

The Effect of Cigarette Smoking on Lung Function in Young Adults with Asthma

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Abstract

Rationale: Life-course persistent asthma and tobacco smoking are risk factors for irreversible airflow obstruction. It is often assumed that smoking and asthma have additive or multiplicative effects on the risk for airflow obstruction, but this has not been demonstrated in prospective studies of children with persistent asthma.

Objectives: To investigate the effects of smoking and asthma on the development of airflow obstruction in a population-based birth cohort followed to age 38 years.

Methods: Reports of childhood asthma from ages 9, 11, and 13 and self-reports of adult asthma at ages 32 and 38 years were used to define childhood-onset persistent asthma ($n = 91$), late-onset asthma ($n = 93$), asthma in remission ($n = 85$), and nonasthmatic ($n = 572$) phenotypes. Cumulative tobacco smoking histories and spirometry were obtained at ages 18, 21, 26, 32, and 38 years. Analyses were by generalized estimating equations adjusting for childhood spirometry, body mass index, age, and sex.

Measurements and Main Results: Smoking history and childhood-onset persistent asthma were both associated with lower FEV₁/FVC ratios. Associations between smoking and FEV₁/FVC ratios were different between asthma phenotypes (interaction $P < 0.001$). Smoking was associated with lower prebronchodilator and post-bronchodilator FEV₁/FVC ratios among subjects without asthma and those with late-onset or remittent asthma, but smoking was not associated with lower FEV₁/FVC ratios among those with childhood-onset persistent asthma.

Conclusions: Childhood-onset persistent asthma is associated with airflow obstruction by mid-adult life, but this does not seem to be made worse by tobacco smoking. We found no evidence that smoking and childhood-persistent asthma have additive or multiplicative effects on airflow obstruction.

Keywords: airflow obstruction; chronic obstructive pulmonary disease; cohort studies

Although tobacco-smoking is the most well known risk factor for the development of chronic obstructive pulmonary disease, it is not the only one (1, 2). Nonsmokers can also develop chronic airflow obstruction, and there is considerable variability in the susceptibility to both symptoms and airflow obstruction among smokers (2). The factors that determine susceptibility to the effects of cigarette smoking remain poorly

understood, but are believed to arise from interactions between genes, environments, and other risk factors (1, 2). Understanding how these interactions lead to chronic airflow obstruction is an important step to reducing the burden of chronic airways disease.

Long-standing asthma can also lead to irreversible airflow obstruction (1, 3, 4). Although the underlying pathologies of asthma and smoking-related airways

disease are usually distinct, patients with refractory asthma often have features of chronic obstructive pulmonary disease and it has been proposed that multiple inflammatory insults to the airway increase the risk of airflow obstruction (5). Because asthma and smoking both cause airway inflammation and obstruction, we would expect smoking to lead to an accelerated decline in airway caliber among people with

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At a Glance Commentary

Scientific Knowledge on the

Subject: Smoking and persistent asthma are risk factors for irreversible airflow obstruction. Adults with asthma who smoke seem to have an enhanced decline in FEV₁/FVC ratios, but it is unknown whether smoking increases the risk of adult airflow obstruction among children with persistent asthma.

What This Study Adds to the

Field: Children with asthma that persisted to adulthood had low FEV₁/FVC ratios by age 38, and more than a third had persistent airflow limitation. Smoking did not increase the risk of airflow obstruction among these participants. Smoking was, however, associated with airflow obstruction among participants without asthma and those with late-onset asthma or asthma in remission. These observations challenge the assumption that children with asthma are more vulnerable to the airway damage inflicted by smoking.

asthma if this hypothesis is correct (2, 3, 6). A key question, therefore, is whether smoking and asthma act synergistically in the development of airflow obstruction.

Cohort studies suggest that adults with asthma have an enhanced decline in lung function if they smoke (7–11). An important limitation of these cohort studies is that they began in adulthood, yet the age of onset of asthma is an important determinant of airflow obstruction (12). People with childhood-onset persistent asthma are more likely to develop airflow obstruction and may be more vulnerable to the effects of other airway insults. Moreover, studies in adulthood may be confounded by reverse causation: susceptible smokers who develop airflow obstruction may develop wheeze and be diagnosed as having asthma. Retrospective reports of childhood asthma may also be affected by recall bias among those with persistent symptoms. Few cohorts have explored the interaction between smoking and childhood-onset asthma using prospectively collected childhood data (11). The Tasmanian Longitudinal Health Study

found an interaction between smoking and both early and late-onset current adult asthma at age 45 years for lower post-bronchodilator FEV₁/FVC ratios, but only for those with atopy (13).

The Dunedin Multidisciplinary Health and Development Study has followed the respiratory health of a population-based birth cohort from age 9 to 38 years. Previous analyses of the cohort have established that both childhood-onset, persistent asthma and tobacco smoking are associated with airflow obstruction in early adulthood (12, 14, 15). In the present analysis we compare the effect of tobacco smoking on lung function among different developmental phenotypes of asthma. Specifically, we aim to test the hypothesis that tobacco smoking has a greater effect on the development of airflow obstruction among participants with childhood-onset persistent asthma.

Methods

The Dunedin Study is a longitudinal investigation of health and behavior in a population-based cohort of 1,037 individuals born in 1972–1973. Study members are primarily of New Zealand/European ethnicity. The cohort has been assessed at ages 3, 5, 7, 9, 11, 13, 15, 18, 21, 26, 32, and 38 years. Written informed consent was obtained for each assessment. The Otago Ethics Committee approved the study.

Respiratory questionnaires were administered at each assessment from age 9 years onward (16–18). We defined childhood asthma as a parent-reported diagnosis of asthma with compatible symptoms or asthma medication use within the previous 12 months at 9, 11, or 13 years. Asthma was defined as late onset if it was first reported after age 13 years. Adult asthma was defined as a self-reported current diagnosis with compatible symptoms or medication use at age 32 or 38 years. From these definitions, four asthma phenotypes were created: (1) no asthma (not reported at any age), (2) childhood asthma that persisted to adulthood (still present at age 32 or 38 yr), (3) late-onset adult asthma (still present at age 32 or 38 yr), and (4) asthma currently in remission (childhood or late-onset, but not present at either age 32 or 38 yr). Current use of inhaled corticosteroids was recorded at each assessment from age 18 to 38 years.

Cumulative tobacco exposure was calculated from the age of starting regular smoking, the reported average number of cigarettes smoked each day up to age 18, and number of cigarettes smoked between each subsequent assessment. One pack-year is equivalent to 20 cigarettes per day for 1 year. Few participants were daily smokers before age 15 and personal tobacco use before age 13 years is assumed to be negligible (19). Exposure to parental smoking was ascertained at ages 7, 9, 11, and 13 (20). At 18, 21, 26, 32, and 38 participants were asked if anyone regularly smoked inside their home and if they were exposed to other people's cigarette smoke at work.

Spirometry was performed at each assessment from 9 to 38 years. Spirometry was repeated after inhalation of salbutamol at 18, 26, 32, and 38 years. Height and weight were measured at each assessment. The primary outcome measure was the FEV₁/FVC ratio. Additional analyses used percent predicted FEV₁ and FVC values based on the National Health and Nutrition Examination Survey reference equations (21).

Statistical Analyses

To assess whether childhood asthma influenced subsequent smoking, we compared the proportion of smokers at each age and the lifetime pack-years between those with and without childhood asthma. We further compared smoking and environmental tobacco smoke exposures among the four asthma phenotypes.

Associations between cumulative smoking and spirometry at ages 18, 21, 26, 32, and 38 years were assessed using generalized estimating equations with correlations between repeated measures on participants modeled using an exchangeable structure to implement linear regression models (22). These models adjusted for sex, age, and mean childhood spirometry values. Because smoking has been found to influence body weight in this cohort (23) and obesity may influence lung function (24, 25), we also adjusted for adult body mass index at the age of assessment in these analyses. Analyses tested for interactions between asthma phenotype and cumulative pack-years smoking using the “no asthma” phenotype as the reference category. Subsequent analyses assessed associations between smoking and spirometry for each phenotype separately. Post-bronchodilator spirometry was not measured in childhood, so these analyses adjusted for childhood

prebronchodilator values. Additional analyses assessed the potential confounding influences of parental smoking, environmental tobacco smoke exposure in adulthood, and inhaled corticosteroid use. Models were checked through inspection of histograms of residuals and scatterplots of residuals against continuous predictors and fitted values.

Persistent airflow limitation at age 38 was defined using a lower limit of normal set at sex-specific cut-points at the fifth percentile for post-bronchodilator FEV₁/FVC ratios among never-smoking participants with never-reported asthma. Binary logistic regression analyses tested for interactions between asthma phenotype and pack-years smoking for persistent airflow limitation at age 38. Subsequent analyses using this outcome were performed for each asthma phenotype separately.

Analyses used all available data with the exception that pregnant women were excluded. One participant with extreme values for percentage predicted lung function caused by developmental abnormalities was also excluded. Analyses used Stata 13 (College Station, TX) and two-sided *P* less than 0.05 was considered statistically significant.

Results

Asthma in childhood did not influence subsequent smoking history: the proportion of ever-smokers by age 38 was 50.9% among those with childhood asthma and 50.8% in the other participants (chi-square test, *P* = 0.991). The proportions of current smokers at age 38 were 28.8% and 25.4% (*P* = 0.418), and among those who had ever smoked, the median total pack-years smoking by age 38 were 11.5 and 10.6, respectively (Wilcoxon-Mann-Whitney test, *P* = 0.932). There were also no significant differences in the proportions of current smokers at each age, ever-smokers by age 38, median pack-years smoking history, proportion of smokers who quit between ages 18 and 38, or history of parental smoking among the four different asthma phenotypes (Table 1). Among those who did not report childhood asthma, cumulative smoking was associated with a higher risk of reporting asthma at ages 32 or 38 years (odds ratio, 1.30; 95% confidence interval [CI], 1.03–1.65 for each 10 pack-years; *P* = 0.028). For those with childhood asthma, there was no

association between cumulative smoking and persistence of asthma in adulthood (odds ratio, 0.91; 95% CI, 0.57–1.45; *P* = 0.687).

Mean FEV₁/FVC ratios and percent predicted FEV₁ values between ages 9 and 13 were lowest in those with childhood-persistent asthma but were also low in those who were to develop late-onset asthma compared with those who never reported asthma (Table 2, Figure 1). At age 38 years, prebronchodilator and post-bronchodilator FEV₁ and FEV₁/FVC values were lowest in those with childhood-persistent asthma and were also lower among those with late-onset persistent asthma. Those who had a history of asthma in remission had lower prebronchodilator FEV₁ values at age 38 compared with never asthma, but post-bronchodilator values and FEV₁/FVC ratios were not significantly different. There were no differences in mean percent predicted FVC values between the asthma phenotypes at either ages 9 to 13 or age 38 years.

Associations between Smoking and Prebronchodilator Spirometry

Across the entire cohort, from the generalized estimating equation models, cumulative smoking was associated with lower prebronchodilator FEV₁/FVC ratios (−1.4% [95% CI, −1.7 to −1.1] for each 10 pack-years; *P* < 0.001), lower FEV₁ values (−1.6% predicted [95% CI, −2.2 to −1.1] for each 10 pack-years; *P* < 0.001), but not with FVC values (0.4% predicted [95% CI, −0.1 to 0.9] for each 10 pack-years; *P* = 0.163). There was a statistically significant interaction between cumulative smoking history and asthma phenotype group for prebronchodilator FEV₁/FVC ratios (*P* = 0.009). Pairwise comparisons indicated that cumulative smoking had a smaller effect on prebronchodilator FEV₁/FVC ratios in those with childhood-persistent asthma compared with those with no asthma history (interaction *P* = 0.001). There were no significant interactions between the other phenotypes and cumulative smoking (all *P* values > 0.1). Analyzing each phenotype separately, cumulative smoking was associated with lower prebronchodilator FEV₁/FVC ratios among those who had no history of asthma, late-onset persistent asthma, and among those with asthma in remission, but not among those with childhood-persistent asthma (Table 3). There were no significant interactions between

asthma phenotype and cumulative smoking for percent predicted FEV₁ or FVC values.

Mean FEV₁/FVC ratios at each age for nonsmokers, moderate smokers (<10 pack-years by age 38), and heavy smokers (≥10 pack-years by age 38) among each asthma phenotype are shown in Figure 1. Scatterplots in Figure 2 show changes in the FEV₁/FVC ratios from the mean ratio at ages 9, 11, and 13 to age 38 for each asthma phenotype according to cumulative pack-years smoking. Cumulative smoking history was associated with a greater decline in FEV₁/FVC ratios to age 38 among all phenotypes except those with childhood-persistent asthma.

Associations between Smoking and Post-bronchodilator Spirometry

Cumulative smoking was also associated with lower post-bronchodilator FEV₁/FVC ratios (−1.4% [95% CI, −1.7 to −1.1] for each 10 pack-years; *P* < 0.001) and lower FEV₁ values (−1.8% predicted [95% CI, −2.3 to −1.1] for each 10 pack-years; *P* < 0.001), but not with FVC values (0.1% predicted [95% CI, −0.4 to 0.7] for each 10 pack-years; *P* = 0.643) across the cohort. There were no significant interactions between cumulative smoking and childhood-persistent asthma for any of the post-bronchodilator spirometry measures (all *P* values > 0.2) (Table 4). However, when groups were analyzed separately, cumulative smoking was associated with lower post-bronchodilator FEV₁/FVC values among all phenotype groups except for those with childhood-persistent asthma (Table 4).

Additional adjustment for parental smoking in childhood and adult exposure to environmental tobacco smoke at home or work made no material difference to the analyses. Neither exposure was significantly associated with the spirometry measures with the exception that adult environmental tobacco smoke was associated with lower prebronchodilator FEV₁ (*P* = 0.042) and a tendency to lower post-bronchodilator FEV₁ values (*P* = 0.085). Inhaled corticosteroid use in adulthood was reported by 56 of 91 (62%) of those with childhood-persistent asthma. There were no statistically significant interactions between inhaled corticosteroid use and smoking for any spirometry measure (all *P* values > 0.1). Restricting the analyses to those who did not use inhaled corticosteroids provided similar findings to the whole group (results not shown).

Table 1. Cigarette Smoking and Environmental Tobacco Smoke Exposure among Asthma Phenotypes

	n	No Asthma (n = 572)	Asthma in Remission (n = 85)	Late-Onset Asthma (n = 92)	Childhood-Persistent Asthma (n = 91)	P Value
Male	841	304/572 (53%)	37/85 (44%)	37/92 (40%)	60/91 (66%)	0.002
Either parent smoked (age 7–13)	840	363/572 (63%)	50/85 (59%)	63/92 (68%)	59/91 (65%)	0.605
Smokers at age 15	814	82/554 (15%)	11/82 (13%)	17/91 (19%)	17/87 (20%)	0.523
Smokers at age 18	757	162/509 (32%)	25/79 (32%)	32/82 (39%)	27/87 (31%)	0.613
Smokers at age 21	805	188/542 (35%)	32/82 (39%)	42/91 (46%)	34/90 (38%)	0.197
Smokers at age 26	825	188/560 (34%)	34/85 (40%)	41/90 (46%)	31/90 (34%)	0.129
Smokers at age 32	833	187/556 (33%)	32/85 (38%)	43/92 (47%)	29/90 (32%)	0.069
Smokers at age 38	821	135/561 (24%)	21/82 (26%)	31/89 (35%)	26/89 (29%)	0.158
Ever-smokers by age 38	819	275/560 (49%)	43/81 (53%)	53/89 (60%)	46/89 (52%)	0.313
Median (25th–75th percentile) pack-years by age 38	417*	10.6 (4.4–17.3)	11.0 (5.0–17.7)	14.7 (4.9–21.0)	9.8 (3.8–17.2)	0.585
Smokers who quit between age 18 and 38	239†	65/157 (41%)	11/25 (44%)	11/30 (37%)	11/27 (41%)	0.953
Adult environmental smoke exposure	840	523/572 (91%)	78/85 (92%)	86/92 (93%)	85/91 (93%)	0.860

Smokers at each age are those who report smoking at least once a day for at least 1 month in the previous year. *P* values are from chi-square tests for categorical variables and Kruskal–Wallis tests for median pack-years.

Numbers in each row vary because of incomplete data, with the following exceptions:

*Analyses restricted to ever-smokers by age 38.

†Analyses restricted to smokers at age 18.

The prevalence of persistent airflow obstruction among each phenotype for those who smoked more or less than 10 pack-years by age 38 is shown in Table 5. There was a statistically significant interaction between cumulative smoking and asthma phenotype for the prevalence of persistent airflow obstruction at age 38

(post-bronchodilator FEV₁/FVC ratio below the lower limit of normal; *P* = 0.004). Odds ratios for persistent airflow obstruction associated with cumulative smoking among each phenotype are shown in Table 6. In contrast with the other phenotypes, smoking was not associated with an

increased risk of airflow obstruction among those with childhood-persistent asthma. Repeating these analyses using the Global Initiative for Chronic Obstructive Lung Disease criterion of a post-bronchodilator FEV₁/FVC ratio less than 70% to define persistent airflow obstruction also provided a significant

Table 2. Spirometry among Asthma Phenotypes

	Total (n = 840)	No Asthma (n = 572)	Asthma in Remission (n = 85)	Late-Onset Asthma (n = 92)	Childhood- Persistent Asthma (n = 91)	P Value
Spirometry at ages 9–13 yr						
Mean FEV ₁ , % predicted	834	103.1	100.9	99.3*	94.8*†‡	<0.001
Mean FVC, % predicted	834	102.1	101.6	100.1	102.9	0.432
Mean FEV ₁ /FVC, %	837	89.1	88.0*	87.8*	81.3*†‡	<0.001
Prebronchodilator spirometry at age 38 yr						
FEV ₁ , % predicted	800	99.5	96.7	94.5*	89.6*†‡	<0.001
FVC, % predicted	800	104.4	102.8	102.6	103.6	0.328
FEV ₁ /FVC, %	800	77.3	76.5	74.9*	69.6*†‡	<0.001
Post-bronchodilator spirometry at age 38 yr						
FEV ₁ , % predicted	786	103.2	101.0	98.6*	95.8*†	<0.001
FVC, % predicted	786	103.3	102.2	101.6	104.9	0.219
FEV ₁ /FVC at age 38, %	786	81.0	80.4	79.0*	73.7*†‡	<0.001
COPD at age 38 yr						
FEV ₁ /FVC <LLN	786	49/538 (9%)	5/76 (7%)	16/86 (19%)*†	30/86 (35%)*†‡	<0.001
FEV ₁ /FVC <70%	786	23/538 (4%)	4/76 (5%)	6/86 (7%)	25/86 (29%)*†‡	<0.001

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; LLN = lower limit of normal defined as the sex-specific fifth percentile among never-smoking participants in the no asthma phenotype.

Numbers in each row vary because of incomplete data or pregnancy at age 38. *P* values are from overall tests of differences between groups using sex-adjusted Wald tests for continuous variables and sex-adjusted logistic regression for categorical variables.

*Values are significantly different from the no asthma phenotype (*P* < 0.05).

†Values are significantly different from the asthma in remission phenotype (*P* < 0.05).

‡Values are significantly different from the late-onset asthma phenotype (*P* < 0.05).

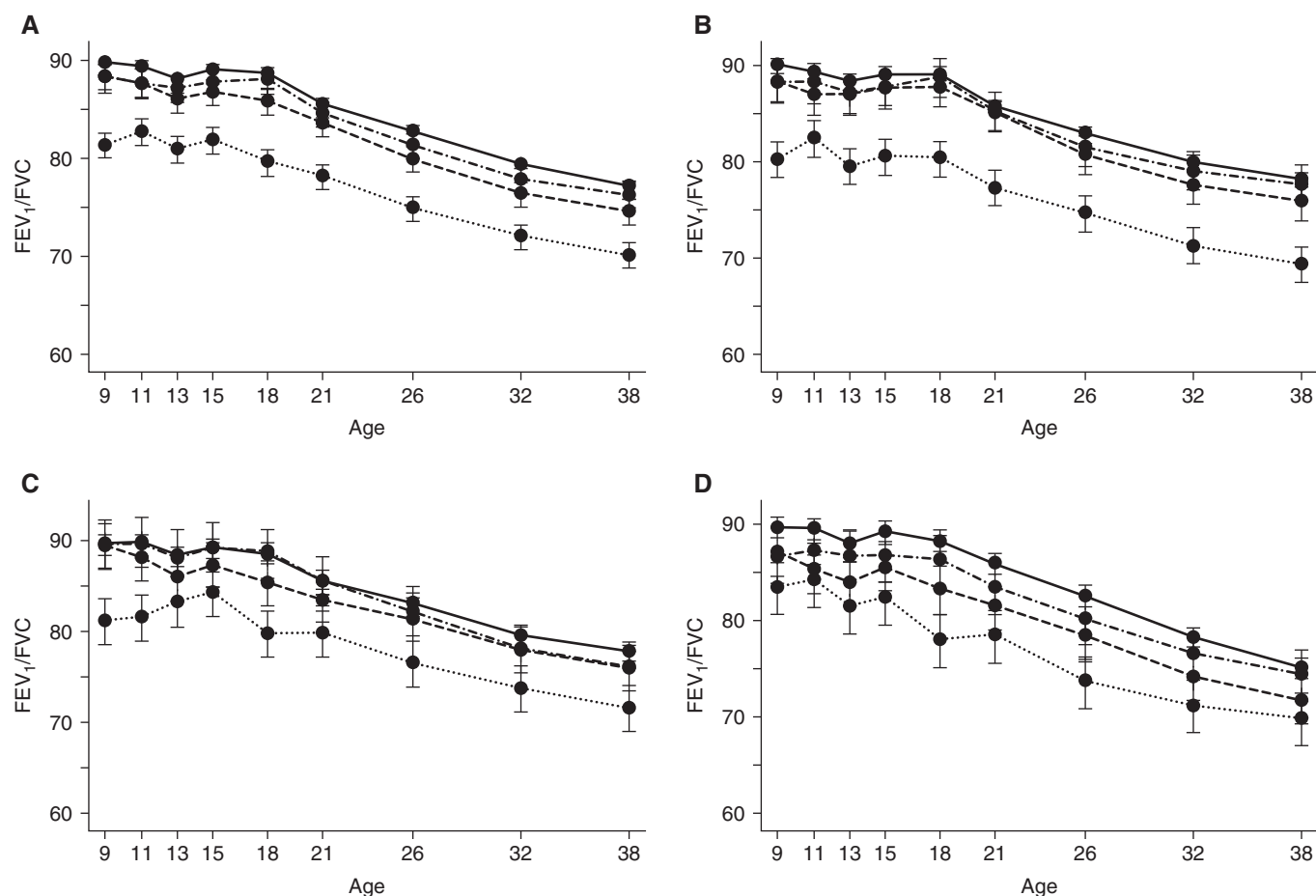


Figure 1. Mean prebronchodilator FEV₁/FVC ratios at each age from 9 to 38: (A) all participants, (B) nonsmokers, (C) light-to-moderate smokers (<10 pack-years), and (D) heavy smokers (≥10 pack-years). *Solid lines* indicate participants never diagnosed with asthma, *dashed lines* indicate those with late-onset asthma, *alternating dash and dot lines* indicate those in remission, and *dotted lines* indicate those with persistent asthma.

interaction ($P = 0.025$) and similar findings for each phenotype (Table 6) (2). Mean prebronchodilator and post-bronchodilator FEV₁/FVC ratios for those who smoked more or less than 10 pack-years among each phenotype at age 38 are shown in Figure 3.

Discussion

In this population-based cohort we confirmed that both childhood-persistent asthma and tobacco smoking were associated with lower FEV₁/FVC ratios indicating the development of airflow obstruction. However, we found no

evidence that smoking had a greater effect on airflow obstruction among those with childhood-persistent asthma. Contrary to our hypothesis that those with childhood-onset persistent asthma would be more vulnerable to the effects of smoking, we found that association between smoking and airflow obstruction was weaker among

Table 3. Associations between Cumulative Smoking and Prebronchodilator Spirometry at Ages 18, 21, 26, 32, and 38 Years

Phenotype	n	FEV ₁ % Predicted			FVC % Predicted			FEV ₁ /FVC Ratio (%)		
		Coef	95% CI	P Value	Coef	95% CI	P Value	Coef	95% CI	P Value
No asthma	566	−1.91	−2.54 to −1.28	<0.001	0.50	−0.12 to 1.12	0.114	−1.62	−1.96 to −1.29	<0.001
Remission	85	−1.69	−3.38 to 0.01	0.052	0.55	−1.05 to 2.15	0.503	−1.54	−2.45 to −0.63	0.001
Late-onset	92	−0.82	−2.43 to 0.80	0.322	0.30	−1.17 to 1.78	0.688	−1.08	−2.12 to −0.05	0.040
Childhood-persistent	91	−1.33	−3.70 to 1.04	0.273	−0.60	−2.58 to 1.38	0.554	−0.50	−1.86 to 0.86	0.467

Definition of abbreviation: CI = confidence interval; Coef = coefficient.

Analyses using generalized estimating equations to implement linear regression models. Coefficients represent the differences in the percent predicted FEV₁ and FVC and the FEV₁/FVC ratio associated with 10 pack-years cumulative smoking. Analyses adjust for the mean percent predicted prebronchodilator FEV₁ and FVC or FEV₁/FVC ratio at ages 9, 11, and 13; age; body mass index; and sex.

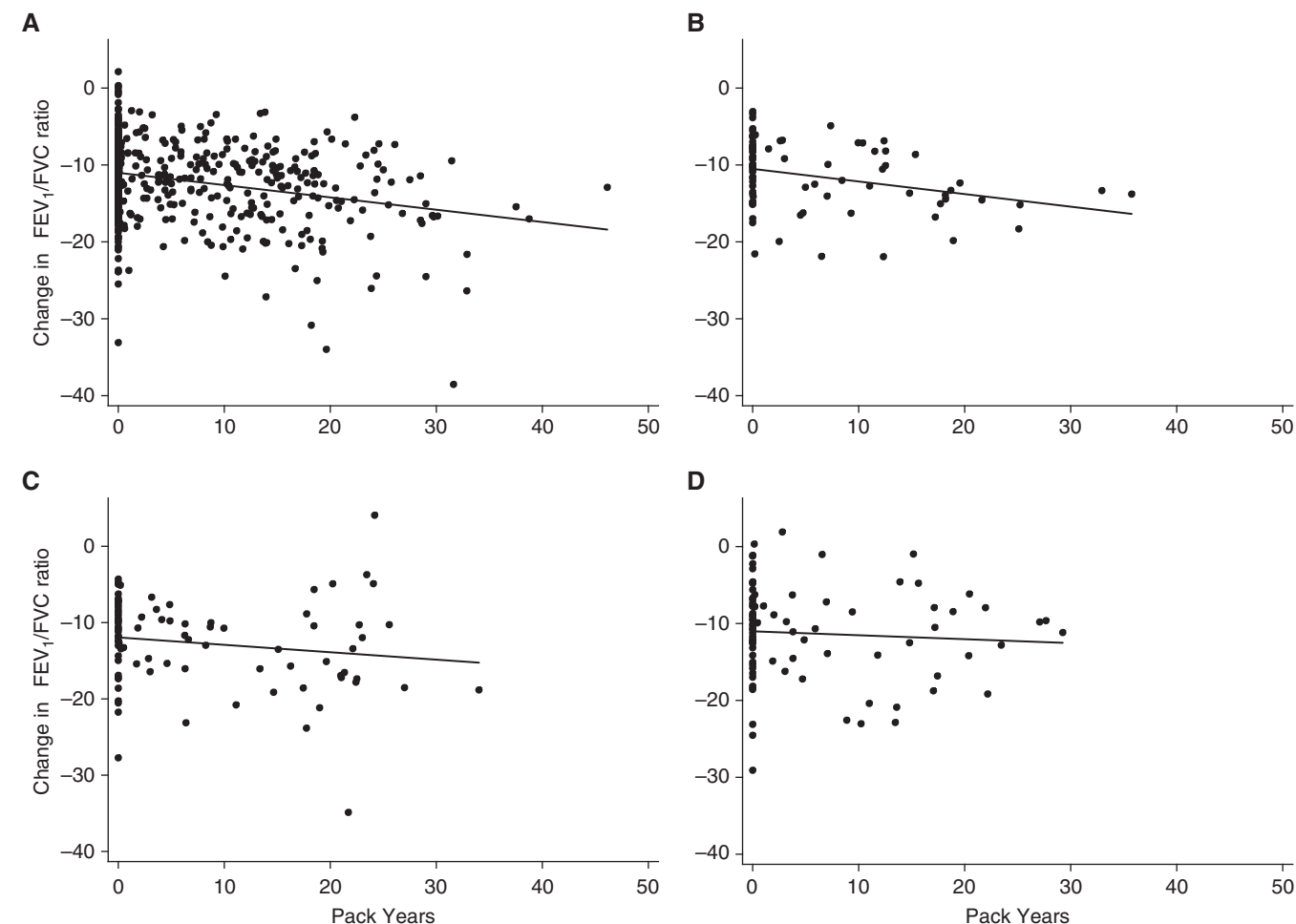


Figure 2. Scatterplots of the change in FEV₁/FVC ratios from ages 9 to 13 to age 38 against cumulative pack-years smoking up to age 38 for each phenotype with fitted linear regression lines. The coefficients of the regression lines associated with each 10 pack-years are (A) no asthma coefficient = -1.68 , $P < 0.001$; (B) remission coefficient = -1.62 , $P = 0.003$; (C) late-onset coefficient = -1.22 , $P = 0.058$; (D) childhood-persistent coefficient = -0.42 , $P = 0.610$.

those with childhood-persistent asthma than participants without asthma.

The lack of association between smoking and airflow obstruction among those with childhood-onset persistent asthma was evident for both

prebronchodilator and post-bronchodilator spirometry. For prebronchodilator FEV₁/FVC there was a statistically significant interaction between cumulative smoking and asthma phenotype suggesting that the effects of smoking differ between

asthma phenotypes. There was also a statistically significant interaction between smoking and asthma phenotype for persistent airflow limitation at age 38: whereas smoking was associated with persistent airflow limitation among other

Table 4. Associations between Cumulative Smoking and Post-Bronchodilator Spirometry at Ages 18, 26, 32, and 38 Years

Phenotype	n	FEV ₁ % Predicted			FVC % Predicted			FEV ₁ /FVC Ratio (%)		
		Coef	95% CI	P Value	Coef	95% CI	P Value	Coef	95% CI	P Value
No asthma	560	-1.74	-2.43 to -1.04	<0.001	0.25	-0.43 to 0.93	0.476	-1.36	-1.70 to -1.02	<0.001
Remission	85	-2.55	-4.35 to -0.76	0.005	-0.21	-1.93 to 1.52	0.815	-1.76	-2.69 to -0.84	<0.001
Late-onset	92	-1.56	-3.24 to 0.11	0.068	0.18	-1.35 to 1.71	0.819	-1.39	-2.31 to -0.48	0.003
Childhood-persistent	91	-1.52	-3.71 to 0.68	0.176	-0.59	-2.46 to 1.28	0.536	-0.81	-1.94 to 0.32	0.162

Definition of abbreviation: CI = confidence interval; Coef = coefficient.
Analyses using generalized estimating equations to implement linear regression models. Coefficients represent the differences in the percent predicted post-bronchodilator FEV₁ and FVC and the FEV₁/FVC ratio associated with 10 pack-years cumulative smoking. Analyses adjust for the mean percent predicted prebronchodilator FEV₁ and FVC or FEV₁/FVC ratio between ages 9 and 13, age, body mass index, and sex.

Table 5. Persistent Airflow Obstruction among Smokers in Each Asthma Phenotype Group

	Never-Smokers [n/n (%)]	<10 Pack-Years [n/n (%)]	≥10 Pack-Years [n/n (%)]	P Value
No asthma	15/271 (6)	13/124 (10)	21/142 (15)	0.006
Remission	0/36 (0)	1/17 (6)	4/22 (18)	0.017
Late-onset	5/35 (14)	2/24 (8)	9/27 (33)	0.069
Child-persistent	17/42 (40)	7/22 (32)	6/22 (27)	0.585

Prevalence of post-bronchodilator FEV₁/FVC ratios below the lower limit of normal at age 38 years among each asthma phenotype according to cumulative smoking history. n/n values represent the number of participants with chronic airflow obstruction and the total number in each group. P values from Fisher exact test.

groups, it was not associated with persistent airflow limitation among those childhood-persistent asthma (Tables 5 and 6, Figure 3). This was found using either a post-bronchodilator FEV₁/FVC ratio below the lower limit of normal or the Global Initiative for Chronic Obstructive Lung Disease criterion to define persistent airflow limitation.

It is notable that those with childhood-persistent asthma had lower mean FEV₁/FVC ratios than all other groups and more than a third had post-bronchodilator FEV₁/FVC ratios below the lower limit of normal by age 38 (Table 5). This confirms other reports that early onset asthma is a strong risk factor for developing chronic obstructive pulmonary disease (1, 3, 4). However, although many of this group of subjects with asthma had airflow obstruction, this was not worse among smokers. The analyses adjusted for the FEV₁/FVC ratios between ages 9 and 13 indicating that this lack of association is unlikely to be explained by early differences in lung function. There was no evidence that having childhood asthma made any difference to subsequent smoking behavior suggesting that the lack of association

between smoking and airflow obstruction in this group was not caused by reduced smoking exposure. We also found no evidence that the effects of smoking on airway obstruction were modified by inhaled corticosteroid treatment among those with childhood-persistent asthma.

The FEV₁/FVC ratio is the preferred measure of airway obstruction because it is largely independent of height, sex, and body habitus, and less dependent on age than absolute measures, such as FEV₁. As expected, smoking was associated with significantly lower FEV₁ values but these associations did not significantly differ between asthma phenotypes. There were no significant associations between smoking and FVC values in any of the asthma phenotypes.

Our findings contrast with several cohort studies of adults, which have reported an enhanced decline in lung function among smokers with asthma, although in most of these studies the effects of asthma and smoking have been additive rather than synergistic. An apparent enhanced decline in lung function among smokers with adult asthma in these studies could be explained by reverse causation.

Smoking is associated with incident asthma in adolescence and adulthood (26–28). A *post hoc* analysis of smokers with late-onset asthma found that most reported starting smoking (median age, 18) before the first report of a diagnosis of asthma (median age, 26) ($P < 0.001$). We also found that those reporting late-onset asthma had higher cumulative smoking histories than the other asthma phenotypes. This suggests that late-onset asthma symptoms may have been caused by smoking in some cases. It is likely that people who develop symptoms after starting to smoke are more susceptible to the adverse effects of smoking on the airways and, hence, adult cohorts may find that smoking is associated with a greater lung function decline among those with adult-onset asthma.

In keeping with this, Aanerud and coworkers (10) found that an enhanced decline in lung function among smokers with asthma was only found for those who reported late-onset asthma. The Melbourne Asthma Cohort also found that smoking did not enhance the decline in lung function among those with childhood-persistent asthma followed to age 50, but did not have sufficient power to evaluate interactions between asthma and smoking (29). The Tucson Epidemiological Study of Airway Obstructive Disease found that smoking was a much stronger risk factor for developing persistent airflow limitation among those with asthma onset after age 25 years than among those who had earlier onset asthma (30). However, as far as we are aware, the Tasmanian Longitudinal Health Study is the only other study to specifically test interactions between smoking and asthma using prospectively collected data from childhood to adulthood (13). Those with current asthma at age 45 had had a greater decline in

Table 6. Cumulative Smoking and Chronic Airflow Limitation among Asthma Phenotype Groups

	n	Lower Limit of Normal			GOLD Criterion		
		Odds Ratio	95% CI	P Value	Odds Ratio	95% CI	P Value
No asthma	537	1.75	1.31–2.33	<0.001	1.79	1.22–2.63	0.003
Remission	75	2.39	1.02–5.62	0.046	2.12	0.84–5.35	0.111
Late-onset	86	1.94	1.11–3.39	0.019	3.08	1.23–7.71	0.016
Child-persistent	86	0.66	0.36–1.22	0.185	0.78	0.42–1.45	0.435

Definition of abbreviations: CI = confidence interval; GOLD = Global Initiative for Chronic Obstructive Lung Disease.

Binary logistic regression analyses of post-bronchodilator FEV₁/FVC ratios below the lower limit of normal or meeting the GOLD criterion of FEV₁/FVC less than 0.7 at age 38 years among each asthma phenotype according to cumulative smoking history. Analyses adjust for sex. Odds ratios represent the odds of chronic airflow limitation associated with each 10 pack-years smoked to age 38 years. See text for definition of lower limit of normal.

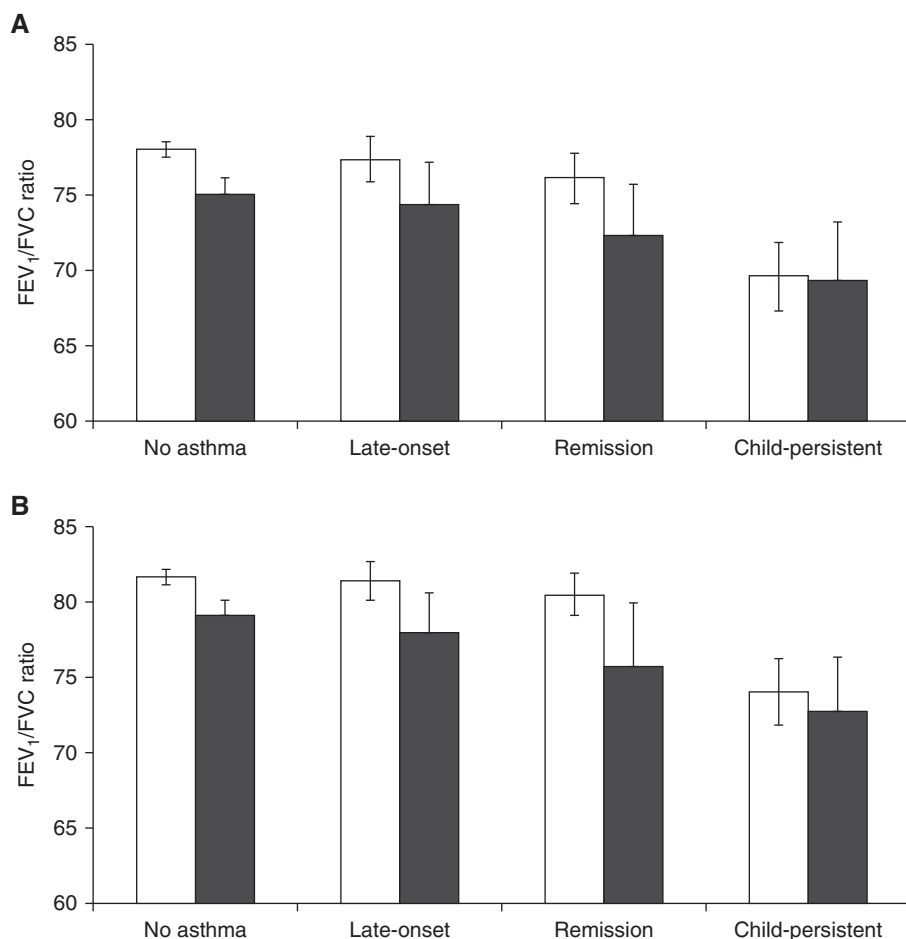


Figure 3. (A) Mean prebronchodilator ratios at age 38 for those who had smoked less than or greater than 10 pack-years among each asthma phenotype. (B) Mean post-bronchodilator ratios at age 38 for those who had smoked less than or greater than 10 pack-years among each asthma phenotype. Error bars show 95% confidence intervals.

post-bronchodilator lung function if they smoked, and the combined effects of smoking and current adult asthma on post-bronchodilator airflow at age 45 were greater than the sum of the individual effects suggesting a synergistic interaction. This interaction included participants with both childhood-onset and late-onset asthma. Another difference in study design is that they preferentially selected those reporting asthma or symptoms of bronchitis in adulthood. These participants may have been more susceptible to the effects of smoking on the airways.

Our findings suggest that people with childhood-onset asthma that persists to adulthood are either less vulnerable to the airway effects of smoking, or that there is already substantial airway damage from asthma making further worsening less evident. Although both asthma and smoking cause airflow obstruction, their airway

inflammatory effects differ. Smoking is reported to modify the inflammatory profile in asthma leading to lower levels of eosinophilic airway inflammation and exhaled nitric oxide, but higher levels of sputum neutrophils (31–34). We have previously shown that participants in this cohort who smoke are less likely to develop atopy during adolescence and early adulthood (20). Hence it is possible that smoking reduces asthmatic and atopic airway inflammation while inducing a nonatopic inflammatory response with little overall net difference in effect on airway caliber. Aanerud and coworkers (10) found that smoking only increased the risk of airflow obstruction among participants reporting early onset asthma who were not atopic (10). This contrasts with the Tasmanian Longitudinal Health Study which reported a three-way asthma-smoking-atopy interaction: smoking only

enhanced the risk of airflow obstruction among subjects with asthma with atopy (13). We could not evaluate this in the Dunedin cohort because nearly all (94%) of those with childhood-persistent asthma were atopic on skin prick testing at age 32 leaving too few study members to statistically examine the effect of smoking on those without atopy.

The Dunedin study has the advantages of high rates of participation at both the childhood and adult assessments, and prospectively collected data at multiple assessments throughout the life-course minimizing recall bias. Because participants were the same age at each assessment, potential confounding by age has been avoided. Limitations include parent- and self-reports of childhood and adult asthma diagnoses, respectively. Because childhood asthma diagnoses were assessed before participants started smoking, it is highly unlikely that this introduced bias. We used an arbitrary cutoff at age 13 years to distinguish between childhood-onset and late-onset asthma, which is similar to the age cutoff used in other studies (35). Another limitation is that the cohort has, to date, only been followed to age 38. Although this has been sufficient to demonstrate significant effects of smoking on airway obstruction in the other groups, it is possible that the effects of tobacco smoking will become more apparent in those with childhood-persistent asthma later in adult life. It is also important to note that the apparent lack of effect of cigarette smoking on airway obstruction among those with childhood asthma does not mean that these people will not be vulnerable to the many other harmful effects of smoking.

In summary, in this population-based cohort followed to age 38 years, there was no evidence that active cigarette smoking enhanced the impairment of airway function among those with childhood-onset persistent asthma. These findings indicate that synergistic interactions between smoking and asthma are unlikely to explain individual differences in the risk of developing chronic airflow obstruction among smokers. ■

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