
<td>118 (21) - 1.6 [-4.2 to +1.1]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early-onset current clinical asthma</td>
<td>&lt; 0.91 py</td>
<td>9 (2) - 1.9 [-5.5 to +1.7]</td>
<td>80 (14) + 5.7 [-8.6 to -2.8]**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 0.91 py</td>
<td>18 (4) - 4.0 [-7.6 to -0.3]*</td>
<td>47 (8) - 8.4 [-12 to -5.1]**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Late-onset current clinical asthma</td>
<td>&lt; 0.91 py</td>
<td>18 (4) - 1.5 [-4.3 to +1.3]</td>
<td>21 (4) - 5.4 [-8.7 to -2.1]**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 0.91 py</td>
<td>29 (7) - 4.0 [-6.9 to -1.1]**</td>
<td>21 (4) - 8.2 [-12 to -4.1]**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Asthma-smoking interaction p = 0.187 p < 0.001

Definitions of Abbreviations: FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; BD, bronchodilator; py, pack-years.

† Multivariable-adjusted model includes sampling weights, gender, current occupation, passive smoking, family history of obstructive lung disease and the interaction term active smoking*lifelong asthma pattern stratified by atopy (n=1,236); plus pre-BD FEV₁ percent predicted at age seven (n=1,009)

‡ Median smoking history was 0.91 pack-years

†† Values expressed as baseline % predicted [95% confidence interval] followed by reduction in % predicted from baseline [95% confidence interval] unless otherwise indicated
### TABLE 3. INDEPENDENT ASSOCIATIONS BETWEEN LIFETIME ASTHMA PATTERNS, ATOPY, ACTIVE SMOKING AND FIXED AIRFLOW OBSTRUCTION IN MIDDLE-AGE†

<table>
<thead>
<tr>
<th>Lifetime asthma pattern</th>
<th>Fixed airflow obstruction, OR [95%CI]†††</th>
<th>Model 1 (N = 114)</th>
<th>Model 2 (N = 113)</th>
<th>Model 3 (N = 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No asthma</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Remitted asthma</td>
<td>0.9 (0.4-2.0)</td>
<td>0.8 (0.4-1.8)</td>
<td>0.9 (0.4-2.0)</td>
<td></td>
</tr>
<tr>
<td>Early-onset current clinical asthma</td>
<td>5.5 (2.4-12)***</td>
<td>4.3 (1.9-9.8)**</td>
<td>3.7 (1.5-9.3)**</td>
<td></td>
</tr>
<tr>
<td>Late-onset current clinical asthma</td>
<td>2.7 (1.2-6.2)*</td>
<td>2.6 (1.1-5.9)*</td>
<td>2.6 (1.03-6.5)*</td>
<td></td>
</tr>
<tr>
<td>Atopy</td>
<td>-</td>
<td>1.7 (1.1-2.8)*</td>
<td>1.5 (0.9-2.5)</td>
<td></td>
</tr>
<tr>
<td>Active smoking, per 10 py increments</td>
<td>1.5 (1.3-1.8)***</td>
<td>1.5 (1.3-1.8)***</td>
<td>1.5 (1.3-1.7)***</td>
<td></td>
</tr>
</tbody>
</table>

Definition of abbreviations: CI, confidence interval; OR, odds ratio; py, pack-year

* p<0.05 ** p<0.01 *** p<0.001

† Reference group = non-atopic, non-asthmatic non-smokers

‡ Multivariable-adjusted models

Model 1 includes sampling weights, gender, lifetime asthma pattern, active smoking history, current passive smoking history, current occupation and family history of obstructive lung disease; with 25, 24, 48 and 17 cases for the corresponding subgroups, no asthma, remitted asthma, early-onset and late-onset current clinical asthma respectively

Model 2 = Model 1 plus atopy

Model 3 = Model 1 plus atopy and pre-BD FEV₁ percent predicted at age seven

†† Regression totals were n = 1049, n = 1043 and n = 859 for models 1-3 respectively
### Table 4: Active Smoking and Phenotypes of Fixed Airflow Obstruction

<table>
<thead>
<tr>
<th>Fixed Airflow Obstruction</th>
<th>Regression total (N)†</th>
<th>Number of cases [n(%N)]</th>
<th>Lifetime active smoking (py)</th>
<th>Per 10 py increments [OR (95%CI)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per se‡</td>
<td>859</td>
<td>100 (12)</td>
<td>14 [0, 27]</td>
<td>1.5 (1.3-1.7)***</td>
</tr>
<tr>
<td>Plus low D_Lco</td>
<td>517</td>
<td>13 (3)</td>
<td>23 [21, 45]</td>
<td>2.8 (1.5-5.1)**</td>
</tr>
<tr>
<td>Plus high TLC</td>
<td>613</td>
<td>24 (4)</td>
<td>18 [0, 38]</td>
<td>1.3 (1.02-1.7)*</td>
</tr>
</tbody>
</table>

Definition of abbreviations: AO, airflow obstruction; CI, confidence interval; D_Lco, diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity; IQR, interquartile range; OR, odds ratio; py, pack years; TLC, total lung capacity

† p=0.030 **p=0.001 ***p<0.001

† Control definition was normal pre- and post-BD spirometry including FEF25-75% levels. The fixed AO plus low D_Lco phenotype includes additional cases with fixed small AO, normal FVC plus low D_Lco

‡ Derived from the multivariable-adjusted regression Model3, from Table 3
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