

The Interplay between the Effects of Lifetime Asthma, Smoking, and Atopy on Fixed Airflow Obstruction in Middle Age

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Rationale: The contribution by asthma to the development of fixed airflow obstruction (AO) 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 AO in middle age.

Methods: The population-based Tasmanian Longitudinal Health Study cohort born in 1961 ($n = 8,583$) and studied with prebronchodilator spirometry in 1968 was retraced ($n = 7,312$) and resurveyed ($n = 5,729$ responses) from 2002 to 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 reweighted for sampling fractions. Multiple linear and logistic regression were used to assess the relevant associations. **Measurements and Main Results:** Main effects and interactions between lifetime asthma, active smoking, and atopy as they relate to fixed AO were measured. The prevalence of fixed AO was 6.0% (95% confidence interval [CI], 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; 95% CI, 1.5–9.3; $P = 0.005$), compared with a 24 pack-year history for late-onset current clinical asthma (odds ratio, 2.6; 95% CI, 1.03–6.5; $P = 0.042$). An

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

People with asthma who smoke are predisposed to poorly controlled asthma and developing chronic obstructive pulmonary disease (COPD). However, the relative and combined impacts of lifetime asthma, active smoking, and atopic sensitization on adult lung function are not well defined.

What This Study Adds to the Field

This study describes a three-way interaction between the effects of asthma, active smoking, and atopy on the fixed airflow obstruction measure that is used to define COPD. This synergy, which largely affects atopic ever-smokers who have current asthma, supports a role for asthma in the development of COPD and strengthens the public health recommendation for people with asthma who smoke to quit.

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J.L.P. and S.C.D. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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interaction (multiplicative effect) was present between asthma and active smoking as it relates to the ratio of post-bronchodilator FEV₁/FVC, but only among those with atopic sensitization.

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

Keywords: fixed airflow obstruction; lifetime asthma; active smoking; atopy; interaction

Obstructive lung diseases are major global health problems, with asthma and chronic obstructive pulmonary disease (COPD) being the two main contributors. COPD that is characterized by fixed post-bronchodilator (BD) airflow obstruction (AO) is currently the fourth leading cause of death worldwide (1). Asthma is not a major cause of death, but it 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-BD 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 those diagnosed with asthma earlier 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-BD FEV₁ that improved by less than 9% predicted after BD use (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 the effects of asthma and active smoking as well as atopy on longitudinal and cross-sectional measures of lung function. An interaction between airway hyperresponsiveness and smoking status as it relates to the decline of post-BD FEV₁ has been described (12). However, this multiplicative effect was not seen when measures such as self-reported asthma and pre-BD FEV₁ were used (13, 14). The European Community Respiratory Health Survey has reported an interaction between the effects of atopy and smoking on pre-BD FEV₁ levels independent of asthma status (15). On the other hand, the European Community Respiratory Health Survey has also reported the effect of an interaction between atopy and current asthma on FEV₁ and FEV₁/FVC levels while adjusting for smoking status (16). These results raise the possibility of a three-way interaction between the effects of current asthma, smoking, and atopy on adult lung function. However, these interactions may have been confounded by preexisting reduced lung function (17–19) in addition to the misclassification of “forgotten” childhood asthma (20).

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

METHODS

Study Design and Population

The study participants were those attending the laboratory study of the fifth 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-BD spirometry. This cohort was retraced and resurveyed from 2002 to 2005. A sample of respondents enriched for asthma and chronic bronchitis participated in a laboratory study from 2006 to 2008, which included a questionnaire, pre- and post-BD spirometry, skin prick testing, lung volumes, and diffusing capacity measurements (see Methods E1 and Table E1 in the online supplement).

Data Collection Methods

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

Clinical Definitions

Early-onset asthma was defined as the presence of asthma or “wheezy breathing” reported at the 1968 and/or 1974 surveys; the parental

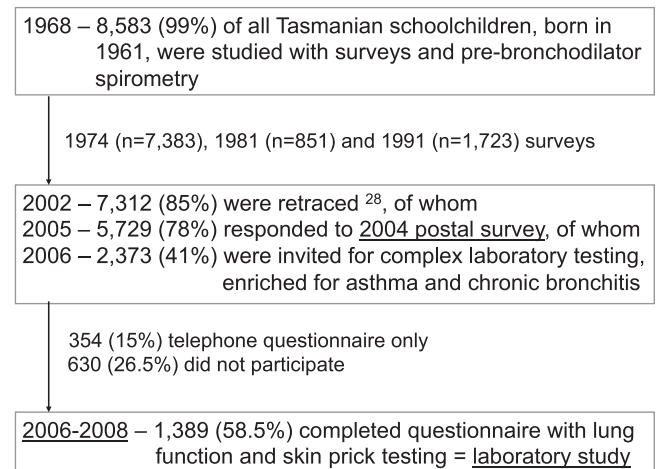


Figure 1. Study design.

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 one or more of eight allergen extracts, where positivity equaled a wheal size greater than or equal to 3 mm larger than the negative control.

Abnormal lung function categories, such as low DL_{CO} and high TLC, were defined using the statistical upper and lower limits of normal of nominated reference equations (29–31). Fixed AO, or AO that was not fully reversible, was defined as post-BD FEV₁/FVC less than the lower limit of normal, regardless of BD reversibility. Fixed small AO was defined as post-BD forced expiratory flow between 25% and 75% of the FVC (FEF_{25–75%}) less than the 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 reweighting 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 (Methods E3). Pre-BD FEV₁ percent predicted at age 7 years that was expressed as a continuous variable, atopy, sampling weights, sex, 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 performed using the statistical software Stata (release 11, Stata Corporation, College Station, TX). 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 and 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 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 asthma. There was a female predominance in the late-onset group. Atopy was present in 82% of those with early-onset and 47 to 54% with late-onset current clinical asthma (Tables E2 and E3).

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

	Men (N = 709)	Women (N = 680)
Age, yr	44.8 (0.8)	44.9 (0.8)
BMI, kg/m ²	28 (4.3)	28 (6.5)
Smoking history		
Never, n (%)	302 (43)	284 (42)
Former, n (%)	198 (28)	203 (30)
Pack-years, median (IQR)	9.3 (2.1–19)	5.5 (1.8–14)
Current, n (%)	203 (29)	172 (25)
Pack-years, median (IQR)	25 (14–35)	18 (8.6–26)
Lifetime asthma, n (%)		
Never	231 (33)	210 (31)
Remitted	322 (45)	268 (39)
Current clinical		
Early-onset	108 (15)	110 (16)
Late-onset	33 (5)	84 (12)
Previous ICS use	64 (9)	87 (13)
Current ICS use	33 (5)	54 (9)
Family history	400 (57)	476 (70)
Atopy, n (%)	416 (59)	352 (52)
Post-BD spirometry		
n (%)	685 (97)	645 (95)
FEV ₁ , L	3.9 (0.6)	2.9 (0.5)
% Predicted	97 (13)	98 (14)
FVC, L	5.0 (0.7)	3.7 (0.5)
% Predicted	98 (12)	99 (12)
FEF _{25–75%} , L/s	3.6 (1.1)	2.9 (0.9)
% Predicted	98 (29)	98 (30)
FEV ₁ /FVC	0.78 (0.07)	0.79 (0.07)
% Predicted	99 (8.6)	98 (8.6)
Predicted LLN [†]	0.69 (0.002)	0.71 (0.002)
FEV ₁ BD-reversibility		
n (%)	671 (95)	645 (95)
Δ ml	143 (182)	104 (126)
% Δ from baseline	4.2 (6.1)	4.1 (5.7)
Single breath DL _{CO} [‡]		
n (%)	570 (80)	554 (81)
mmol/min/kPa	10.4 (1.8)	7.9 (1.5)
ml/min/mm Hg	31.0 (5.5)	23.6 (4.5)
% Predicted	104 (17)	102 (18)
Lung volumes		
n (%)	629 (89)	592 (87)
TLC, L	7.3 (1.1)	5.5 (0.8)
% Predicted	105 (13)	110 (13)
Residual volume, L	2.1 (0.7)	1.8 (0.5)
% Predicted	102 (33)	105 (29)
RV/TLC ratio, %	28 (6.9)	31 (7.2)

Definition of abbreviations: BMI = body mass index; DL_{CO} = diffusing capacity of the lung for carbon monoxide; FEF_{25–75%} = forced expiratory flow between 25% and 75% of the FVC; ICS = inhaled corticosteroid; IQR = interquartile range; LLN = lower limit of normal; post-BD = post-bronchodilator; RV = residual volume; SPT, skin prick tests.

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

*Complete data were 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 fifth 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.

More than one-half (57%) of those attending were ever-smokers, and 9.5% (n = 130) had a smoking history of at least 30 pack-years. Almost one-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 AO, for whom the mean (SD) FEV₁/FVC was 0.64 (0.06), and the mean FEV₁ was 80.8 (14.2) % 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-BD FEV₁ values from 1968.

Reweighted Population Prevalence

The prevalence of fixed AO adjusted for the entire TAHS cohort was 6.0% (95% CI, 4.5–7.5), with no significant difference by sex (Figure 2; Table E4). When adopting the GOLD criteria definition for COPD stages II to IV that specify an FEV₁ 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 sex.

Fixed AO Measures

We observed a two-way interaction (multiplicative effect) between the effects of active smoking and asthma on post-BD FEV₁/FVC levels, but only for those with atopic sensitization (*P* value for three-way interaction = 0.0495) (Table 2). In other words, subjects with current clinical asthma with atopy who smoked more than the median value had reductions in post-BD FEV₁/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_{25–75%} (*P* = 0.003) and post-BD FEV₁ levels (*P* = 0.007) but not BD reversibility (*P* = 0.090), DL_{CO} (*P* = 0.060), or TLC levels (*P* = 0.904).

Fixed AO 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 7 years. When atopy was added to the

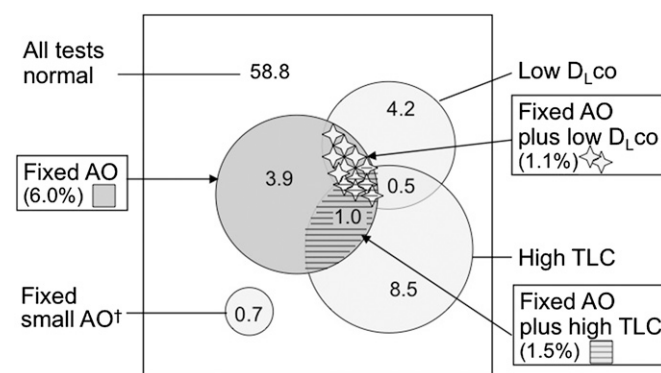


Figure 2. Population phenotype prevalence of fixed airflow obstruction (AO) and abnormal lung function measures (%). Shown is a nonproportional Venn diagram of the reweighted percentages, where overlapping fixed AO phenotypes have been labeled using text boxes. [†]Fixed small AO plus low diffusing capacity of the lung for carbon monoxide (DL_{CO}) prevalence was 0.1%.

TABLE 2. INTERACTION BETWEEN EFFECTS OF ASTHMA AND SMOKING ON POST-BRONCHODILATOR FEV₁/FVC LEVELS, STRATIFIED BY ATOPY

Asthma Pattern	Active Smoking (Pack-Years)*	Atopy Status (N = 1,009)			
		Nonatopic (N = 443)		Atopic (N = 566)	
		n (%)	Post-BD FEV ₁ /FVC % Predicted (95% CI)†	n (%)	Post-BD FEV ₁ /FVC % Predicted (95% CI)†
No asthma	<0.91	97 (22)	96 (92 to 100)	72 (13)	97 (92 to 101)
	≥0.91	97 (22)	−1.4 (−2.3 to −0.5)‡	64 (11)	+0.4 (−0.6 to +1.4)
Remitted asthma (any age of onset)	<0.91	79 (18)	+0.3 (−1.9 to +2.5)	143 (25)	−0.2 (−2.8 to +2.4)
	≥0.91	96 (22)	−0.6 (−3.0 to +1.8)	118 (21)	−1.6 (−4.2 to +1.1)
Early-onset current clinical asthma	<0.91	9 (2)	−1.9 (−5.5 to +1.7)	80 (14)	−5.7 (−8.6 to −2.8)§
	≥0.91	18 (4)	−4.0 (−7.6 to −0.3)‖	47 (8)	−8.4 (−12 to −5.1)§
Late-onset current clinical asthma	<0.91	18 (4)	−1.5 (−4.3 to +1.3)	21 (4)	−5.4 (−8.7 to −2.1)‡
	≥0.91	29 (7)	−4.0 (−6.9 to −1.1)‡	21 (4)	−8.2 (−12 to −4.1)§
Asthma–smoking interaction		P = 0.187		P < 0.001	

Definition of abbreviations: BD = bronchodilator; CI = confidence interval.

Multivariable-adjusted model includes sampling weights, sex, 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, Table E3); plus pre-BD FEV₁ percent predicted at age 7 years (n = 1,009).

*Median smoking history was 0.91 pack-years.

†Values expressed as baseline % predicted (95% CI) followed by reduction in % predicted from baseline (95% CI) unless otherwise indicated.

‡P < 0.01.

§P < 0.001.

‖P < 0.05.

model, this estimate was reduced by 22% and was further reduced by 14% when pre-BD FEV₁ at age 7 years was added subsequently. This fully adjusted estimate for early-onset current clinical asthma was equivalent to 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 packs of cigarettes daily, in contrast to smoking 1.7 packs daily for the late-onset group. The pack-year equivalents increased when the data were reanalyzed 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).

Significant relationships were seen between active smoking and fixed AO, as well as fixed AO in the presence of coexistent low DL_{CO} or high TLC (Table 4). When using categorical data (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, DL_{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 asthma, respectively. We also identified the effects of novel interactions between lifetime active smoking and asthma on multiple measures of fixed AO, but only among those with atopic sensitization.

TABLE 3. INDEPENDENT ASSOCIATIONS BETWEEN LIFETIME ASTHMA PATTERNS, ATOPY, ACTIVE SMOKING, AND FIXED AIRFLOW OBSTRUCTION IN MIDDLE AGE

	Fixed Airflow Obstruction, OR (95% CI)		
	Model 1 (N = 114)	Model 2 (N = 113)	Model 3 (N = 100)
Lifetime asthma pattern			
No asthma	1	1	1
Remitted asthma	0.9 (0.4–2.0)	0.8 (0.4–1.8)	0.9 (0.4–2.0)
Early-onset current clinical asthma	5.5 (2.4–12)*	4.3 (1.9–9.8)†	3.7 (1.5–9.3)†
Late-onset current clinical asthma	2.7 (1.2–6.2)‡	2.6 (1.1–5.9)‡	2.6 (1.03–6.5)‡
Atopy	—	1.7 (1.1–2.8)‡	1.5 (0.9–2.5)
Active smoking, per 10 pack-year increments	1.5 (1.3–1.8)*	1.5 (1.3–1.8)*	1.5 (1.3–1.7)*

Definition of abbreviations: CI = confidence interval; OR = odds ratio.

Reference group = nonatopic nonsmokers without asthma. Multivariable-adjusted models. Model 1 includes sampling weights, sex, 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 current clinical asthma, 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 7 years. Regression totals were n = 1,049, n = 1,043, and n = 859 for Models 1–3, respectively.

*P < 0.001.

†P < 0.01.

‡P < 0.05.

TABLE 4. ACTIVE SMOKING AND PHENOTYPES OF FIXED AIRFLOW OBSTRUCTION

	Regression Total, N	Number of Cases, n (% N)	Lifetime active smoking, pack-years	
			Median pack-years (IQR)	Per 10 pack-year Increments, OR (95% CI)
Fixed airflow obstruction				
<i>Per se</i> *	859	100 (12)	14 (0–27)	1.5 (1.3–1.7) [†]
Plus low DL _{CO}	517	13 (3)	23 (21–45)	2.8 (1.5–5.1) [‡]
Plus high TLC	613	24 (4)	18 (0–38)	1.3 (1.02–1.7) [§]

Definition of abbreviations: AO = airflow obstruction; CI = confidence interval; DL_{CO} = diffusing capacity of the lung for carbon monoxide; IQR = interquartile range; OR = odds ratio.

Control definition was normal pre- and post-BD spirometry including FEF_{25–75%} levels. The fixed AO plus low DL_{CO} phenotype includes additional cases with fixed small AO, normal FVC, plus low DL_{CO}.

* Derived from the multivariable-adjusted regression Model 3, from Table 3.

[†] $P < 0.001$.

[‡] $P = 0.001$.

[§] $P = 0.030$.

Using the lower limit of normal for the post-BD FEV₁/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 FEV₁/FVC ratio of less than 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 sex-specific estimates for 12 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- to 49-year-old 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. First, our study was able to adjust for the confounding effects of atopy and childhood lung function. Second, 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. Third, older participants took part in the New Zealand study, with 89% of those with COPD being older than 50 years of age.

Although 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-BD 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. Although the strength of the association between late-onset current clinical asthma and fixed AO was lower than for early-onset current clinical asthma, the higher daily pack-year equivalent since age of diagnosis was consistent with other data that have shown subjects with late-onset asthma having worse lung function despite a shorter duration of disease (37).

Smokers with asthma have increased asthma symptoms compared with nonsmokers with asthma (11). This may be because smoking further increases bronchial hyperreactivity (38) and/or because it decreases the efficacy of inhaled corticosteroids (39). Consistent with this biological plausibility, we detected the effect of a two-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 three-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 benefit not only from ending the smoking effect but also from any future effect derived from the asthma–smoking interaction, and this might be relevant to individuals without atopy to a lesser extent (Table E3). This specific interplay between asthma, smoking, and atopy that relates to post-BD FEV₁/FVC levels may in part explain the considerable variation seen in the natural course of COPD (40).

Atopy and airway hyperreactivity 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-BD) 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-BD FEV₁ levels when aged 7 years, which is relevant to subjects with asthma whose lung function levels have been shown to be largely established by the age of 6 years (17, 45, 46). However, we do not have information on post-BD FEV₁ levels in childhood, which is the more relevant confounder of the association between childhood asthma and fixed AO in middle age. Thus, our study cannot provide a definitive answer to the time sequence relating childhood asthma to the development of fixed AO 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 women (20). This may in part explain the associations between

female sex, low FEV₁, and new adult-onset asthma described by Antó and colleagues (47), wherein the recurrence of “forgotten childhood asthma/wheezy breathing” as a clinical disease in adulthood may have been a confounder.

Our use of DL_{CO} and lung volume measurements provided some important findings. Almost 20% of our cases with fixed AO had coexistent low DL_{CO}, and 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. First, the use of sampling weights allowed the calculation of prevalence estimates of each of the lung function phenotypes for the entire TAHS population. Second, the prospective documentation of asthma from 1968, when study subjects were aged 7 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. Third, 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 AO at an age when COPD was starting to emerge, rather than addressing causation of disease. As discussed above, the progression of fixed AO, which is COPD, could not be adequately assessed due to the absence of post-BD measurements in childhood. The participation rate in our laboratory study was modest, although 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 nonattendees (Table E1). Additionally, although linear regression analyzed continuous data from all participants, logistic regression analyzed 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 although 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 before 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.

Conclusions

This prospective cohort study has used comprehensive clinical details and lung function measurements to determine the phenotype prevalence of fixed AO in a large population-based cohort. Active smoking and early-onset and late-onset current clinical asthma were each found to contribute substantially to having fixed AO in middle age. There was no independent association between atopy and fixed AO, 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 AO in atopic smokers with current clinical asthma, in whom reduced post-BD FEV₁/FVC levels are integral to the definition of COPD. For atopic subjects with current asthma 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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**The interplay between
lifetime asthma, smoking and atopy
on fixed airflow obstruction
in middle-age**

Online Data Supplement

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Online Data Supplement

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Methods E1: Laboratory study design, 1968-2008

Study design, briefly, the TAHS started in 1968 when almost all seven-year old children attending school in Tasmania (n=8,583) were enrolled in a respiratory health study. Their parents completed a questionnaire concerning each child's respiratory symptoms and the child underwent a clinical examination and lung function tests. Follow up surveys were completed in 1974, 1981, and 1992. Of the original 1968 cohort, 7,312 (85.2%) were traced to an address in 2004. From those, a completed respiratory questionnaire was returned by 5,729 (78.4%) (1), and a subgroup (n = 2,373) was invited to participate in a more detailed clinical study. This sub-group was selected based on participation in previous follow-up studies, and enriched for a history of asthma and cough with sputum. Of the 2,373 invited, 1389 (58.5%) attended the laboratory, another 354 (15%) completed a telephone questionnaire only, and 630 (26.5%) withdrew. At the clinical visit between 2006 and 2008, participants completed a detailed interviewer-administered questionnaire and underwent comprehensive lung function testing that included skin prick tests for allergy. Laboratory testing was performed in four Australian states, which included Tasmania, Victoria, New South Wales and Queensland.

Of the laboratory attendees, technically acceptable post-bronchodilator (BD) spirometry, diffusing capacity (D_{LCO}) levels adjusted to a standard hemoglobin concentration and corrected for the presence of carboxyhemoglobin, and lung volume measurements were obtained from 1,330 (96%), 1,124 (81%) and 1,221 (88%) participants respectively. Only 1,025 (74%) of attendees, or 43% of those invited, completed these tests satisfactorily. With the addition of skin prick testing, 1,021 (73%) had complete lung function data.

Tables E1: Clinical comparisons between study subgroups

	Laboratory visit, selected from 2004 postal survey respondents (N=5,729)		
	Attended with lung function data (N=1,389)		Not attended (N=4,229) [†]
	Complete* (n=1,025)	Incomplete (n=364)	
Prospective asthma history			
At 7 years (1968)	357 (35)	168 (46)	469 (11)
At 13 years (1974) [‡]	290 (28)	115 (32)	375 (9)
At 44 years (2004)			
Early-onset asthma	486 (47)	177 (49)	673 (16)
Late-onset asthma	150 (15)	55 (15)	442 (10)
Family history asthma	662 (65)	214 (59)	215 (5.1)
Chronic bronchitis			
Current CB symptoms	127 (12)	42 (12)	214 (5)
Ever CB symptoms	205 (20)	72 (20)	308 (7)
Active smoking history			
Never smoked	436 (43)	151 (41)	1642 (39)
Former smoker	313 (31)	105 (29)	1276 (30)
Current smoker	275 (27)	111 (30)	1292 (31)
Allergy-ever history			
Reported allergies**	612 (60)	211 (58)	1915 (45)
Plus eczema or hayfever	799 (78)	288 (79)	2848 (67)
<i>Definition of abbreviations:</i> CB, chronic bronchitis			
Results expressed as the number of participants (% of subtotal)			
* Providing test results for spirometry, diffusing lung capacity, lung volumes, hemoglobin and carboxyhemoglobin were present and technically adequate. N=1,021 if skin prick testing was included.			
[†] Insufficient clinical data on an additional 107 participants			
[‡] Total numbers for the 1974 follow-up were 1,307 for attendees and 3,788 for non-attendees			
** Includes allergy to food/ dust/ medicine/ pets/ pollens/ animals/ grass/ trees/ flowers			

Compared to those with postal survey data only, the laboratory attendees were a sample enriched for asthma and symptomatic chronic bronchitis of whom almost two-thirds reported a family history of asthma. Adjustment for this enrichment in the regression analyses was achieved using a sampling weight variable. There were no clear differences in smoking rates or self-reported allergy history between laboratory attendees and non-attendees, and there was no clinical variation between laboratory attendees who did or did not complete the full lung function testing.

Methods E2: Clinical definitions, lung function and skin prick testing

Asthma-ever, based on participant recall, was defined as an affirmative response to either the 2004 postal question “Have you, at any time in your life suffered from attacks of asthma or wheezy breathing?” or the 2006 laboratory survey question “Have you ever had asthma?” Current clinical asthma was defined by asthma-related symptoms and/or healthcare access for asthma within the last 12 months. The remainder with asthma-ever was considered to have remitted asthma, regardless of age of onset.

Chronic bronchitis-ever was defined as an affirmative response to the following two questions “Have you, at any time in your life, suffered from cough with phlegm in the chest (with or without a cold)” and “have you had a cough with phlegm on most days for at least three months of each year for two consecutive years” ***Current chronic bronchitis*** was defined as an affirmative response to the questions “Are there months in which you have phlegm in your chest on most days”; “Do you bring up this phlegm on most days for at least three months each year”; and “For how many years have you had this phlegm”, answering either option 2 “2-5 years” or 3 “more than 5 years.”

Pre- and post-BD spirometry was performed using the EasyOne™ ultrasonic Spirometer (nidd, Medizintechnik, AG, Switzerland). Participants were asked not to smoke for 4-6 hours prior to testing. Forced expiratory volume in one second (FEV₁) was recorded as the best of three attempts that met American Thoracic Society (ATS) and European Respiratory Society (ERS) criteria (2). Spirometry was repeated 10 minutes after 200µg of salbutamol administered via spacer. Significant BD-reversibility was defined as an increase in FEV₁ from baseline by at least 12% and

200ml during a single testing session (ATS/ERS criteria) (3). Predicted values for FEV₁, forced vital capacity (FVC) and forced expiratory flow rate (FEF_{25-75%}) were calculated from age, height and gender using equations by Hankinson *et al* (4). Only three participants reported taking an inhaled beta-2-agonist within 4 hours of testing and another three took prednisolone within 24 hours of testing.

Single breath nitrogen washout D_{LCO} values were performed according to the ATS/ERS guidelines being two technically acceptable D_{LCO} measurements within 10% or 3 ml CO_(STPD)/min/mm Hg of the average D_{LCO} (5), and included adjustment to a standard hemoglobin concentration and correction for the presence of carboxyhemoglobin. Predicted values were calculated using two sets of reference equations, first by Roca *et al* that were derived using age, height, gender and a weight covariate for females (6), and second by Thompson *et al* (7) that used an additional ex-smoker covariate for males. The conversion factor used for D_{LCO} (ml/min/mmHg) was $2.986 \times T_{LCO}$ (mmol/min/kPA) (8). The reference equations by Roca *et al* were not adopted since a much higher prevalence of low D_{LCO} was estimated, largely as a result of the weight co-efficient being eight times higher in women.

Lung volume measurements were performed according to the ATS/ERS guidelines, where total lung capacity (TLC) was derived by adding functional residual capacity (FRC) to inspiratory capacity (IC), from the mean of two technically acceptable measurements (agreement within 5%) (9). Predicted values for TLC, FRC and IC were calculated from age, height and gender using equations by Quanjer *et al* (10).

Skin Prick Tests (SPT) were performed for eight aeroallergens (EBOS Groups Pty Ltd, Australia): *Dermatophagoides Pteronyssinus*, Cat Pelt, *Cladosporioides*, *Alternaria Tenuis*, *Penicillium mix*, *Aspergillus Fumigatus*, Perennial Rye Grass and 8 Mixed Grasses. A wheal size of at least 3mm greater than the negative control was regarded as indicating sensitivity.

Methods E3: Linearity between active smoking and lung function

To confirm whether a linear relationship existed between active smoking and fixed measures and phenotypes of fixed airflow obstruction, first, smoking was categorized into multiples of 10 pack-years, and then the categorical and pseudo-continuous forms of this variable were compared by means of the likelihood ratio test. Given no significant differences between the two models for either post-BD FEV₁/FVC levels expressed as a percentage of the predicted value ($p = 0.44$) or fixed airflow obstruction ($p = 0.97$), there was little evidence against the null hypothesis that the relationship was linear. A comparison for fixed AO/fixed small AO plus low D_{LCO} was not possible given an absence of cases for those smoking less than 10 pack-years. Using the assumption of linearity, linear and logistic regression techniques were used.

Castaldi *et al* recently described the relationship between active smoking and FEV₁ to be non-linear, with an initial strong negative effect of total pack-year history followed by a lesser effect for additional pack-years from approximating 30% to 50% of the predicted value.(11) This FEV₁ level corresponds to the ‘severe’ and ‘very severe’ categories of chronic obstructive pulmonary disease (COPD) as defined by the GOLD criteria.(12) Of the TAHS participants with fixed AO, only 5% (n=6) met the criteria

for severe COPD or higher with the majority having either mild (n=68, 54%) or moderate COPD (n=52, 41%), thereby supporting a linear relationship between active smoking and FEV₁ for our study.

Active smoking was entered as a continuous variable in the logistic regression models (i.e. per ten pack-years, Tables 3 and 4 of main text) and in the linear models containing interaction terms (median 0.91 pack-years, Table 2 of main text). The separate associations of asthma within each smoking stratum were reported if an interaction was present.

Table E2: Smoking history in subgroups of asthma and atopy

Atopic status/ smoking history	Lifetime asthma pattern (N=1,009)							
	None (n=330)		Remitted asthma (n=436)		Current clinical asthma			
					Early-onset (n=154)		Late-onset (n=89)	
	N (%)	p-years [†]	n (%)	p-years [†]	N (%)	p-years [†]	n (%)	p-years [†]
Non-atopic								
< 0.91 pack-years	97 (29)	0 [0,0]	79 (18)	0 [0,0]	9 (6)	0 [0,0]	18 (20)	0 [0,0]
≥ 0.91 pack-years*	97 (29)	15 [9,26]	96 (22)	14 [7,27]	18 (12)	18 [8,25]	29 (33)	24 [8,30]
Atopic-sensitization								
< 0.91 pack-years	72 (22)	0 [0,0]	143 (33)	0 [0,0]	80 (52)	0 [0,0]	21 (24)	0 [0,0]
≥ 0.91 pack-years*	64 (19)	14 [5,27]	118 (27)	16 [7,26]	47 (31)	19 [9,26]	21 (24)	14 [5,26]

Definition of abbreviations: IQR, interquartile range; p-years, pack-years.

* Median smoking history was 0.91 pack-years. Ex-smokers and current smokers comprised 50.5 and 49.5% of the non-atopic subgroup, and 48.5 and 51.5% of the atopic subgroup respectively

[†] Active smoking results are expressed as median pack-years [interquartile range].

* Includes participants with adequate adult spirometry, available childhood lung function, active and passive smoking history, occupational and family history of obstructive lung disease

Amongst those who reported a smoking history*, the median [IQR] values were similar between atopic and non-atopic individuals, besides the median pack-year exposure for those with late onset current clinical asthma. When participants without childhood lung function

were included (n = 1,236), there was no change in pack-year smoking history for non-asthmatic smokers with and without atopy.

Table E3: Asthma-smoking-atopy interaction on post-BD FEV₁/FVC levels, without adjustment for childhood lung function

Asthma pattern	Active smoking [‡]	Atopy, as defined by SPT (N=1,236) [†]			
		Non-atopic (N=544)		Atopic (N=692)	
		n (%)	Post-BD FEV ₁ /FVC % predicted [95%CI] ^{††}	n (%)	Post-BD FEV ₁ /FVC % predicted [95%CI] ^{††}
No asthma	< 0.91 py	120 (22)	97 [94 to 101]	84 (12)	96 [92 to 101]
	≥ 0.91 py	114 (21)	- 1.5 [-2.3 to -0.7]*	83 (12)	+ 0.1 [-0.8 to +0.9]
Remitted asthma (any age of onset)	< 0.91 py	99 (18)	+ 0.0 [-2.0 to +2.0]	160 (23)	+ 0.2 [-2.2 to +2.5]
	≥ 0.91 py	125 (23)	- 0.7 [-2.9 to +1.4]	149 (22)	- 1.2 [-3.6 to +1.2]
Early-onset current clinical asthma	< 0.91 py	14 (3)	- 3.3 [-6.4 to -0.1]*	93 (13)	- 5.9 [-8.5 to -3.3]***
	≥ 0.91 py	21 (4)	- 4.8 [-8.1 to -1.6]**	64 (9)	- 9.0 [-12 to -6.0]***
Late-onset current clinical asthma	< 0.91 py	20 (4)	- 2.2 [-4.9 to +0.4]	31 (4)	- 4.3 [-7.2 to -1.4]**
	≥ 0.91 py	31 (6)	- 5.4 [-8.0 to -2.7]***	29 (4)	- 6.8 [-10 to -3.4]***
Asthma-smoking interaction		p = 0.006		p < 0.001	

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

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

[†] Multivariable-adjusted model includes sampling weights, gender, current occupation, passive smoking, family history of obstructive lung disease plus the interaction term active smoking*lifelong asthma, stratified by atopy status

[‡] 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

Using multiple linear regression analysis, we observed a multiplicative association between active smoking and asthma on post-BD FEV₁/FVC levels, with and without atopic-sensitization, but with additional variation across these two strata (p for 3-way interaction = 0.009). This variation was most apparent for ever-smokers with early-onset current clinical asthma, for whom the 2-way asthma-smoking interaction on lung function was present only in those with atopic-sensitization. Within the subgroup of non-asthmatic ever-smokers, reductions in FEV₁/FVC levels were not seen for those atopic despite a similar smoking history to those without atopy (total n = 90, p for 2-way interaction = 0.007, see Table E2).

Of the 153 participants excluded from this regression analysis, 59 had technically unacceptable post-BD spirometry; 5 were without skin prick testing; and the remainder had incomplete clinical data for lifetime active smoking (n=27), lifetime asthma (n=23), current passive smoking (n=20), current occupation (n=6) and/or family history of obstructive lung diseases (n=15).

Table E4: Gender-specific prevalence of the entire TAHS cohort *

Lung function pattern	Total (% [95%CI])	Male (% [95%CI])	Female (% [95%CI])
Fixed AO (per se) [†]	6.0 [4.5-7.5]	4.6 [2.8-6.4]	7.5 [5.2-9.8]
- Without partial BD-reversibility [‡]	4.6 [3.3-5.8]	3.6 [2.0-5.2]	5.6 [3.6-7.6]
- With partial BD-reversibility	1.4 [0.7-2.2]	-	-
Fixed AO, FEV ₁ specified to <80% of predicted value	1.8 [1.0-2.7]	1.6 [0.5-2.6]	2.2 [0.9-3.4]
Fixed AO, FEV ₁ specified to <80% of predicted value and using GOLD criteria ^{**}	1.8 [0.9-2.6]	1.6 [0.6-2.7]	1.9 [0.7-3.1]
Fixed small AO ^{††}	0.7 [0.2-1.2]	-	-
Fixed AO/ fixed small AO plus low D _L co	1.2 [0.5-1.8]	1.0 [0.2-1.9]	1.3 [0.3-2.3]
Fixed AO plus high TLC	1.5 [0.7-2.2]	1.9 [0.7-3.1]	1.0 [0.1-1.8]
Fixed AO plus high residual volume ^{††}	1.3 [0.7-2.0]	-	-

Definitions of Abbreviations: AO, airflow obstruction; ATS/ERS, American Thoracic Society / European Respiratory Society; BD, bronchodilator; CI, confidence interval; D_Lco, diffusing capacity of the lung for carbon monoxide; FEV₁, forced expiratory volume in one second; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

* Prevalence re-weighted by sampling fractions derived from 1968, 1974 and 2004 surveys

[†] Consists of the mutually exclusive subgroups, with and without partial BD-reversibility as defined by ATS/ ERS criteria (3),

[‡] Does not fulfill ATS/ ERS criteria for BD-reversibility (3)

^{**} COPD is defined by post-bronchodilator FEV₁/FVC <0.7 (12) and not the lower limit of normal predicted values

^{††} Un-weighted case numbers were insufficient to perform logistic regression analyses

The comparisons between the prevalence of fixed AO (COPD) in the TAHS cohort and the international centers studied in the BOLD Study (13), were performed using the GOLD criteria (12) with the FEV₁ specified to <80% of the predicted value^{**}.

Table E5: Current clinical asthma association with fixed AO, by study design

	Pack-year estimates equivalent to the association of current clinical asthma and fixed AO	
	Early-onset	Late-onset
Complete regression model [†]		
Prospective design [‡]	33 (24-41)**	24 (14-34)*
Retrospective design	42 (32-52)***	28 (21-36)***
Baseline model (without adjusting for atopy and FEV ₁ 68) ^{††}		
Prospective design	40 (32-46)***	24 (16-31)*
Retrospective design	47 (40-54)***	31 (23-40)***
<i>Definition of abbreviations:</i> AO, airflow obstruction; FEV ₁ 68, forced expiratory volume in one second measured in 1968. Results expressed as the number of pack-years (95%CI) *$p < 0.05$ **$p < 0.01$ ***$p < 0.001$ [†] Complete multivariable-adjusted model includes sampling weights, gender, lifetime asthma pattern, active smoking and current passive smoking history, current occupation, family history of obstructive lung disease plus atopy and childhood lung function. [‡] Includes childhood lung function (FEV ₁ 68) plus prospective asthma history ^{††} Reference 14		

The prospective design for the complete regression model features the data from the 1968 survey, that is, asthma history and pre-bronchodilator spirometry.

When childhood asthma was reassessed in a cross-sectional or retrospective manner, in other words when the onset of asthma was assessed by retrospective recall in middle-age *and* the childhood lung function was omitted, the pack-year equivalents for early-onset current clinical asthma increased by 27%. This suggests that those who smoke more heavily preferentially remember their childhood asthma and/or wheezy breathing.

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