Dose-dependent association of smoking and bronchial hyperresponsiveness

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ABSTRACT Our aim was to study the association of smoking habits and environmental tobacco smoke (ETS) exposure with bronchial hyperresponsiveness (BHR).

A random sample of 292 adults was examined using a structured interview, spirometry, skin prick tests, exhaled nitric oxide fraction (F_{ENO}) and bronchial histamine challenge.

A large majority of subjects with BHR were smokers or ex-smokers. Starting to smoke before 20 years of age was significantly associated with BHR, as was current smoking, quantity of smoking and ETS exposure. The severity of BHR increased significantly with increasing pack-years of exposure ($p<0.001$). Current smokers with decreased lung function were at a particularly high risk of BHR. Impaired forced expiratory volume in 1 s and mean maximal expiratory flow were independent determinants for more severe BHR, regardless of age. In multivariate analysis, smoking remained an independent determinant for BHR after adjustment for impaired lung function and other covariates: $\geqslant 15$ pack-years yielded an odds ratio of 3.00 (95% CI 1.33–6.76) for BHR. The association between BHR and F_{ENO} was dependent on smoking habits.

The results indicate that smoking is a significant risk factor for BHR, with a dose-dependent pattern, and that the severity of BHR increases with pack-years. The findings strongly suggest assessment of smoking habits in subjects with BHR.

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Introduction

Smoking causes chronic airway obstruction, which mostly develops gradually from peripheral airways towards large airways [1, 2]. Large-scale international studies have shown that smoking is a risk factor for bronchial hyperresponsiveness (BHR) [3–5], but whether the quantity of smoking exposure is associated with the severity of BHR is still in question. A dose-dependent association of smoking and small airway obstruction as possible independent trigger factors for BHR severity has not been explored in detail.

There are only a few recent epidemiological studies that have assessed a large variety of possible determinants of BHR [6, 7]. The majority of epidemiological studies on BHR are descriptive and have reported their results of BHR as a dose–response slope or dose–response rate [8]. Translating these measures of BHR into clinical practice is laborious, thus they have been used only in research [5, 7]. BHR testing is a common tool in diagnosing asthma, but the effects of smoking have been unclear when interpreting causes of BHR [9]. The association of BHR and smoking has been studied mostly in selected populations [10–12].

We aimed to study the effects of smoking, environmental tobaccos smoke (ETS) exposure and exhaled nitric oxide fraction (F_{ENO}) on BHR in adult subjects representing the general population in Helsinki, the capital of Finland. Bronchial responsiveness was assessed by a dosimetric method with histamine [13], which has been in clinical use for over three decades in Finland. The effect of the quantity of smoking exposure on BHR severity, defined by a provocative dose of histamine inducing a 15% decrement in forced expiratory volume in 1 s (FEV_1) in two clinically validated cut-off levels (PD_{15} 1.6 mg and 0.4 mg [13]), was calculated by multiple regression analysis. When calculating the effects of current smoking status, pack-years and ETS on BHR, variables of ventilatory function and of small airway obstruction were used as co-variates.

Subjects and methods

Study cohort

The study sample consisted of 292 randomly selected subjects, who had taken part in a postal questionnaire survey in Helsinki in 1996 [14]. The population of the FinEsS I postal survey (n=8000) was randomly selected from the Finnish population register and designed to correspond to the general population with respect to age and sex. The participation rate of the FinEsS I study was 76% (n=6062). Of the participants, 1200 were randomly invited to participate in the FinEsS II clinical study, and half of those (n=600) were randomly selected to take part in this BHR study. The participation rate for the FinEsS II clinical study was 54% (n=643) [15] and for the BHR study 45.4% (n=292).

This BHR study sample represents well the original study cohort from 1996 in terms of age, sex and prevalence of asthma, respiratory symptoms, and smoking habits [15]. The age range was 26–66 years (mean 47 years) and 58% were female. The baseline FEV_1 of the studied subjects ranged from 60% to 136% of predicted Finnish reference values [16]. The Helsinki University Central Hospital ethics committee approved the study, and all subjects gave signed informed consent. Demographic data are presented in tables 1 and 2.

Clinical examinations

BHR challenge tests were carried out within 2 weeks of an initial clinical visit including a structured interview, spirometry with bronchodilation test and skin prick tests (SPTs) [17]. The interview was performed by a physician, and a trained nurse performed the spirometry and the SPTs. SPTs were performed in subjects aged <61 years with two controls (positive control: histamine 10 $mg \cdot mL^{-1}$; negative control: glycerine solvent) and 15 allergens [15]. The interview consisted of questions about respiratory symptoms, family history of asthma and allergy, living conditions, occupation, smoking habits, and ETS exposure.

BHR test

Inclusion criteria for the BHR test were a pre-test FEV_1 value of $\geqslant$60% predicted or $\geqslant$1.5 L, no respiratory infection within 4 weeks prior to testing, no marked heart diseases (myocardial infarction within 3 months, unstable coronary disease, dysfunction or arrhythmia) and no stroke. Subjects were allowed to use their regular medication, except β_2-agonists and antihistamines (no short-acting β-agonists for 12 h or long-acting β-agonists for 48 h and no antihistamines for 5 days before testing). 18 subjects were excluded because of low baseline FEV_1.

The bronchial challenge was conducted with histamine by a dosimetric method with controlled tidal breathing by using the Spira Electro 2 jet nebuliser (Spira Respiratory Care Center Ltd, Hämeenlinna, Finland) [13]. Subjects inhaled buffered histamine diphosphate aerosol in four-fold increasing doses. The end-point was a fall of $\geqslant$15% in FEV_1 or used maximum noncumulative dose of histamine of 1.6 mg. After the histamine challenge, post-bronchodilation (0.4 mg salbutamol (Ventoline, GlaxoSmithKline, Brentford,

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TABLE 1 Demographic data of the subjects studied

	Male	Female	Total
Subjects	123	169	292
Age years	45.2±9.5 (28–65)	47.3±10.6 (26–66)	46.4±10.2 (26–66)
Height m	1.74±0.06 (1.61–1.86)	1.63±0.07 (1.46–1.74)	1.69±0.08 (1.46–1.86)
Weight kg	80.0±12.6 (43–110)	70.6±13.8 (48–105)	75.6±14.0 (43–110)
Spirometry			
FEV1 L	4.06±0.70 (2.35–5.90)	2.87±0.51 (1.71–4.50)	3.37±0.84 (1.71–5.90)
FEV1# % pred	94±12 (62–127)	94±12 (71–129)	94±12 (62–129)
FVC L	5.28±0.82 (3.09–8.03)	3.65±0.61 (2.15–5.39)	4.34±1.07 (2.15–8.03)
FVC# % pred	99±11 (67–127)	99±12 (72–145)	99±12 (67–145)
FEV1/FVC %	77±6	78±6	78±6
FEV1/FVC# % pred	95±7 (71–113)	95±6 (80–115)	95±7 (71–115)
MEF50 $L \cdot s^{-1}$	4.43±1.33 (1.40–8.11)	3.37±0.98 (1.41–6.33)	3.82±1.26 (1.40–8.11)
MEF50# % pred	82±24 (30–147)	77±20 (39–137)	79±22 (30–147)
Smoking			
Pack-years	10.30±12.57 (0–47)	7.21±10.18 (0–39)	8.51±11.33 (0–47)
Smoking history			
Nonsmokers	47 (38.2)	74 (43.8)	121 (41.4)
Ex-smokers	30 (24.4)	45 (26.6)	75 (25.7)
Smokers	46 (37.4)	50 (29.6)	96 (32.9)
ETS			
Ever¶	84 (68.3)	131 (77.5)	215 (73.6)
Both at work and at home	49 (39.8)	65 (38.5)	114 (39.0)
Inhaled corticosteroids+	3 (2.4)	6 (3.6)	9 (3.1)

Data are presented as n, mean±SD (range) or n (%). Predicted values according to VILJANEN *et al.* [16]. FEV1: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity; MEF50: maximal expiratory flow at 50% of FVC; ETS: environmental tobacco smoke. #: lung function values, n=291; ¶: at work and/or at home; +: daily use of inhaled corticosteroids ⩾200 μg.

TABLE 2 Smoking as a risk factor for bronchial hyperresponsiveness (BHR) in terms of odds ratios, univariate analysis

	Subjects	PD15 ⩽1.6 mg		PD15 ⩽0.4 mg	
		BHR	OR (95% CI)	BHR	OR (95% CI)
Subjects	292				
Age started smoking					
Nonsmokers	121	19	1	3	1
⩾20 years	42	9	1.46 (0.60–3.55)	3	3.03 (0.59–15.61)
<20 years	129	34	**1.92 (1.03–3.60)**	12	**4.03 (1.11–14.67)**
Pack-years n					
<8.5#	65	8	0.75 (0.31–1.83)	1	0.62 (0.06–6.03)
⩾8.5	106	35	**2.65 (1.40–5.00)**	14	**5.99 (1.67–21.45)**
<5	45	4	0.52 (0.17–1.63)	0	
5–15	55	12	1.50 (0.67–3.35)	3	2.27 (0.44–11.62)
>15	71	27	**3.29 (1.66–6.54)**	12	**8.00 (2.17–29.45)**
Smoking status					
Nonsmokers	121	19	1	3	1
Ex-smokers	75	12	1.02 (0.47–2.25)	5	2.81 (0.65–12.12)
Current smokers	96	31	**2.56 (1.34–4.91)**	10	**4.57 (1.22–17.12)**
Smoking history ⩾1 year	160	39	1.53 (0.86–2.72)	15	**4.45 (1.26–15.72)**
Current smoking status					
Nonsmokers and ex-smokers¶	197	31	1	8	1
0–4 cigarettes per day	36	11	**2.34 (1.05–5.25)**	2	1.38 (0.28–6.80)
5–14 cigarettes per day	29	10	**2.80 (1.19–6.60)**	2	1.74 (0.35–8.63)
⩾15 cigarettes per day	30	10	**2.66 (1.14–6.23)**	6	**5.88 (1.88–18.38)**

Data are presented as n, unless otherwise stated. PD15: provocative dose causing a 15% fall in forced expiratory volume in 1 s. #: mean of pack-years in the whole cohort, 8.5; ¶: nonsmokers and ex-smokers, and one missing included (n=197). Bold type represents statistical significance.

UK) *via* Volumatic® (GlaxoSmithKline, London, UK)) FEV_1 was measured. PD_{15} was calculated by interpolation [18].

Within 2 weeks prior to the bronchial challenge tests, flow–volume spirometry was performed using a Vmax22 Spirometer (SensorMedics, Yorba Linda, CA, USA), according to the 1994 criteria of American Thoracic Society (ATS) [19]. We recorded the largest FEV_1 and forced vital capacity (FVC) from at least three acceptable curves, and the flow parameters, such as the mean maximal expiratory flow at 50% of FVC (MEF_{50}), were obtained from the curve with the biggest sum of FEV_1 and FVC. Bronchodilation response was measured after the histamine test. A nose clip was used at all spirometric examinations. In 95% of the subjects, the F_{ENO} was measured at the 50 $mL \cdot s^{-1}$ flow rate according to the 1999 ATS criteria [20]. The F_{ENO} measurements were performed before the BHR testing.

Definitions

The definitions used in the present study are presented in table 3.

Statistical analyses

BHR severity, risk factors and symptoms associated with BHR were determined at two different cut-off levels of PD_{15}. Risk factors for BHR were calculated by multiple logistic regression analysis, which included as independent variables age, sex, family history of asthma and determinants that were significant in the univariate analysis. For the analysis, the mean values of age (47 years) and pack-years (8.5) were used. The results are expressed as odds ratios (95% CI). Chi-squared and Fisher's exact tests were used to assess differences between groups. Furthermore, $p<0.05$ was considered statistically significant. The analyses were repeated for individuals <45 years and $\geqslant 45$ years of age to define the effects of smoking exposure as a potential inception for BHR measured in the two age groups.

Statistical Package for Social Sciences (SPSS version 15.0 for Windows; IBM, Chicago, IL, USA) and StatXact 8_2007 (Cytel Inc., Cambridge, MA, USA) were used for the statistical analysis.

TABLE 3 Definitions

BHR	Histamine $PD_{15} \leqslant 1.6$ mg
Marked BHR	Histamine $PD_{15} \leqslant 0.4$ mg
BHR severity [13]	
Severe	$PD_{15} \leqslant 0.100$ mg
Moderate	PD_{15} 0.101– $\leqslant 0.400$ mg
Mild	PD_{15} 0.401– $\leqslant 1.600$ mg
None	$PD_{15} \geqslant 1.601$ mg
Normal FEV_1	$\geqslant$80% pred
Normal FVC	$\geqslant$80% pred
Normal FEV_1/FVC	$\geqslant$88% pred
Normal MEF_{50}	$\geqslant$63% pred
Physician-diagnosed asthma	Subjects who answered ''yes'' to the question: ''Have you been diagnosed as having asthma by a physician?''
Childhood wheeze	Subjects who answered ''yes'' to the question: ''Have you been diagnosed as having asthma or have you had wheeze in childhood?''
Atopy	At least one positive skin prick test reaction to any of the tested allergens or reported symptoms of allergic rhinoconjunctivitis
Nonsmoker	Never-smoker or smoking <4 cigarettes per month
Ex-smoker	Those who had quit smoking $\geqslant$12 months prior to the study
Exposure to ETS	The subjects were asked three separate questions about ETS: ''Have you ever been exposed to environmental tobacco smoke at home/at work/ generally in the surroundings?'' The answer alternatives of all three questions were: ''never'', ''yes previously, not any more'' and ''yes, currently''
ETS exposure ever	ETS at home or at work, or both, currently or previously
ETS exposure present	ETS currently at the time of the study at home, at work, or both

BHR: bronchial hyperresponsiveness; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; MEF_{50}: maximal expiratory flow at 50% of FVC [21]; ETS: environmental tobacco smoke; PD_{15}: provocative dose of histamine inducing a 15% fall in FEV_1; % pred: % predicted.

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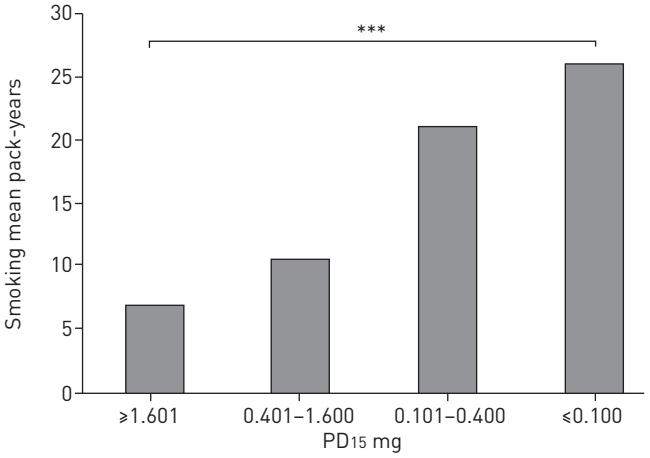

FIGURE 1 Association of the severity of bronchial hyperresponsiveness (BHR) and history of smoking (pack-years). BHR is classified according to the provocative dose of histamine inducing a 15% fall in forced expiratory volume in 1 s (PD_{15}) [13] as: no BHR (>1.6 mg), mild (0.401–1.6 mg), moderate (0.101–0.4 mg) and severe (⩽0.1 mg) in an adult general population sample of Helsinki (n=292). p-value represents test for trend. ***: p<0.001.

Results

Smoking

Smoking increased the risk of BHR (table 2). BHR severity increased parallel to increasing number of pack-years (p<0.001) (fig. 1). Of the subjects with marked BHR, 56% were smokers and 28% ex-smokers *versus* 28% smokers and 27% ex-smokers among the subjects without BHR. Start of smoking before the age of 20 years (n=129) yielded an odds ratio of 4.03 (95% CI 1.11–14.67) for marked BHR and the corresponding values for a start of smoking before 15 years was 5.38 (95% CI 1.14–25.37), with nonsmokers as reference. No one who had started smoking after the age of 26 years had marked BHR.

The association of pack-years with BHR and marked BHR became significant at only 1+ pack-year (OR 1.91, 95% CI 1.05–3.49 and OR 4.07, 95% CI 1.15–14.39, respectively). A smoking history of ⩾8.5 pack-years yielded an odds ratio of 2.65 (95% CI 1.40–5.00) for BHR and 5.99 (95% CI 1.67–21.45) for marked BHR. Having a smoking history of >15 pack-years resulted in an odds ratio of 8.00 (95% CI 2.17–29.45) for marked BHR, and, combined with obstruction, in values of 12.85 (95% CI 3.36–49.09). Current smokers with impaired ventilatory function defined as FEV_1 <80% pred, FEV_1/FVC <0.7 and MEF_{50} <63% pred, were all at a high risk for BHR (OR 10.17, 8.37 and 6.85, respectively) (table 4).

In the multivariate analysis, smoking remained as an independent determinant of BHR and marked BHR when co-variates, including impaired lung function and other determinants of BHR that were significant in the univariate analysis, were taken into account (table 5). Smoking >15 pack-years remained significantly associated with both BHR and marked BHR after adjustment for age, female sex, wheezing or asthma in childhood, FEV_1 <80% pred and MEF_{50} <63% pred (table 4). Besides ventilatory function variables, asthma or wheeze during childhood also remained as significant risk factors for BHR in the multivariate analysis.

Environmental tobacco smoke

Of the subjects with marked BHR, 33% reported ETS exposure at the time of the study *versus* 17% among those not having BHR. ETS at home and at work were associated with marked BHR (OR 3.73, 95% CI 1.05–13.17 and OR 4.65, 95% CI 1.32–16.42, respectively). However, exposure to tobacco smoke in nonsmokers only was not significantly associated with BHR.

Ventilatory function

Low baseline FEV_1 values correlated with low PD_{15} values (p<0.001).

Baseline FEV_1 <80% pred together with obstruction (FEV_1/FVC <0.7) increased the risk of BHR, yielding an odds ratio of 5.73 (95% CI 1.75–18.73) (table 4). In univariate analysis of lung function variables, MEF_{50} below the lower limit of normal (LLN) appeared as a strong determinant for BHR and marked BHR. When MEF_{50}<LLN was the only sign of decreased ventilatory function, it was significantly associated with BHR (OR 2.65, 95% CI 1.21–5.82).

F_{ENO} in relation to BHR

The association between F_{ENO} and BHR was strongly dependent on smoking habits (fig. 2). In nonsmokers with BHR, F_{ENO} was >25 ppb and significantly higher compared to the remaining subjects (p=0.008).

TABLE 4 Lung function, smoking, and risks for PD_{15} ⩽1.6 mg and PD_{15} ⩽0.4 mg, analysed by univariate and multivariate analysis

Independent variables	Subjects	Dependent variables			
		PD_{15} ⩽1.6 mg		PD_{15} ⩽0.4 mg	
		BHR	OR (95% CI)	BHR	OR (95% CI)
Univariate analysis	292				
Lung function					
FEV_1 <80% pred	38	19	**4.91 (2.40–10.04)**	10	**10.98 (4.01–30.11)**
FEV_1/FVC <0.7	23	11	**3.92 (1.64–9.38)**	8	**13.81 (4.76–40.09)**
MEF_{50} <63% pred	77	37	**6.99 (3.79–12.89)**	15	**17.02 (4.77–60.68)**
FEV_1<80% pred and FEV_1/FVC <0.7	12	7	**5.73 (1.75–18.73)**	7	**34.24 (9.36–125.17)**
FEV_1<80% pred and MEF_{50} <63% pred	24	15	**7.80 (3.22–18.89)**	10	**23.13 (7.90–67.69)**
Current smokers and lung function	96				
Smokers with FEV_1 <80% pred	22	15	**10.17 (3.93–26.31)**	8	**14.86 (5.08–43.49)**
Smokers with FEV_1/FVC <0.7	12	8	**8.37 (2.43–28.82)**	7	**34.24 (9.36–125.17)**
Smokers with MEF_{50} <63% pred	37	21	**6.85 (3.30–14.23)**	10	**11.44 (4.16–31.43)**
Multivariate analysis	292				
Age ⩾45 years			0.56 (0.27–1.14)		0.52 (0.14–2.00)
Lung function					
FEV_1 <80% pred			**2.69 (1.06–6.84)**		**5.78 (1.55–21.54)**
MEF_{50} <63% pred			**5.53 (2.70–11.32)**		**8.34 (1.82–38.18)**
Female[#]			**2.12 (1.04–4.34)**		0.93 (0.26–3.34)
Wheezing or asthma in childhood[¶]			**3.99 (1.24–12.85)**		1.05 (0.09–11.74)
Smoking pack-years					
Nonsmokers			1		1
0–5			0.45 (0.14–1.50)		[+]
5–15			1.30 (0.53–3.22)		1.40 (0.23–8.61)
>15			**3.00 (1.33–6.76)**		**5.80 (1.27–26.62)**
Multivariate analysis	292				
Age ⩾45 years			0.61 (0.31–1.21)		0.67 (0.20–2.31)
Lung function					
MEF_{50} <63% pred			**7.64 (3.92–14.88)**		**19.04 (4.77–75.97)**
Female[#]			1.92 (0.97–3.80)		0.69 (0.22–2.14)
Wheezing or asthma in childhood[¶]			**4.15 (1.35–12.76)**		1.77 (0.17–18.13)
Smoking pack-years					
Nonsmokers			1		1
<8.5			0.64 (0.24–1.68)		0.45 (0.04–4.79)
⩾8.5			**2.58 (1.26–5.31)**		**5.00 (1.25–19.92)**

Data are presented as n, unless otherwise stated. PD_{15}: provocative dose of histamine inducing a 15% fall in forced expiratory volume in 1 s (FEV_1); BHR: bronchial hyperresponsiveness; % pred: % predicted; FVC: forced vital capacity; MEF_{50}: maximal expiratory flow at 50% of FVC [21]. [#]: males as reference group; [¶]: "no" as reference group; [+]: n=0.

Current exposure to ETS was associated with a lower F_{ENO} (13.2 ppb) compared to nonexposed subjects (19.3 ppb) (p=0.002).

Influence of age

The association of smoking with BHR was examined in two age groups: those <45 years of age (group 1: mean age 36 years; n=126) and those ⩾45 years of age (group 2: mean age 54 years; n=166). The prevalence of BHR did not differ between groups 1 and 2 (19.8% *versus* 22.3%, respectively), whereas marked BHR was more common in group 2 (4.8% *versus* 7.2%). Group 1 included more nonsmokers (46.8% *versus* 37.3%) and the number of pack-years was lower than in group 2 (mean 5.6 *versus* 10.8). The proportion of subjects having obstruction defined as FEV_1/FVC <88% pred was the same in groups 1 and 2 (30.4% *versus* 30.1%, respectively) but obstruction defined as FEV_1/FVC <0.7 was more common in group 2 (1.6% *versus* 12.0% for groups 1 and 2, respectively).

In group 1, smoking and LLN of FEV_1 were not significantly associated with BHR (OR 1.78, 95% CI 0.68–4.46 and OR 1.93, 95% CI 0.54–6.86, respectively), but both these factors increased the risk for BHR in group 2

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TABLE 5 Risk for PD_{15} ⩽1.6 mg and PD_{15} ⩽0.4 mg, analysed by multivariate analysis

Independent variables	Dependent variables	
	PD_{15} ⩽1.6 mg	**PD_{15} ⩽0.4 mg**
Age >47 years	0.70 (0.36–1.38)	0.63 (0.17–2.36)
Female[#]	**2.14 (1.08–4.24)**	1.05 (0.31–3.53)
FEV_1 <80% pred	**4.58 (2.07–10.12)**	**10.75 (3.20–36.11)**
Family history of asthma[¶]	1.64 (0.75–3.62)	1.42 (0.34–5.97)
Allergy[¶,+]	0.63 (0.33–1.21)	0.48 (0.15–1.60)
Wheezing or asthma in childhood[¶]	**3.66 (1.22–11.05)**	2.18 (0.23–21.11)
Smoking history[§]		
Non smokers	1	1
<15 pack-years	0.92 (0.41–2.07	1.51 (0.22–10.23)
⩾15 pack-years	**3.87 (1.77–8.43)**	**9.91 (1.83–53.53)**

Data are presented as OR (95% CI). Bronchial hyperresponsiveness (BHR) tested in April–June was included in the model, nonsignificant (for PD_{15} ⩽1.6 mg OR 0.95, 95% CI 0.47–1.92 and for PD_{15} ⩽0.4 mg OR 1.98, 95% CI 0.60–6.52). Environmental tobacco smoke exposure at work included in the model (for BHR OR 2.02, 95% CI 1.00–4.10, and for marked BHR OR 1.98, 95% CI 0.60–6.52) did not change the significance of the factors. PD_{15}: provocative dose of histamine inducing a 15% fall in forced expiratory volume in 1 s (FEV_1); % pred: % predicted. [#]: males as reference group; [¶]: "no" as reference group; [+]: atopy or symptoms of allergic rhinoconjunctivitis; [§]: in pack-years, current and ex-smokers included.

(OR 3.55, 95% CI 1.42–8.91 and OR 11.10, 95% CI 3.84–32.10, respectively). In the multivariate analyses, age-adjusted determinants for BHR did not differ from analyses performed without age in the models (tables 4 and 5). Of the lung function parameters, MEF_{50} <63% pred increased the risk regardless of age: in group 1, when sex, wheezing or asthma in childhood and smoking (pack-years) were included in the multivariate model, odds ratios for BHR and marked BHR were 3.39 (95% CI 1.20–9.55) and 13.60 (95% CI 1.88–98.23), respectively.

Discussion

In this study, we found a dose-dependent association of smoking and the severity of BHR in an adult sample of the general population. The present study indicates that increasing smoking exposure, defined by pack-years, is associated with more severe BHR. The association remained significant even after adjustment of effects on BHR of decreased lung function (FEV_1), airway obstruction and peripheral airflow limitation at baseline. In the multivariate model, a history of asthma or wheezing in childhood and female sex were also independent determinants of BHR.

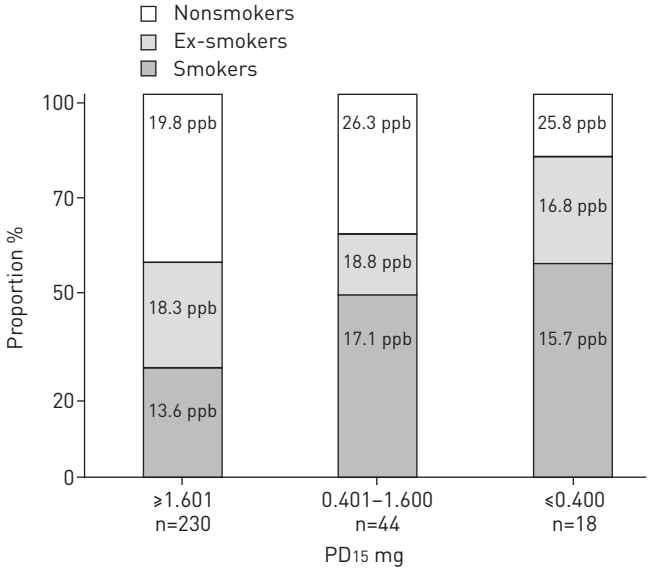

FIGURE 2 Smoking categories with mean exhaled nitric oxide fraction (F_{ENO}) by severity groups of bronchial hyperresponsiveness (BHR) [13] (none (provocative dose causing a 15% fall in forced expiratory volume in 1 s (PD_{15}) ⩾1.601 mg), mild (PD_{15} 0.401–1.600 mg) and marked (PD_{15} ⩽0.400 mg)) in an adult general population sample of Helsinki, Finland. Nonsmokers: mean F_{ENO} 20.8 ppb; ex-smokers: mean F_{ENO} 18.3 ppb; smokers: mean F_{ENO} 14.6 ppb. n=292. p-values express test for trend. Mean±SD F_{ENO} is 18.1±13.47 ppb (range 2.13–95.60 ppb). p=0.004.

Generally, the risk factors were most strongly associated among subjects aged ⩾45 years, whereas in subjects aged <45 years significant associations with BHR were diluted, except for MEF_{50} <63% pred.

We found that the majority of the current smokers had started to smoke at the age of 15–19 years. Starting to smoke at age 7–20 years doubled the risk of having BHR and increased the risk for marked BHR fourfold. Starting to smoke very early in life, at age 7–14 years, increased the risk for marked BHR in adulthood more than five-fold. Categorisation of smoking exposure by pack-years revealed more significant associations than the use of general terms of current smoking status, *i.e.* nonsmokers, ex-smokers or current smokers. Acute effects of exposure to tobacco smoke were not studied.

Our results indicate that ETS exposure and smoking interfere with $F_{E}NO$ values in detecting airway inflammation in a general population, similar to the results recently found by NADIF *et al.* [22]. Smoking exposure plays an inestimable role in evaluating the $F_{E}NO$ levels of an individual, thus probably explaining some of the contradictory results found in former studies of the associations of BHR with other measurements of airway regulation and inflammation [23, 24]. Biological measurements of exposure to tobacco smoke were not performed, which results in a somewhat incomplete quantification of ETS exposure.

The inclusion criteria for participation in a study of BHR have an impact on the final outcomes. In this general population cohort, the prevalence of BHR was 21%, and patients with severe or moderate BHR constituted 6% of those studied [17], the latter result fairly consistent with current data on prevalence of asthma among adults in Finland [14, 15].

However, in our study, as in all BHR studies, several of the most severe patients were excluded because of their low baseline FEV_1 value. Thus, their severely decreased ventilatory function cannot be taken into account when calculating the risk factors or determinants of increased BHR. The hypothesis of the effect of the size of the airway calibre, and sex differences, are both important determinants of BHR [25], as shown in the multivariate model presented. The methodological considerations of BHR testing and comparison of the results in epidemiological studies lack this part of critical evaluation [26]. In a majority of the BHR studies, only predicted values of lung function are used in the evaluation of risk factors. This might exclude the eventual effect of decreased ventilatory reserves on BHR, particularly among elderly subjects.

As a surrogate variable of peripheral airway obstruction, we used the MEF_{50} from the baseline spirometry to investigate the role of flow limitation typical of a history of smoking. The repeatability and reliability of the measure is known to be lower and less precise than that of FEV_1 [27]. However in our study cohort, the quality and representativeness of the spirometric measurements have been evaluated [28], and the mean FEV_1 and FVC of predicted values in the present study sample conformed well to current Finnish reference values.

We found that impaired MEF_{50} was strongly associated with BHR. In addition, smoking >15 pack-years as an independent risk factor for BHR remained stable after adjustment for both MEF_{50} and FEV_1<LLN in the multivariate model. As a sign for early airway closure, MEF_{50}<LLN independently associated with an increased risk for BHR and marked BHR to the same magnitude as a decreased FEV_1 value. Results from other studies, also assessed in general adult population samples, report a close association of decreased FEV_1 and increased BHR [3, 29, 30], but, to our knowledge, the associations of MEF_{50} and BHR with histamine in adult general populations have not previously been published.

Results of the analysis in individuals aged <45 years and ⩾45 years suggested that exposure to tobacco smoke is a potential inception for BHR after middle age. Pathologically defined BHR appears after lifelong exposures, such as tobacco smoke exposure. This is in line with the results gained from larger epidemiological BHR studies, in which remodelling changes caused by tobacco have been suggested to cause the increased BHR in a longitudinal setting [7]. As reported by VAN DEN BERGE *et al.* [12], the critical role of inflammatory cells, such as neutrophils, macrophages and lymphocytes, and air trapping in relation to BHR serves as a characterisation tool in the distinction of phenotypes of chronic airway diseases. Prospective studies have shown significant reduction in BHR in asthmatic smokers after quitting; thus smokers should be assisted in quitting [10, 11].

Limitations of the present general population study are obvious due to the small sample size of slightly less than 300 subjects. However, we could show similar associations of BHR and smoking as presented in studies among selected patient populations, such as asthmatics, subjects with allergy and with chronic obstructive pulmonary disease [10–12, 31].

The present study was performed before 2006, when smoking was banned in public places and restaurants in Finland. Along with the public ban of smoking, smoking habits have started to decrease in Finland [32]. A decrease in the prevalence of respiratory symptoms and lung function disturbances may be a consequence of the decrease in smoking, as found in prospective studies in asthmatic smokers after quitting [10, 11, 31, 33].

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In conclusion, smoking and BHR were dose-dependently associated even after correction for effects of impaired lung function, female sex and a history of asthma or wheezing during childhood. The severity of BHR increased with increasing number of pack-years, and starting to smoke before 20 years yielded a greater risk of over four-fold for marked BHR, thus indicating that smoking exposure is a trigger factor for BHR in middle age and older. Low MEF_{50}, as a single spirometric measure, presented the highest odds ratio for BHR, indicating a significant association of impaired airflow limitation with BHR. Smoking and ETS exposure confounded the association of F_{ENO} and BHR. Our results support antismoking actions and legislative restrictions of ETS exposure both at work and at home. Assessment of smoking habits in subjects with BHR is important.

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