Respiratory Medicine (2006) **100**, 1423–1430

ELSEVIER

respiratoryMEDICINE

Smoking cessation—but not smoking reduction—improves the annual decline in FEV_1 in occupationally exposed workers ☆

Abraham B. Bohadana[a,b,*], Fredrik Nilsson[c], Ake Westin[c], Nadine Martinet[b], Yves Martinet[b]

[a]*INSERM ERI 11, Faculté de Médecine, B.P. 184-9, Av de la Forêt de Haye, 54505 Vandoeuvre-lès-Nancy Cedex, France*
[b]*Service de Pneumologie, CHU de Nancy, INSERM EMI 0014, Vandoeuvre-lès-Nancy, France*
[c]*Pfizer Consumer Healthcare, Clinical Research, Helsingborg, Sweden*

Received 9 September 2005; accepted 9 November 2005

KEYWORDS
Smoking cessation;
Smoking reduction;
Airway hyperresponsiveness;
FEV_1;
Occupational exposure

Summary
Introduction: Individuals exposed both to cigarette smoke and respiratory pollutants at work incur a greater risk of development of airway hyperresponsiveness (AHR) and accelerated decline in forced expiratory volume in 1 s (FEV_1) than that incurred by subjects undergoing each exposure separately. We examined whether smoking cessation or smoking reduction improves AHR and thereby slows down the decline in FEV_1 in occupationally exposed workers.
Methods: We examined 165 workers (137 males and 28 females) participating in a smoking cessation programme. Nicotine tablets were used for smoking cessation or smoking reduction. Respiratory symptoms were assessed by questionnaire, FEV_1 by spirometry and AHR by methacholine challenge test. At 1 year, subjects were classified into quitters, reducers, or continuing smokers.
Results: Sixty-seven subjects completed the study (32 quitters; 17 reducers; 18 continuing smokers). Respiratory symptoms improved markedly in quitters ($P<0.001$ for all comparisons) and less so in reducers (P values between 0.163 and 0.027). At 1 year, FEV_1 had slightly but significantly improved in quitters ($P = 0.006$ vs. smokers; $P = 0.038$ vs. reducers) and markedly deteriorated in reducers and continuing

Abbreviations: FTND, Fagerström test for nicotine dependence; CO, carbon monoxide; MAC, methacholine airway challenge; AHR, airway hyperresponsiveness; DRS, adjusted reciprocal dose response slope (DRS = 1/[%fall FEV_1/μmol+2.5]), FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity

☆This study was supported by Pfizer Consumer Healthcare.

*Corresponding author. INSERM ERI 11, Faculté de Médecine, B.P. 184-9, Av de la Forêt de Haye, 54505 Vandoeuvre-lès-Nancy Cedex, France. Tel.: +33 383 68 39 21; fax: +33 383 68 39 19.
E-mail address: abraham.bohadana@nancy.inserm.fr (A.B. Bohadana).

0954-6111/$ - see front matter
doi:10.1016/j.rmed.2005.11.005

smokers. Concurrent, 1-year change in AHR did not differ significantly among the groups.
Conclusion: In occupationally exposed workers, stopping smoking markedly improved respiratory symptoms and, in males, slowed the annual decline in FEV_1. Smoking reduction resulted in smaller improvements in symptoms but deterioration in FEV_1. These findings were independent of AHR. While smoking cessation should remain the ultimate goal in workplace cessation programmes more studies are necessary to better ascertain the benefits of smoking reduction.

Introduction

An association exists between cigarette smoking and the development of airflow obstruction, with a dose–response relationship between the amount of tobacco smoked and both the level of obstruction and an accelerated decline in forced expiratory volume in 1 s (FEV_1).[1,2] Occupational exposure—if sufficiently intense or prolonged—may also independently induce chronic airflow obstruction.[3] Although the risk is smaller than with tobacco smoking, it does affect a large proportion of the population and its contribution to the ultimate incidence of airflow obstruction is not negligible.

The development of airflow obstruction in smokers and occupationally exposed individuals seems to be correlated with the subject's response to non-specific airway challenge. Studies have found airway hyperresponsiveness (AHR) to be a predictor of progression of airflow obstruction both in non-exposed smokers[4] and workers in dusty occupations.[5,6]

We therefore postulated that workers undergoing exposure both to cigarette smoke and respiratory pollutants at work incur a greater risk of development of AHR and airflow obstruction than that incurred by subjects undergoing each exposure separately. For occupationally exposed smokers, stopping smoking could be an important intervention to reduce (or reverse?) AHR and, hopefully, slow the decline in lung function. However, existing smoking cessation treatments only help motivated smokers who are ready to quit; thus, additional measures likely to reduce death or illness such as smoking reduction should be given consideration.[7,8]

As part of a smoking cessation programme designed for occupationally exposed workers we prospectively collected a large body of serial methacholine responsiveness and lung function data. Our aim was to investigate the 1-year impact of smoking cessation or smoking reduction on airway responsiveness and decline in lung function.

Methods

Subjects

The study enrolled occupationally exposed workers (working in dusty occupations for $\geqslant 1$ year) aged 18–65 years, who had smoked for >3 years and were willing to quit or reduce smoking. All worked in the Nancy area. Exclusion criteria included a history of illness judged by the investigator likely to influence the subject's participation such as myocardial infarction within the previous 3 months; unstable angina; severe cardiac arrhythmia; pregnancy or breastfeeding; and use of nicotine replacement during the previous 6 months. Workers being treated for asthma or chronic obstructive pulmonary disease (COPD) were not included but referred to our outpatient clinic.

All subjects gave informed consent and the study protocol was approved by the local ethics committee.

Study, design and medication

The study was an open controlled exploratory study. Eligible subjects were encouraged to quit or, if unable, to reduce their smoking. They used nicotine 2 mg sublingual tablets ad libitum for 3 months. Highly dependent smokers (Fagerström Test for Nicotine Dependence [FTND][9] score $\geqslant 6$) used 2 tablets/h; low-dependent smokers (FTND score <6) used 1 tablet/h. The dose was tapered off during months 4–6. No further use of nicotine replacement was allowed during the 6 months follow-up period to 1 year. All medications were supplied by Pfizer Consumer Healthcare, Helsingborg, Sweden.

Assessments

Seven visits were arranged the day before quit-day (Visit 1) and at 1 week (Visit 2), 2 weeks (Visit 3), 8 weeks (Visit 4), 12 weeks (Visit 5), 6 months (Visit 6), and 1 year (Visit 7) after quitting. At visit 1,

patient characteristics and vital signs were assessed. A smoking history was obtained and the carbon monoxide (CO) content of expired air was measured using an EC50 Bedfont monitor (Technical Instruments, Sittingbourne, England). Readings were recorded in parts per million (ppm) of CO (non-smokers <10 ppm; smokers 10–75 ppm).[10] Pulmonary function was measured according to the American Thoracic Society recommended standards.[11] Spirometry was performed in the sitting position with subjects expiring maximally into an electronic spirometer (Minato, Autospiro AS-500) after a maximal inspiratory manoeuver. At least 3 volume–time and flow–volume curves were obtained and the forced vital capacity (FVC) and the FEV_1 calculated. These parameters were expressed in absolute terms and as a percentage of predicted.[12]

Methacholine airway challenge test[13] was performed at visits 1, 4, 6 and 7. After baseline spirometry, the subject inhaled diluent (normal saline), followed by spirometry. Subjects whose baseline values were normal and whose FEV_1 fell by $<10\%$ after inhalation of diluent received three cumulative doses of methacholine (0.4, 2.8 and 7.6 μmol, respectively) via a nebuliser delivering particles 3 μm in diameter. Spirometry was performed before and 3–5 min after methacholine inhalations. Subjects whose FEV_1/FVC was $\leqslant 80\%$, baseline $FEV_1 \leqslant 70\%$, or whose FEV_1 fell by $\geqslant 10\%$ after saline, received an initial dose of methacholine of 0.2 μmol. The test was discontinued if the FEV_1 fell by $\geqslant 20\%$ vs. baseline.

Methacholine responsiveness was analysed as both a categorical and continuous variable. The former was a fall in FEV_1 equal to or greater than 20% (AHR+). The latter was the linear two-point dose–response slope (DRS), calculated as the percentage of fall of FEV_1 at last dose divided by the total dose of methacholine administered.[14] A constant of +2.5 was added to all DRS values and values were expressed as 1/slope+2.5 in order to achieve approximate normality (Gaussian distribution) in a large number of non-exposed subjects.[13] The *lower* the value of this adjusted reciprocal DRS the *greater* the airway responsiveness.

Respiratory symptoms were recorded using the Respiratory Changes Questionnaire[15] which evaluates cough, phlegm, shortness of breath and bronchitis, using the question: "How do you feel now compared to 6 months ago?" Response options were: 1 = much worse, 2 = worse, 3 = no change, 4 = better and 5 = much better. The statistical evaluation was performed on differences between baseline and 1 year.

Atopic status was measured at baseline by skin prick test reaction to house dust, house dust mites, animal danders, pollens, moulds, wheat, rye, oat, and barley flours, and bakers' yeast. A 9% codeine phosphate solution and saline were used as positive and negative controls. After 15 min, wheal size was recorded as the long axis and its perpendicular. A test was positive if the mean wheal size at 15 min was $\geqslant 3$ mm.[5] Atopy was defined as one or more positive reactions.

Smoking status

Subjects were classified into: (1) "sustained quitters" (complete abstinence at every visit; expired CO <10 ppm); (2) "reducers" (reduction in cigarette consumption vs. baseline; exhaled CO lower than baseline after $\geqslant 6$ h of active smoking); (3) "continuing smokers" (failure to decrease the number of cigarettes compared with baseline).

Statistical analysis

Statistical analysis was carried out with the SAS statistical software.[16] Data were summarized using means, standard deviations, and percentages. Categorical variables were compared using the χ^2-test or the Fisher exact test. For continuous variables *t*-tests were used. At baseline, the relationship between potential explanatory variables (age, sex, tobacco consumption, symptoms, and atopy) and airway responsiveness (adjusted reciprocal DRS) was assessed using multiple linear regression analysis. Within-group analysis was carried out examining the trend in change in adjusted reciprocal DRS and FEV_1 over time for quitters, reducers and sustained smokers, and by comparing the trend of each group vs. that of the other groups by repeated measures ANOVA (RM ANOVA).

Results

Baseline characteristics

A total of 165 workers (75 bakers, 25 hairdressers, 14 woodworkers, 11 painters, and 40 miscellaneous exposures) participated in the study. One male subject refused to perform the methacholine challenge testing at entry leaving 164 files for analysis of responsiveness.

The baseline characteristics of the participants are shown in Table 1. Workers completing the study tended to be older, have lower CO levels and be less

Table 1 Characteristics of exposed workers at inclusion.

Parameter	All workers ($n = 165$)*	Workers lost to follow-up ($n = 97$)	Workers completing the study ($n = 67$)	P value†
Demographics				
Male/female	137/28	78/19	58/9	—
Age (years)	37.6 (9.1)	35.7 (8.7)	40.3 (9.1)	*0.001*
Height (cm)	173.1 (7.4)	173.1 (7.7)	173.0 (7.0)	NS
Weight (kg)	74.6 (14.1)	74.7 (15.0)	74.1 (12.8)	NS
Smoking history				
FTND score	6.5 (2.1)	7.0 (2.0)	5.7 (1.9)	*0.001*
Carbon monoxide (ppm)	31.2 (10.5)	32.6 (10.5)	29.3 (10.4)	*0.049*
Pack/year	30.2 (17.8)	29.6 (18.5)	31.0 (16.9)	NS
Symptoms				
Cough	2.62 (0.66)	2.67 (0.62)	2.55 (0.70)	NS
Phlegm	2.72 (0.57)	2.71 (0.56)	2.73 (0.59)	NS
Shortness of breath	2.42 (0.65)	2.31 (0.68)	2.57 (0.58)	NS
Bronchitis	2.82 (0.40)	2.79 (0.43)	2.85 (0.36)	NS
Atopy yes, n (%)	45 (27%)	27 (28%)	18 (27%)	NS
Pulmonary function tests				
FEV_1, % predicted	87.2 (12.5)	86.5 (12.2)	88.1 (12.9)	NS
FVC, % predicted	94.1 (12.0)	92.9 (11.4)	95.8 (12.8)	NS
FEV_1/FVC % observed	77.4 (8.1)	78.1 (7.8)	76.4 (8.3)	NS
Airway responsiveness*				
AHR+, yes (%)				
Men	52 (38%)	28 (36%)	20 (34.5%)	NS
Women	20 (71.5%)	14 (74%)	7 (78%)	NS
P value	*0.002*	*0.006*	*0.025*	
DRS				
Men	0.217 (0.112)	0.225 (0.112)	0.207 (0.112)	NS
Women	0.158 (0.090)	0.167 (0.099)	0.140 (0.078)	NS
P value	*0.010*	*0.071*	*0.089*	

FTND = Fagerström test for nicotine dependence.
FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; AHR+, positive methacholine airway challenge [fall in $FEV_1 > 20\%$]; DRS, adjusted reciprocal dose–response slope 1/[%fall FEV_1/μmol+2.5].
The italic values concern the P values for VERTICAL comparisons between men and women.
*One male subject refused to perform methacholine challenge testing.
†For comparisons between workers having completed the study vs. workers lost to follow-up.

nicotine dependent than the workers lost to follow-up. No significant differences between the two groups were found in terms of symptoms, atopy, lung function and airway responsiveness. However, analysis by gender found women to be more hyperreactive than men in all groups; using the adjusted reciprocal DRS the difference was significant only for the group as a whole.

The relative contribution of potential variables for DRS was assessed in the group as a whole by multiple linear regression analysis (constant = 0.111; $R^2 = 0.21$). Baseline FEV_1 (coefficient = 0.0034; SE = 0.006; $P < 0.001$) and female gender (coefficient = −0.0752; SE = 0.0210; $P < 0.001$) were the only variables correlated with DRS; the presence of bronchitis was of borderline significance (coefficient = −0.0386; SE = 0.0196; $P = 0.051$).

Impact of smoking status on symptoms, lung function and airway responsiveness

Sixty-seven subjects (40.6% of total) completed the study. Of these 32 (19.4% of total) were sustained quitters; 17 (10.3% of total) had reduced smoking

Table 2 One-year change in symptoms* in occupationally exposed smokers according to their final smoking status.

Smoking status at 1 year	*n*	Cough			*T*-test	Phlegm			*T*-test	Shortness of breath			*T*-test	Bronchitis			*T*-test
		Baseline	One-year change†			Baseline	One-year change†			Baseline	One-year change†			Baseline	One-year change†		
		Mean (SD)	Mean (SD)	*P*‡		Mean (SD)	Mean (SD)	*P*‡		Mean (SD)	Mean (SD)	*P*‡		Mean (SD)	Mean (SD)	*P*‡	
Quitters	32	2.63 (0.71)	1.53 (1.14)	<0.001§	<0.001§	2.72 (0.52)	1.41 (1.0)	<0.001§	<0.001§	2.69 (0.59)	1.34 (0.94)	<0.001§	<0.001§	2.88 (0.34)	0.81 (0.90)	<0.001§	<0.001§
Reducers	17	2.53 (0.80)	0.59 (1.12)	0.046§	0.046§	2.76 (0.75)	0.35 (1.00)	0.163	0.027§	2.53 (0.62)	0.53 (0.94)	0.034§	0.027§	2.82 (0.39)	0.47 (0.80)	0.027§	0.027§
Smokers	18	2.44 (0.62)	0.33 (0.84)	0.111	0.111	2.72 (0.57)	0.00 (0.59)	1.000	0.083	2.39 (0.50)	0.33 (0.84)	0.111	0.083	2.83 (0.38)	0.17 (0.38)	0.083	0.083

P value for reduction between groups: cough $P = 0.005$, phlegm $P < 0.00005$, shortness of breath $P = 0.0001$, bronchitis $P = 0.0224$.

*Symptoms were rated using 1 = much worse, 2 = worse, 3 = no change, 4 = better, 5 = much better.

†Change in respiratory symptoms from baseline, increase in rating score.

‡*P* value for change within groups after 1 year.

§Significant $P < 0.05$.

by 50% or more and 18 (10.9% of total) were continuing smokers.

The impact of smoking status on symptoms is shown in Table 2. Smoking cessation improved symptoms markedly, while smoking reduction improved all symptoms but phlegm. No change was noticed in symptom scores among continuing smokers.

Table 3 shows the impact of smoking intervention on FEV_1 and DRS. Six male participants refused to perform the challenge test thus leaving 61 files for analysis (29 bakers, 10 hairdressers, 5 painters, 4 printers, 4 woodworkers, and 9 in miscellaneous occupations). From the 61 remnants 31 were quitters, 17 reducers and 13 continuing smokers. At 1 year, a slight improvement was found in FEV_1 among quitters and a marked deterioration among reducers and continuing smokers. Using RM ANOVA the differences were significant only for comparisons between quitters and reducers ($P = 0.038$) or smokers ($P = 0.006$).

Concurrent changes in the adjusted reciprocal DRS showed a slight improvement in quitters and reducers but an aggravation in continuing smokers but the differences among the various groups were not significant. Incidentally, changes of borderline significance were seen for comparisons between smokers and the other groups.

Discussion

This study showed that in occupationally exposed workers smoking cessation markedly improved symptoms and slightly improved the annual decline in FEV_1; reducing smoking resulted in smaller improvements in symptoms but deterioration in FEV_1. In addition, the study found that the 1-year change in FEV_1 was not modulated by airway responsiveness.

The improvement in respiratory symptoms in quitters was not surprising. Although no similar data are available for comparison, this finding is in line with cross-sectional studies in the general population showing lower prevalence rates of symptoms in ex-smokers compared with smokers[17] and with longitudinal studies showing that most intermittent symptoms decrease fairly rapidly after smoking cessation.[18]

Smoking reduction resulted in smaller improvements in symptoms. Once again, data from working populations are not available for comparison. An anecdotal report of a patient with COPD found an improvement in symptoms after drastic smoking reduction.[19] In a case study ($n = 17$) all five

Table 3 Lung function and airway responsiveness at inclusion and 1 year in occupationally exposed workers ($n = 61$) stratified by smoking status, plus smoking characteristics at inclusion.

Parameter		Quitters $n = 31$ (SD)	Reducers $n = 17$ (SD)	Smokers $n = 13$ (SD)
FEV_1	Baseline survey*	87.2 (12.3)	87.5 (14.0)	88.4 (14.9)
	Eight weeks	0.09 (0.29)	0.04 (0.23)	0.04 (0.23)
	Six months	0.01 (0.33)	−0.004 (0.32)	−0.15 (0.18)
	One year	0.04 (0.31)	−0.14 (0.27)	−0.16 (0.24)
P value†	*Quitters* vs.	—	*P = 0.038*	*P = 0.006*
	Reducers vs.	—	—	*P = 0.554*
DRS	Baseline survey	0.209 (0.128)	0.195 (0.088)	0.176(0.093)
	Eight weeks	−0.005 (0.075)	0.020 (0.057)	0.024 (0.088)
	Six months	0.002 (0.082)	0.030 (0.077)	0.015 (0.048)
	One year	0.012 (0.079)	0.036 (0.107)	−0.012 (0.056)
P value†	*Quitters* vs.	—	*P = 0.531*	*P = 0.053*
	Reducers vs.	—	—	*P = 0.057*
FTND at inclusion	5.4 (1.8)	6.0 (1.9)	5.7 (2.2)	
Pack years at inclusion	29.8 (19.7)	28.3(12.0)	35.0 (16.9)	

DRS: adjusted reciprocal dose–response slope = 1/[%fall FEV_1/μmol+2.5]; FEV_1 = forced expiratory volume in 1 s; FTND = Fagerström test for nicotine dependence.

*Percent predicted.

†By repeated measures ANOVA (RM ANOVA).

patients with airflow obstruction who could maintain a substantial reduction (from 30 to 6 cigarettes a day) for 18 months showed improved symptoms (and lung function).[20] In our study, 13 of 17 reducers were able to cut their cigarette consumption by 50% or more, which probably have improved symptoms through a decrease in airway inflammation.[21] The less pronounced improvement of symptoms in reducers is in line with data from the general population[7] and asthmatics.[8]

There was a positive effect of smoking cessation on lung function, with quitters showing a slight increase in FEV_1 at end-study. Although small in absolute terms (~40 mL) such improvement is clinically important as it causes an upward shift of FEV_1 decline with ageing thus contributing to prevent airway disability. Moreover, this improvement in FEV_1 in quitters contrasted with the marked deterioration in reducers and continuing smokers. This beneficial effect of smoking cessation in workers undergoing occupational exposure has not been reported previously; it suggests that for ordinary levels of exposure the adverse respiratory effects of smoking outweigh those of occupational pollutants.

The improvement in FEV_1 in quitters and its deterioration in reducers and continuing smokers was not modulated by airway responsiveness (Table 3, lower panel). This was rather surprising given the well-known relation between baseline airway calibre and airway responsiveness documented previously in the general population[22] and occupationally exposed workers.[13]

How to interpret this discrepancy? One possible explanation is the greater intrasubject variability in measures of responsiveness compared with FEV_1. Another possibility is that, although closely linked, the level of airway obstruction and the occurrence of increased responsiveness are separate phenomena. This idea is not new. In the Lung Health Study[23] part of the benefit from smoking cessation on the change in AHR could not be accounted for by the beneficial effect on the decline in FEV_1. In an earlier study, Kraan and colleagues[24] treated patients with allergic asthma with inhaled budesonide and noted a maximal improvement in FEV_1 within 2 weeks, while the airway responsiveness also improved but only several weeks later; they concluded that the improvement in AHR was not only due to a change in airway calibre. We speculate that this factor might have played a role in our results as baseline FEV_1 explained only 21% of the variability of DRS (see Results).

This study has potential limitations. First, the sample size at end-study was small. However, numerous would-be participants were unable to enrol due to working constraints; in addition, there was a high dropout rate as is common in cessation

trials. Notwithstanding, the subsamples of quitters, reducers and continuing smokers were sufficient for us to note a significant change in symptoms and FEV_1. These results are strengthened by our inclusion of young smokers since in slightly affected or unaffected subjects there is virtually no room for improvement. Second, the period of observation was relatively small. However, since cigarette smoking is deleterious for the lungs, a longer observation period could only aggravate symptoms and the annual decline in FEV_1 in smokers, thus rendering the difference with respect to quitters even more significant. Finally, the exposure was heterogeneous in nature. However, all substances involved are likely to cause airway inflammation and airflow obstruction.[3] Incidentally, although no environmental assessments could be performed (the subjects worked in shops scattered over a large area), the working conditions remained stable throughout follow-up making it unlikely that the improvement in symptoms and lung function in quitters was due to changes in exposure.

In conclusion, this study documented the beneficial effect of smoking cessation on symptoms and decline in FEV_1 in workers undergoing workplace exposure to respiratory pollutants. A less marked effect on symptoms was also noted in reducers. Further, the study showed that the 1-year change in lung function was not modulated by AHR, suggesting that airway calibre might not be the only determinant of airway responsiveness. Finally, the study highlights the need to better ascertain the benefits of smoking reduction as this approach might act as a gateway to complete cessation.[25]

Acknowledgments

The authors are indebted to Mrs. S. Klein for performing the methacholine challenge tests, to Pascal Wild, Ph.D. for his comments and suggestions and to the subjects for their participation.

Contributions of authors: Abraham Bohadana had the original idea, recruited the subjects, co-designed the study and drafted the report. Fredrik Nilsson co-designed the study and managed the data. Äke Westin performed statistical analysis. Nadine Martinet and Yves Martinet provided critical appraisal and review. All authors approved the final version of this paper.

Contributions of the funding support: Apart from F. Nilsson and A. Westin the funding body had no contribution on the preparation of this paper.

Competing interests: None to declare.

References

1. Fletcher C, Peto R. The natural history of chronic airflow obstruction. *Br Med J* 1977;**1**:1645–8.
2. Xu X, Dockery DW, Ware JH, et al. Effects of cigarette smoking on rate of loss of pulmonary function in adults: a longitudinal assessment. *Am Rev Respir Dis* 1992;**146**:1345–8.
3. Becklake M. Chronic airflow limitation: its relationship to work in dusty occupations. *Chest* 1985;**88**:608–17.
4. Tashkin DP, Altose MD, Connett JE, for the Lung Health Study Research Group, et al. Methacholine reactivity predicts changes in lung function over time in smokers with early chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1996;**153**:1802–11.
5. Tabona M, Chan-Yeung M, Enarson D, et al. Host factors affecting longitudinal decline in lung spirometry among grain elevator workers. *Chest* 1984;**85**:782–6.
6. Pham QT, Mur JM, Chau N, et al. Prognostic value of acetylcholine challenge test: a prospective study. *Br J Ind Med* 1984;**41**:267–71.
7. Bolliger CT, Zellweger J-P, Danielsson T, et al. Influence of long term smoking reduction on health risk markers and quality of life. *Nicotine Tobacco Res* 2002;**4**:433–9.
8. Tonnesen P, Pisinger C, Hvidberg S, et al. Effects of smoking cessation and reduction in asthmatics. *Nicotien Tobacco Res* 2005;**7**:139–48.
9. Fagerström KO, Schneider NG. Measuring nicotine dependence: a review of the Fagerström Tolerance Questionnaire. *J Behav Med* 1989;**12**:159–82.
10. Jarvis MJ, Russell MA, Saloojee Y. Expired air carbon monoxide: a simple breath test of tobacco smoke intake. *Br Med J* 1980;**281**:484–5.
11. American Thoracic Society: Standardization of spirometry. 1994 update. *Am J Respir Crit Care Med* 1995;**152**:1107–36.
12. Quanjer PhH, Tammeling GJ, Cotes JE, et al. Lung volumes and forced ventilatory flows. Report working party. Standardization of lung function tests. European Community for steel and coal. *Eur Respir J* 1993;**6**(Suppl 16):5–40.
13. Bohadana AB, Massin N, Wild P, et al. Respiratory symptoms and airway responsiveness in apparently healthy workers exposed to flour dust. *Eur Respir J* 1994;**7**:1070–6.
14. O'Connor G, Sparrow D, Taylor D, et al. Analysis of dose–response curves to methacholine. An approach suitable for population studies. *Am Rev Respir Dis* 1987;**136**:1412–7.
15. European Community Respiratory Health Survey. Variations in the prevalence of respiratory symptoms, self reported asthma attacks, and use of asthma medication in the European Community Respiratory Health Survey (ECRHS). *Eur Respir J* 1996;**9**:687–95.
16. SAS/STAT. *User's Guide. Version 6*. Cary, NC: SAS Institute; 1989.
17. Rijcken B, Schouten JP, Weiss ST, et al. The relationship of nonspecific bronchial hyperresponsiveness to respiratory symptoms in a random population sample. *Am Rev Respir Dis* 1987;**136**:62–8.
18. Kryzanovski M, Robbins DR, Lebowitz MD. Smoking cessation and changes in respiratory symptoms in two populations followed for 13 years. *Int J Epidemiol* 1993;**22**:666–73.
19. Fagerström K. From reduced smoking to quitting: improvements in COPD symptom and lung function: a case report. *Nicotine Tobacco Res* 2001;**3**:93–4.
20. Jimenez-Ruiz C, Solano S, Viteri S, et al. Harm reduction—a treatment approach for resistant smokers with tobacco related symptoms. *Respiration* 2002;**69**:452–5.
21. Rennard SI, Daughton D, Fujita J, et al. Short-term smoking reduction is associated with reduction in measures of lower

respiratory tract inflammation in heavy smokers. *Eur Respir J* 1990;**3**:752–9.
22. Sparrow D, O'Connor GT, Rosner B, et al. The influence of age and level of pulmonary function on nonspecific airway responsiveness. The Normative Aging Study. *Am Rev Respir Dis* 1991;**143**:978–82.
23. Wise RA, Kanner RE, Lindgren P, for the Lung Health Study Research Group, et al. The effect of smoking intervention and inhaled bronchodilator on airways reactivity in COPD. *Chest* 2003;**124**:449–58.
24. Kraan J, Koetter GH, Van der Mark THW, et al. Dosage and time effects of inhaled budesonide on bronchial hyperreactivity. *Am Rev Respir Dis* 1988;**137**:44–8.
25. Fagerstrom KO. Can reduced smoking be a way for smokers not interested in quitting to actually quit? *Respiration* 2005;**72**:216–20.