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Smoking and lung function among adults with newly onset asthma

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ABSTRACT

Introduction Smoking increases the risk of asthma and reduces lung function among subjects with and without asthma. We assessed the effects of smoking on lung function reflecting both central and small airways among adults with newly onset asthma.

Methods In a population-based study, 521 (response rate 86%) working-aged adults with clinically defined newly diagnosed asthma answered a questionnaire on personal smoking and other factors potentially influencing lung function, and performed spirometry. We applied multiple linear regression analysis to estimate the relations between smoking and lung function adjusting for confounding.

Results Among asthmatics, FEV_1 level was reduced significantly, on average 208 mL, related to regular smoking (adjusted effect estimate −0.208, 95% CI −0.355 to −0.061) and 245 mL in relation to former smoking, that is, among those who quit less than a year ago (−0.245, 95% CI −0.485 to −0.004). In contrast, FEV_1 was not significantly related to occasional smoking or former smoking among those who quit over a year ago. Forced expiratory flow (FEF) levels (L/s) were also significantly reduced among regular smokers ($FEF_{25–75\%}$: −0.372, 95% CI −0.607 to −0.137; $FEF_{50\%}$: −0.476, 95% CI −0.750 to −0.202). An exposure–response pattern related to both daily smoking rate and lifetime cumulative smoking was seen both among men and women.

Conclusions This study provides new evidence that among working-aged adults with new asthma, regular smoking and former smoking reduce lung function levels with a dose–response pattern. The lung function parameters applied as outcomes reflect both larger and smaller airways.

Key messages

- This study aims to assess the effects of smoking on pre-bronchodilator and post-bronchodilator lung function measures that reflect both larger and smaller airways in adults with newly onset asthma.
- Among adults with newly onset asthma, lung function measures (FEV_1, $FEF_{25–75\%}$) were significantly reduced in current regular smokers and in recent former smokers (ie, quit less than a year ago) when compared with never smokers; furthermore, dose–response patterns were found between daily smoking rate or life-time cumulative smoking and lung function measures.
- This study is the first to clarify the effects of smoking on smaller airways lung function, measured as forced expiratory flows, in a larger sample of patients with adult-onset asthma, and to provide effect estimates for lung function parameters measured both prior to and after the bronchodilation test.

INTRODUCTION

Smoking is a major determinant of morbidity and mortality worldwide. It causes many chronic diseases, including coronary heart disease and chronic obstructive pulmonary disease (COPD). Tobacco smoke is a mixture of 4000 different compounds, many of which are carcinogenic or irritative.[1] Cigarette smoking is still increasing in many low-income, middle-income and even high-income countries, especially among women.[2]

Jayes and colleagues summarised recently the evidence of the effect of smoking on the development of asthma among adults.[3] The summary-effect estimate, based on eight studies published from 1985 to 2013, was 1.61 (95% CI 1.07 to 2.42). In our population-based incident case–control study of adult-onset asthma, the risk of developing asthma was significantly higher among current smokers, with an adjusted OR of 1.33 (95% CI 1.00 to 1.77), and among ex-smokers, with an adjusted OR of 1.49 (1.12 to 1.97) compared with never-smokers.[4] Among current smokers, the risk increased up to 14 cigarettes per day, and a similar trend was observed in relation to cumulative smoking. Asthma is among the most common chronic diseases in working-aged adults. Thus, it would be important to address whether smoking has adverse effects on lung function in adults with asthma. In our systematic search, one previous study had addressed the relation between smoking and lung function in asthmatic adults. Little is known about the effects of tobacco smoke on small airways, especially among smokers with adult-onset asthma.

We assessed the relations between current, former and life-time cumulative smoking and

lung function among adults with newly onset asthma. In addition to basic forced expiratory volumes (FEV_1 and FVC), our lung function outcomes of interest included also mean forced expiratory flow between 25% and 75% of FVC ($FEF_{25–75\%}$) and forced expiratory flow at 50% of FVC ($FEF_{50\%}$), as estimates of small airways function.

METHODS

Study design

This is a cross-sectional study based on a population-based case–control study of incident asthma, the Finnish Environment and Asthma Study (FEAS).[4–13] The study population for this substudy included 521 working-aged adults with newly onset asthma. The ethics committees of the Finnish Institute of Occupational Health and Tampere University Hospital approved the study.

Definition and recruitment of asthma cases

The new cases of asthma were recruited at all healthcare facilities diagnosing asthma in the study area, that is, Pirkanmaa District, including the university hospital clinic, offices of the private-practising pulmonary physicians and public healthcare centres. In addition, the National Social Insurance Institution of Finland invited to participate all patients who had received reimbursement rights for asthma medication in this area during the study period and who had not yet participated. The following diagnostic criteria for asthma were applied for all participants: (1) presence of at least one asthmatic symptom (cough, phlegm production, wheezing and/or breathlessness) and (2) demonstration of reversibility in airways obstruction in lung function investigations.[5] These criteria were compatible with the Finnish criteria required for the diagnosis of asthma at the time of the study.[14] We confirmed the date and criteria of the asthma diagnosis for all subjects from their medical records. In addition, we also checked that they did not have any previous asthma diagnosis or long-term use of asthma medications, as our interest was in adult-onset asthma. Eligible subjects were asked to sign an informed consent. Altogether, 521 subjects (response rate 86%) had verified asthma, and 486 of these had both spirometry and complete questionnaire information on exposures, and they formed the present study population.

Smoking information

Information on smoking was collected with a self-administered questionnaire inquiring about current and former smoking, smoking rate, and duration and quitting of smoking. The following questions were inquired: Do you smoke currently? (yes, regularly; yes, occasionally; no, I quit less than 12 months ago; no, I quit over 12 months ago; no, I never smoked regularly); How many years have you smoked?; How much do you/did you smoke on average? (cigarettes, cigars and pipefuls per day, or per week for occasional smokers).

Measurement methods

Questionnaire

The self-administered questionnaire has been described in detail elsewhere.[4–13]

Lung function measurements

We applied the same lung function protocol to all patients with suspected asthma, including baseline spirometry with a bronchodilation test and 2 weeks of peak expiratory flow follow-up with morning and evening measurements.[4–13] Spirometry was recorded before and after bronchodilating medication with a pneumotachograph-type disposable flow transducer connected to a computer (Medikro 905; Medikro, Kuopio, Finland). Measurements were conducted according to the standards of the American Thoracic Society[15] at the time of the study. We judged potential presence of obstruction using the reference values derived from the Finnish source population, as described elsewhere.[16]

Statistical methods

Our outcomes of interest were lung functions of (1) larger airways, measured as FEV_1 and FVC, and (2) smaller airways, measured as mean forced expiratory flow between 25% and 75% of FVC ($FEF_{25–75\%}$) and forced expiratory flow at 50% of FVC ($FEF_{50\%}$). These were measured before and after the bronchodilation test. We applied multiple linear regression to estimate the relations between the current and previous smoking and cumulative smoking and the average lung function levels. First, we adjusted for the three core covariates: age, sex and height. We built the full model by adding into the model also exposure to dampness and moulds, exposure to secondhand smoking and education as an indicator of socioeconomic status, in addition to the three core covariates mentioned before. We have previously described variables dampness and moulds[5 17] and secondhand smoking in detail.[8] We fitted a model with occasional and regular smoking and previous smoking quit recently and earlier. We also fitted a model with both current smoking rate and cumulative lifetime smoking. In both analyses, the reference category for the current analyses consisted of never-smokers with adult-onset asthma. We estimated the relations of interest separately for men and women.

RESULTS

Characteristics of the study population and exposures

Characteristics of the study population including smoking behaviour are presented in table 1. A total of 27.6% of the study subjects were current smokers, 5.8% occasional smokers and 25.5% ex-smokers. Among ex-smokers, 6.2% had quit smoking less than 12 months ago. We used post-bronchodilator spirometry values (FEV_1:FVC<0.7) to define airflow obstruction. Among the 390 subjects who underwent post-bronchodilator spirometry, the prevalence of airflow obstruction was 19.2%, 27.0% in men and 15.0% in women.

Table 1 Characteristics of the study population, the Finnish Environment and Asthma Study subjects with adult-onset asthma 1997–2000

	Men (n=167)		Women (n=319)		Total (n=486)	
Characteristic	**n**	**%**	**n**	**%**	**n**	**%**
Age, years						
21–29	36	21.6	64	20.1	100	20.6
30–39	40	24.0	61	19.1	101	20.8
40–49	37	22.2	81	25.4	118	24.3
50–59	39	23.4	89	27.9	128	26.3
60–64	15	9.0	24	7.5	39	8.0
Education						
No vocational schooling	36	21.6	65	20.4	101	20.8
Vocational course	22	13.2	61	19.1	83	17.1
Vocational institution	61	36.5	78	24.5	139	28.6
College-level education	29	17.4	73	22.9	102	21.0
University or corresponding	19	11.4	42	13.2	61	12.6
Smoking*						
Never	53	31.7	172	53.9	225	46.3
Former	61	36.5	63	19.8	124	25.5
Quit smoke >12 months	48	28.7	46	14.4	94	19.3
Quit smoke <12 months	13	7.8	17	5.3	30	6.2
Current	52	31.1	82	25.7	134	27.6
Occasional	8	4.8	20	6.3	28	5.8
Regular	44	26.4	62	19.4	106	21.8
Smoking rate for regular smokers (cigarettes per day)†						
1–14	14	31.8	38	61.3	52	49.1
≥15	30	68.2	22	35.5	52	49.1
Cumulative smoking for regular smokers (cigarette-years)‡						
1–199	10	22.7	26	41.9	36	34.0
≥200	34	77.3	32	51.6	66	62.3

*Smoking status missing for 1 man and 2 women.
†Smoking rate missing for 2 women.
‡Cigarette-year missing for 4 women.

Smoking and lung function in larger airways

In the analyses adjusting for all covariates mentioned and including current regular, occasional and previous smoking, pre-bronchodilator FEV_1 level was reduced significantly, on average 208 mL, related to current regular smoking (effect estimate −0.208, 95% CI −0.355 to −0.061) and 245 mL in relation to former smoking quit less than a year ago (−0.245, 95% CI −0.485 to −0.004) (table 2). However, FEV_1 was not related to occasional smoking only or to former smoking when quit over a year ago. FEV_1:FVC ratio showed a similar pattern to that observed in FEV_1, with reduced levels related to regular and former smoking (table 2). The effect estimates related to current regular smoking were greater among men than among women. Among men, FEV_1 levels were on average 235 mL lower in current regular smokers compared with never smokers. Among women, such effect on was 151 mL. FEV_1:FVC was significantly reduced among both men and women smokers, while the differences in FVC levels were small. Online supplementary table 1 shows that the effect estimates for smoking based on post-bronchodilator lung function levels were slightly smaller for FEV_1, but larger for FEV_1:FVC compared with corresponding pre-bronchodilator effect estimates.

Table 3 elaborates potential dose–response patterns for the effects of smoking on larger airways lung function parameters. Both daily smoking rate and cumulative life-time smoking show dose–response effect estimates on FEV_1 and FEV_1:FVC. In the total

Table 2 Smoking and pre-bronchodilator FEV_1, FVC and FEV_1:FVC in working-age adults with newly diagnosed asthma, the Finnish Environment and Asthma Study 1997–2000

	Effect estimate, FEV_1, L		Effect estimate, FVC, L		Effect estimate, FEV_1:FVC	
Smoking	**β**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**
All*	n=480†		n=478‡		n=478§	
Never	Reference		Reference		Reference	
Quit >1 year ago	0.026	−0.127 to 0.178	0.056	−0.097 to 0.209	−0.007	−0.032 to 0.017
Quit <1 year ago	**−0.245**	**−0.485 to −0.004**	−0.065	−0.304 to 0.173	**−0.041**	**−0.079 to −0.002**
Occasional	−0.033	−0.277 to 0.211	−0.045	−0.287 to 0.197	0.010	−0.029 to 0.049
Regular	**−0.208**	**−0.355 to −0.061**	−0.055	−0.202 to 0.092	**−0.054**	**−0.077 to −0.030**
Men¶	n=166†		n=165‡		n=165§	
Never	Reference		Reference		Reference	
Quit >1 year ago	0.025	−0.297 to 0.346	−0.088	−0.381 to 0.205	0.016	−0.031 to 0.063
Quit <1 year ago	−0.428	−0.902 to 0.046	−0.207	−0.635 to 0.221	−0.063	−0.131 to 0.006
Occasional	0.033	−0.564 to 0.631	0.045	−0.495 to 0.585	−0.004	−0.090 to 0.083
Regular	−0.235	−0.568 to 0.098	−0.109	−0.410 to 0.192	**−0.051**	**−0.099 to −0.003**
Women¶	n=314†		n=313‡		n=313§	
Never	Reference		Reference		Reference	
Quit >1 year ago	0.025	−0.134 to 0.184	0.155	−0.022 to 0.332	−0.023	−0.053 to 0.007
Quit <1 year ago	−0.144	−0.394 to 0.105	−0.085	−0.363 to 0.192	−0.021	−0.067 to 0.026
Occasional	−0.018	−0.247 to 0.211	−0.104	−0.359 to 0.151	0.015	−0.028 to 0.058
Regular	**−0.151**	**−0.296 to −0.007**	0.002	−0.159 to 0.163	**−0.045**	**−0.072 to −0.018**

*Adjusted for sex, age, height, education, past 12 months secondhand smoking (SHS), lifetime cumulative SHS, and mould odour.
†Pre-bronchodilator FEV_1 is available for 486 participants (167 men and 319 women), of whom smoking status missing for 3 (1 man and 2 women) and height is missing for 3 women.
‡Pre-bronchodilator FVC is available for 484 participants (166 men and 318 women) of whom smoking status missing for 3 (1 man and 2 women) and height is missing for 3 women.
§Pre-bronchodilator FEV_1:FVC is available for 484 participants (166 men and 318 women) of whom smoking status missing for 3 (1 man and 2 women) and height is missing for 3.
¶Adjusted for age, height, education, past 12 months SHS, lifetime cumulative SHS and mould odour.

population, a significant reduction of 168 mL in FEV_1 and 3.9% in FEV_1:FVC was seen per smoking rate of 10 cigarettes per day. The effect estimates were somewhat larger among women than among men (FEV_1 133 mL vs 84 mL; FEV_1:FVC 4.0% vs 2.6%). The overall effects of cumulative smoking were 69 mL per 100 cigarette-years on FEV_1 and 1.5% on FEV_1:FVC. Again, larger effect estimates were detected among women (table 3). Online supplementary table 2 presents the dose-related effect estimates for post-bronchodilator lung function parameters, and these show a similar pattern of effects as described for pre-bronchodilator lung function values.

Smoking and lung function in smaller airways

Table 4 shows the effects of smoking on lung functions reflecting smaller airways, measured before and after the bronchodilation test. Pre-bronchodilator $FEF_{25–75\%}$ was reduced significantly, on average 372 mL/s (−0.372, −0.607 to −0.137), as was pre-bronchodilator $FEF_{50\%}$, on average 476 mL/s (−0.476, −0.750 to −0.202), in relation to regular smoking. The effects estimates were similar among both men and women, although they were statistically significant only among women, probably because they constituted a larger group. The effect estimates calculated for post-bronchodilator values were slightly greater.

There was a significant dose–response pattern between both daily smoking rate and cumulative smoking and $FEF_{25–75\%}$ and $FEF_{50\%}$, as shown in table 5. There was evidence of effect among both men and in women, but statistically significant effect estimates mainly in women only.

DISCUSSION

Our large population-based study included 521 adult-onset asthma cases who were recruited over a 2.5-year study period. A total of 486 of them had acceptable spirometry. This is the first study to address potential effects of active smoking on lung function among subjects with new adult-onset asthma. We estimated the effects of smoking on lung functions measured both

Table 3 Daily smoking rates and cumulative cigarette-years in regular smokers and pre-bronchodilator lung function of larger airways (FEV_1, FVC and FEV_1:FVC) in asthmatics, the Finnish Environment and Asthma Study 1997–2000

	FEV_1 (L)		FVC (L)		FEV_1:FVC	
	β	95% CI	β	95% CI	β	95% CI
All*						
Smoking rate	n=327†‡§		n=326‡§¶		n=326‡§**	
Never-smoker	Reference		Reference		Reference	
Regular smoker 1–14 cigarettes/day	−0.091	−0.274 to 0.092	0.003	−0.182 to 0.188	−0.026	−0.056 to 0.004
Regular smoker ≥15 cigarettes/day	**−0.348**	**−0.541 to −0.154**	−0.086	−0.281 to 0.110	**−0.084**	**−0.116 to −0.053**
Per 10 cigarettes/day	**−0.168**	**−0.256 to −0.080**	−0.047	−0.136 to 0.042	**−0.039**	**−0.053 to −0.025**
Cumulative smoking	n=325†§††		n=324§¶††		n=324§**††	
Regular smoker 1–199 cigarette-years	−0.050	−0.268 to 0.167	0.055	−0.165 to 0.274	−0.027	−0.063 to 0.008
Regular smoker ≥200 cigarette-years	**−0.319**	**−0.497 to −0.142**	−0.096	−0.275 to 0.084	**−0.072**	**−0.101 to −0.043**
Per 100 cigarette-years	**−0.069**	**−0.099 to −0.039**	−0.026	−0.056 to 0.005	**−0.015**	**−0.019 to −0.010**
Men‡‡						
Smoking rate	n=97†		n=97¶		n=97**	
Never-smoker	Reference		Reference		Reference	
Regular smoker 1–14 cigarettes/day	−0.030	−0.470 to 0.410	−0.049	−0.446 to 0.348	−0.003	−0.069 to 0.063
Regular smoker ≥15 cigarettes/day	−0.259	−0.651 to 0.132	−0.005	−0.358 to 0.349	**−0.080**	**−0.139 to −0.021**
Per 10 cigarettes/day	−0.084	−0.255 to 0.088	0.0008	−0.153 to 0.155	−0.026	−0.052 to 0.0005
Cumulative smoking	n=97†		n=97¶		n=97**	
Regular smoker 1–199 cigarette-years	0.092	−0.416 to 0.600	0.098	−0.362 to 0.558	−0.012	−0.091 to 0.066
Regular smoker ≥200 cigarette-years	−0.285	−0.664 to 0.094	−0.081	−0.424 to 0.262	**−0.065**	**−0.123 to −0.007**
Per 100 cigarette-years	−0.034	−0.088 to 0.021	0.002	−0.047 to 0.052	**−0.010**	**−0.019 to −0.002**
Women‡‡						
Smoking rate	n=230†‡§		n=229‡§¶		n=229‡§**	
Never-smoker	Reference		Reference		Reference	
Regular smoker 1–14 cigarettes/day	−0.151	−0.335 to 0.033	−0.011	−0.217 to 0.195	**−0.037**	**−0.070 to −0.004**
Regular smoker ≥15 cigarettes/day	−0.181	−0.407 to 0.046	0.020	−0.234 to 0.273	**−0.063**	**−0.104 to −0.022**
Per 10 cigarettes/day	**−0.133**	**−0.239 to −0.027**	−0.009	−0.128 to 0.110	**−0.040**	**−0.059 to −0.021**
Cumulative smoking	n=228†§††		n=227§¶††		n=227§**††	
Regular smoker 1–199 cigarette-years	−0.138	−0.355 to 0.078	0.007	−0.234 to 0.249	−0.036	−0.074 to 0.003
Regular smoker ≥200 cigarette-years	−0.187	−0.381 to 0.007	0.015	−0.201 to 0.232	**−0.062**	**−0.097 to −0.027**
Per 100 cigarette-years	**−0.058**	**−0.099 to −0.017**	−0.015	−0.061 to 0.031	**−0.016**	**−0.023 to −0.008**

*Adjusted for sex, age, height, education, past 12 months secondhand smoking (SHS), lifetime cumulative SHS and mould odour.
†FEV_1 is available for 331 regularly smoking or never-smoking participants (97 men and 234 women).
‡Smoking rate is missing for 2 women for daily smoking.
§Height is missing for 2 women.
¶FVC is available for 330 regularly smoking or never-smoking participants (97 men and 233 women).
**FEV_1:FVC is available for 330 regularly smoking or never-smoking participants (97 men and 233 women).
††Cigarette-years is missing for 4 women.
‡‡Adjusted for age, height, education, past 12 months SHS, lifetime cumulative SHS and mould odour.

before and after the bronchodilation test. A total of 27.6% of asthmatics were current smokers, while 25.5% were former smokers. Among these ex-smokers, 6.2% had quit less than 12 months ago.

Our main finding was that among asthmatics, both current regular smoking and recent former smoking were related to a significantly reduced FEV_1 level. The effect estimates were on average 208 mL lower in

Table 4 Smoking and lung function of small airways (FEF_{50} and $FEF_{25–75\%}$) in working-age adults with newly diagnosed asthma, the Finnish Environment and Asthma Study 1997–2000

	Pre-bronchodilator effect estimate				Post-bronchodilator effect estimate			
	FEF_{50} (L/s)		$FEF_{25–75\%}$ (L/s)		FEF_{50} (L/s)		$FEF_{25–75\%}$ (L/s)	
Smoking	β	95% CI	β	95% CI	β	95% CI	β	95% CI
All*	n=470†		n=469‡		n=386§		n=386¶	
Never	Reference		Reference		Reference		Reference	
Quit >1 year ago	−0.120	−0.406 to 0.166	−0.025	−0.269 to 0.220	−0.248	−0.604 to 0.109	−0.101	−0.400 to 0.198
Quit <1 year ago	**−0.5360**	**−0.980 to −0.091**	**−0.406**	**−0.791 to −0.021**	−0.498	−1.040 to 0.045	−0.463	−0.927 to 0.001
Occasional	0.113	−0.347 to 0.573	0.188	−0.204 to 0.580	−0.200	−0.761 to 0.362	0.070	−0.413 to 0.553
Regular	**−0.476**	**−0.750 to −0.202**	**−0.372**	**−0.607 to −0.137**	**−0.557**	**−0.877 to −0.236**	**−0.394**	**−0.663 to −0.124**
Men**	n=164†		n=165‡		n=135§		n=136¶	
Never	Reference		Reference		Reference		Reference	
Quit >1 year ago	0.142	−0.398 to 0.683	0.118	−0.344 to 0.579	−0.074	−0.834 to 0.685	0.061	−0.559 to 0.681
Quit <1 year ago	−0.596	−1.393 to 0.202	−0.624	−1.305 to 0.058	−0.198	−1.269 to 0.872	−0.432	−1.305 to 0.442
Occasional	−0.158	−1.163 to 0.847	−0.118	−0.976 to 0.740	−0.283	−1.538 to 0.973	0.170	−0.912 to 1.253
Regular	−0.284	−0.849 to 0.281	−0.279	−0.760 to 0.201	−0.377	−1.124 to 0.370	−0.217	−0.822 to 0.389
Women**	n=306†		n=304‡		n=251§		n=250¶	
Never	Reference		Reference		Reference		Reference	
Quit >1 year ago	−0.267	−0.616 to 0.082	−0.115	−0.412 to 0.182	−0.335	−0.720 to 0.051	−0.180	−0.513 to 0.152
Quit <1 year ago	−0.462	−0.999 to 0.075	−0.236	−0.705 to 0.233	**−0.730**	**−1.328 to −0.132**	−0.457	−0.994 to 0.080
Occasional	0.273	−0.233 to 0.779	0.352	−0.077 to 0.781	−0.196	−0.774 to 0.381	−0.037	−0.535 to 0.461
Regular	**−0.489**	**−0.802 to −0.177**	**−0.368**	**−0.635 to −0.101**	**−0.598**	**−0.923 to −0.272**	**−0.436**	**−0.719 to −0.154**

*Adjusted for sex, age, height, education, past 12 months secondhand smoking (SHS), lifetime cumulative SHS and mould odour.
†Pre-bronchodilator FEF_{50} is available for 473 participants (165 men and 308 women), of whom smoking status is missing for 3 (1 man and 2 women).
‡Pre-bronchodilator $FEF_{25–75\%}$ is available for 472 participants (166 men and 306 women), of whom smoking status is missing for 3 (1 man and 2 women).
§Post-bronchodilator FEF_{50} is available for 388 participants (136 men and 252 women), of whom smoking status is missing for 2 (1 man and 1 woman).
¶Post-bronchodilator $FEF_{25–75\%}$ is available for 388 participants (137 men and 251 women), of whom smoking status is missing for 2 (1 man and 1 woman).
**Adjusted for age, height, education, past 12 months SHS, lifetime cumulative SHS and mould odour.

smokers and 245 mL among former smokers who quit less than a year ago compared with never smokers. Interestingly, there was no indication of adverse effects among subjects who quit over a year ago, suggesting a recovery from the adverse effects of smoking. For FVC and FEV_1:FVC, we detected similar associations. A dose–response pattern was detected in relation to both daily smoking rate and life-time cumulative smoking.

We also estimated the effects of smoking on lung function parameters reflecting small airways. Small airways lung function parameters were related to both daily smoking rate and cumulative smoking, showing statistically significant dose–response patterns. The effect estimates for women were consistently greater than estimates for men, indicating that a given amount of smoking harms the lungs of women more than the lungs of men.

Validity of results

We were able to recruit a high proportion of new cases of asthma (response rate 86%) in the study area by a thorough recruitment system through the healthcare system and with the help of the National Social Insurance Institution (NSII). The national social insurance covers the whole Finnish population and the medication files of NSII have practically full coverage of asthmatics requiring regular treatment. Thus, any major selection bias is unlikely in our study.

Questionnaire-based exposure information may include some misclassification. To reduce any information bias, we had introduced the study to the participants as a study on environmental factors and asthma in general, with no special focus on smoking.

Some of the smoking categories, especially ex-smokers who quit less than 12 months ago, were small resulting wide CIs often including the null value. These results should be interpreted with caution.

We were able to adjust for a number of potential confounders including sex, age, height, education and exposure to secondhand smoke, in regression analyses, so we were able to eliminate these factors as potential explanations for our results.

Table 5 Daily smoking rates and cumulative cigarette-years in regular smokers and FEF_{50} and $FEF_{25–75\%}$ in asthmatics, the Finnish Environment and Asthma Study 1997–2000

	Pre-bronchodilator		Pre-bronchodilator		Post-bronchodilator		Post-bronchodilator	
	FEF_{50} (L/s)		$FEF_{25–75\%}$ (L/s)		FEF_{50} (L/s)		$FEF_{25–75\%}$ (L/s)	
	β	95% CI	β	95% CI	β	95% CI	β	95% CI
All*								
Smoking rate	n=320†‡		n=320‡§		n=272¶**		n=274**††	
Never-smoker	Reference		Reference		Reference		Reference	
Regular smoker 1–14 cigarettes/day	−0.205	−0.556 to 0.146	−0.192	−0.490 to 0.105	−0.072	−0.468 to 0.324	0.021	−0.317 to 0.360
Regular smoker ≥15 cigarettes/day	**−0.767**	**−1.133 to −0.401**	**−0.586**	**−0.895 to −0.277**	**−1.083**	**−1.500 to −0.666**	**−0.871**	**−1.227 to −0.516**
Per 10 cigarettes/day	**−0.344**	**−0.511 to −0.177**	**−0.278**	**−0.419 to −0.136**	**−0.459**	**−0.653 to −0.265**	**−0.364**	**−0.531 to −0.198**
Cumulative smoking	n=318†‡‡		n=318§‡‡		n=270**§§		n=272††§§	
Regular smoker 1–199 cigarette-years	−0.275	−0.697 to 0.147	−0.113	−0.468 to 0.242	−0.095	−0.577 to 0.387	0.070	−0.341 to 0.481
Regular smoker ≥200 cigarette-years	**−0.610**	**−0.948 to −0.273**	**−0.557**	**−0.841 to −0.274**	**−0.835**	**−1.225 to −0.446**	**−0.695**	**−1.025 to −0.364**
Per 100 cigarette-years	**−0.118**	**−0.175 to −0.061**	**−0.097**	**−0.145 to −0.049**	**−0.177**	**−0.241 to −0.113**	**−0.142**	**−0.197 to −0.087**
Men¶¶								
Smoking rate	n=95†		n=96§		n=81¶		n=83††	
Never-smoker	Reference		Reference		Reference		Reference	
Regular smoker 1–14 cigarettes/day	0.254	−0.510 to 1.019	−0.009	−0.638 to 0.655	0.761	−0.235 to 1.757	0.679	−0.153 to 1.511
Regular smoker ≥15 cigarettes/day	−0.509	−1.174 to 0.156	−0.390	−0.965 to 0.186	**−0.958**	**−1.815 to −0.101**	**−0.738**	**−1.471 to −0.004**
Per 10 cigarettes/day	−0.142	−0.439 to 0.155	−0.134	−0.386 to 0.118	−0.314	−0.717 to 0.088	−0.243	−0.582 to 0.097
Cumulative smoking	n=95†		n=96§		n=81¶		n=83††	
Regular smoker 1–199 cigarette-years	0.143	−0.766 to 1.051	0.206	−0.541 to 0.953	0.502	−0.732 to 1.736	0.594	−0.414 to 1.601
Regular smoker ≥200 cigarette-years	−0.354	−1.010 to 0.302	−0.427	−0.984 to 0.130	−0.611	−1.487 to 0.246	−0.498	−1.239 to 0.242
Per 100 cigarette-years	−0.049	−0.145 to 0.046	−0.044	−0.125 to 0.036	**−0.138**	**−0.266 to −0.010**	**−0.111**	**−0.218 to −0.004**
Women¶¶								
Smoking rate	n=225†‡		n=224‡§		n=191¶**		n=191**††	
Never-smoker	Reference		Reference		Reference		Reference	
Regular smoker 1–14 cigarettes/day	**−0.426**	**−0.826 to −0.027**	−0.317	−0.654 to 0.019	**−0.423**	**−0.835 to −0.012**	−0.279	−0.633 to 0.076
Regular smoker ≥15 cigarettes/day	**−0.653**	**−1.140 to −0.166**	**−0.504**	**−0.911 to −0.097**	**−0.936**	**−1.451 to −0.422**	**−0.763**	**−1.202 to −0.323**
Per 10 cigarettes/day	**−0.395**	**−0.623 to −0.166**	**−0.304**	**−0.496 to −0.113**	**−0.518**	**−0.761 to −0.274**	**−0.405**	**−0.614 to −0.196**
Cumulative smoking	n=223†‡‡		n=222§‡‡		n=189¶§§		n=189**§§	
Regular smoker 1–199 cigarette-years	−0.465	−0.937 to 0.008	−0.276	−0.676 to 0.123	−0.344	−0.832 to 0.145	−0.173	−0.596 to 0.250
Regular smoker ≥200 cigarette-years	**−0.592**	**−1.009 to −0.175**	**−0.514**	**−0.861 to −0.166**	**−0.861**	**−1.300 to −0.421**	**−0.714**	**−1.088 to −0.339**
Per 100 cigarette-years	**−0.152**	**−0.240 to −0.063**	**−0.126**	**−0.200 to −0.053**	**−0.208**	**−0.299 to −0.118**	**−0.169**	**−0.246 to −0.091**

Continued

Table 5 Continued

	Pre-bronchodilator		Pre-bronchodilator		Post-bronchodilator		Post-bronchodilator	
	FEF_{50} (L/s)		$FEF_{25-75\%}$ (L/s)		FEF_{50} (L/s)		$FEF_{25-75\%}$ (L/s)	
	β	95% CI	β	95% CI	β	95% CI	β	95% CI

*Adjusted for age, height, education, past 12 months secondhand smoking (SHS), lifetime cumulative SHS and mould odour.
†Pre-bronchodilator FEF_{50} is available for 322 regularly smoking or never-smoking participants (95 men and 227 women).
‡Smoking rate is missing for 2 women for daily smoking.
§Pre-bronchodilator $FEF_{25-75\%}$ is available for 322 regularly smoking or never-smoking participants (96 men and 226 women).
¶Post-bronchodilator FEF_{50} is available for 273 regularly smoking or never-smoking participants (81 men and 192 women).
**Smoking rate is missing for 1 woman for daily smoking.
††Post-bronchodilator $FEF_{25-75\%}$ is available for 275 regularly smoking or never-smoking participants (83 men and 192 women).
‡‡Cigarette-years is missing for 4 women.
§§Cigarette-years is missing for 3 women.
¶¶Adjusted for sex, age, height, education, past 12 months SHS, lifetime cumulative SHS and mould odour.

Synthesis with previous knowledge

We have previously shown in FEAS that both personal smoking[4] and exposure to environmental tobacco smoke[8] increase the risk of developing asthma. A Danish study has reported evidence that the lung function levels among subjects with asthma are in general lower and the average annual decline is greater than among subjects without asthma.[18] They discussed that the difference detected could reflect a difference detectable at the time of the diagnosis or an increased decline of lung function over time. They also provided evidence that the effect of smoking on lung function is stronger among subjects with asthma.[18] In a cohort study of 5057 subjects initially 18–30 years of age, the average FEV_1 decline from the peak levels through the age 40 was 8.5% among never-smokers with no asthma, 10%–11% among individuals without asthma and currently smoking ≥15 cigarettes/day as well as among never-smokers with asthma, and 18% among those with both asthma and currently smoking ≥15 cigarettes/day.[19] Based on our systematic search of literature, our study is the first one that assesses potential effects of smoking on lung function among subjects with newly diagnosed asthma. Besides studying the effects on forced expiratory volumes (FEV_1 and FVC), we also addressed potential effects on smaller airways, using $FEF_{25-75\%}$ and $FEF_{50\%}$ as the outcome variables.

Our results suggest that the effects of smoking on lung function start operating already before the asthma is diagnosed. This points towards a phenomenon that the effects of smoking on airways inflammation lead to the onset of asthma and reduction in lung function concurrently. Thus, asthmatics seem to constitute a group especially vulnerable to the adverse effects of smoking on lung function.

Reduced forced expiratory flows have been identified as early effects of smoking on smaller airways lung function among previously healthy subjects. Already in the 1970s, McFadden and Linden[20] and Walter *et al*[21] postulated that small airways obstruction contributes to airflow limitation at mid and late phases of FEVs. In asthma, the clinical implication of reduced mid forced expiratory flows is that they increase the risk for long-term persistence of asthma as well as poor asthma outcomes.[22 23] These adverse effects seem to be independent of the magnitude of the reductions in FEV_1 or FEV_1:FVC. Persistently reduced forced expiratory flows (eg, $FEF_{25-75\%}$) have been postulated to reflect the small airways phenotype of asthma.[24] On the other hand, the disadvantages related to these lung function measures includes poorer reproducibility compared with FEV_1 and their contribution to clinical decision-making has been questioned.[25] In a retrospective analysis of community-managed asthma, $FEF_{25-75\%}$ was associated with severity of asthma defined by treatment steps.[26]

Smoking among asthmatics is associated with poor control and increased severity of asthma, as well as with more rapid decline in FEV_1 and poor therapeutic

response to corticosteroids.[27] This was suggested to be explained by an alteration in airway inflammatory cell phenotypes. We were able to identify only two previous studies on the effects of smoking on small airways lung function among patients with asthma. In the Melbourne Atopy Cohort Study,[28] early-life tobacco smoke exposure perinatally was associated with reduced pre-bronchodilator FEV_1, FEV_1:FVC and $FEF_{25–75\%}$. Boulet *et al*[29] compared small samples of smoking and non-smoking patients with asthma visiting asthma clinic, and found that smokers had more respiratory symptoms, a lower $FEF_{25–75\%}$ and FEV_1:FVC ratio and lung diffusing capacity. Induced sputum showed higher neutrophil counts. They concluded that smoking patients with asthma showed features that were similar to those detectable in the early stages of COPD. The present study appears to be the first one to clarify the effects of smoking on small airways lung function, measured as forced expiratory flows, in a larger sample of patients with adult-onset asthma, and to provide effect estimates for lung function parameters measured both prior to and after the bronchodilation test.

The trend that we detected showing a reduced FVC in men who were regular smokers may also indicate the presence of small airways obstruction, as this finding in asthma may be due to airway closure and air trapping.[30] In a longitudinal adult asthma study, the accelerated annual decline in lung function among smokers included FEV_1, FEV_1:FVC and also FVC,[31] which is consistent with our findings. In a review of pulmonary function tests of patients with newly diagnosed asthma, 8% had a true restrictive impairment.[32]

CONCLUSIONS

This study provides new evidence that regular smoking is related to reduced lung function levels among working-aged adults with newly onset asthma. The study also shows that smoking has harmful effects on lung function parameters reflecting both central and small airways measured both before as well as after the bronchodilation test. Observations of consistent dose–response patterns in the detected harmful effects strengthen the causal inference based on the findings and provide a strong message for both clinicians and public health professionals that those who have asthma should be advised and supported not to take up smoking or to quit if they already have this habit.

Contributors JJKJ participated in conception and design of the study, acquisition of data, planning analyses and data interpretation, and wrote the article and serves as the corresponding author and the guarantor of the paper, taking responsibility for the integrity of the work as a whole. PS participated in data analysis and data interpretation and drafted the article. TKL analysed the data and participated in data interpretation and critical revision of the article. SH participated in data analysis and interpretation of data and critical revision of the manuscript. LPM provided expertise in clinical respiratory physiology. MSJ participated as the PI of the project in conception and design of the study, acquisition of data, planning analyses and data interpretation, and critical revision of the manuscript. All authors approved the final version of the manuscript to be submitted.

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