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Ventilatory lung function in young cigarette smokers: a study of susceptibility

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ABSTRACT: The objective of this study was to estimate the effect of cigarette smoking on ventilatory lung function among young adults with special emphasis on the recognition of susceptible subgroups.

In a cross-sectional study of 1,044 adults aged 15–40 yrs, a statistically significant linear relationship between quantity of smoking in cigarette-years and level of forced expiratory volume in one second (FEV_1) was found. Among current cigarette smokers, FEV_1 level was on average 35 ml lower for each 100 cigarette-years of exposure (corresponding to smoking of ten cigarettes per day for 10 yrs) compared to lifelong non-smokers in a linear regression adjusted for confounding.

Potentially susceptible subgroups were studied by introducing interaction terms between quantitative smoking and gender, wheezing, atopy, asthma, childhood respiratory illness and exposure to environmental tobacco smoke during the growth period, to the additive linear regression model explaining the FEV_1 level. Wheezing was found to modify the effect of smoking significantly: the FEV_1 level was on average 68 ml lower for each 100 cigarette-years due to interaction between smoking and wheezing. An introduction of the interaction term eliminated the independent effect of smoking.

The results suggest that the detrimental effect of smoking on FEV_1 in young adults may be limited to individuals with wheezing. Thus, the presence of wheezing among smokers indicates a higher risk for low level of ventilatory lung function compared to smokers who do not wheeze.
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Cigarette smoking has been shown to be a predominant determinant of ventilatory lung function level in a number of cross-sectional studies [1–12]. Some studies have indicated a dose-response relationship between forced expiratory volume in one second (FEV_1) and the number of cigarettes smoked [4, 10, 11]. Longitudinal studies have demonstrated an accelerated rate of decline of FEV_1 with age among smokers [13–21], and personal smoking has been shown to lead to a significant decrease in the growth rate of FEV_1 in children [22]. The study by FLETCHER and PETO [13] suggested that only a minority of smokers eventually develops disabling obstructive airways disease. This has lead to a concept of the "susceptible smoker". However, the determinants of this susceptibility have not yet been identified.

There is also evidence that factors other than smoking contribute to the development of ventilatory impairment. For instance, the role of age and $alpha_1$-antitrypsin deficiency is firmly established. Other putative determinants of ventilatory lung function are genetic factors (such as respiratory diseases in first degree relatives, ABO-blood group, and ABH-secretor status), atopy and nonspecific airways hyperresponsiveness, childhood respiratory illness, the presence of other respiratory diseases and symptoms, socioeconomic status, alcohol consumption, exposure to environmental tobacco smoke (ETS), outdoor air pollution and certain occupational exposures [23, 24]. The possibility that some of these factors might modify the effect of cigarette smoking on lung function is a conceptually plausible explanation for differences in individual susceptibility.

Obstructive airways disease develops gradually over time. A better understanding of the early stages in the evolution of ventilatory impairment would facilitate disease prevention. Studies on the effects of cigarette smoking during early adulthood may help identify factors that determine the susceptibility of individuals to the hazardous effects of tobacco smoke early in the development of ventilatory impairment.

The objective of the present study was to examine the effect of smoking on ventilatory lung function in young adults and to evaluate the possibility of the modification of this effect by factors which might characterize an individual's sensitivity to the effect of tobacco smoke.

Methods

Study population

The study population consisted of 1,044 young Caucasian adults, who were 15–40 yrs of age in 1980, when the information for the present study was gathered. The study population was recruited from two downtown Montreal banking institutions, a junior college and a high school by sending a letter of invitation. Volunteer rates were 25% and 61% in the two banks and 28% in the high school. The college volunteer rate was unknown because the rules did not permit individual letters of invitation to be sent. Those who were pregnant at the time of examination were not tested. A total of 1,167 subjects were examined and after excluding non-Caucasians, those with technically unsatisfactory flow volume curves and those not in the desired age range, the final study population consisted of 1,044 subjects. In a comparison of the characteristics of the study population and the source population in the four institutions no important differences were found with respect to age, gender or smoking status. Details of the study population have been described previously [25]. The only difference between the present study population and that of the previous report was that the asthmatics and those in the age range 36–40 yrs were included in the present study.

Measurements

All subjects answered a standardized interviewer-administered respiratory questionnaire (ATS-DLD-78-A) [26]. Each subject then performed three maximal expiratory flow manoeuvres, which were recorded with a heated Fleisch No. 4 pneumotachygraph. The largest FEV_1 from the acceptable tracings was used in the analysis. Thirty five (3.4%) subjects had only one acceptable spirometry curve. Their measurements are included in the final results, since their exclusion did not effect the results of regression analysis. The previous report includes a more detailed description of the lung function measurements [25].

Statistical methods

Outcome. Measured FEV_1 was used as the outcome to describe the level of ventilatory function. The outcome was used unadjusted to leave it in the most understandable and natural form. This was also justified by VOLLMER *et al.* [27] in their empirical comparison of models with unadjusted and adjusted outcomes, in which adjustment for height by dividing the outcome by height or some power function of it was shown to bring no improvement compared to a model in which height was included as an independent variable. Age and Quetelet index ($100 \times (\text{weight}/\text{height}^2)$) were also included as independent determinants in the regression model, rather than calculating adjusted or predicted values.

Exposure. Quantitative effect of cigarette smoking in current smokers was measured in cigarette-years, which were calculated by multiplying the duration of smoking by the average number of cigarettes smoked daily from the start of the habit. The contrast of current cigarette smoking with lifelong nonsmoking was achieved by including in the regression analysis indicator ("dummy") variates of ex-smoking of cigarettes (1=yes, 0=no) and other smoking (1=current or ex-smoker of pipe or cigar, 0=no pipe or cigar smoking) in addition to the quantitative variate of cigarette-years for current smokers. Outcome in the reference category was thus defined when all the variates of smoking were 0, and the reference category stayed "clean" by use of ex-smoker and other smoker indicators [28].

Fourteen subjects who had exposure of 500 or more cigarette-years (c–y) were excluded from the final regression analysis, since there was not enough information to get a reliable estimate of the effect of exposure above this value (the frequency distribution was 11 subjects with 500–599 c-y, 2 subjects with 600–699 c-y and 1 subject with 700–799 c-y).

Covariates. All potential determinants of FEV_1 level measured in the study were considered as potential confounders of the outcome-exposure relationship. The following variates were examined: age, gender, height, Quetelet index, wheezing, atopy, doctor-diagnosed asthma, early childhood respiratory illness, regular exercise, exposure to ETS during the growth period and occupational exposures to dust and to chemical fumes for a year or more. Height and weight (Quetelet index) are physiological determinants of ventilatory lung function level. Wheezing was considered in the analysis as an indicator of bronchial hyperresponsiveness according to the rationale given in the Epidemiology Standardization Project of ATS-DLD-78-A [26]. The study subjects represent an age range, which covers both late growth and early decrease in the natural development of ventilatory lung function [29]. The relationship between FEV_1 and age was thus expected to be nonlinear. Instead of using complex second degree parametric function, subjects were divided into two categories (0 if ≤25 yrs and 1 if >25 yrs) according to the age at which lung function is thought to have attained a plateau [30, 31]. This procedure was considered to control main part of potential confounding by age.

Wheezing was defined as being present, when the subject gave an affirmative answer to any of the questions: Does your chest ever sound wheezy or whistling when you have a cold? Occasionally apart from colds? On most days or nights? Wheezing was defined as being absent, when the answers to all of the above questions were negative. Atopy, doctor-diagnosed asthma, childhood respiratory illness and occupational exposure to dust or chemical fumes were defined as dichotomous variates based on the standardized questions of ATS-DLD-78-A.

The exposure to ETS was classified according to the answer (yes or no) to the question: Did any member of your family living at home smoke cigarettes while you

were growing up? The categorization of exercise habits was based on the question: Do you exercise regularly in competitive or recreational sport (1=yes, 0=no) ?

Analytic approach. In bivariate analyses, the mean FEV_1 level was studied in categories of determinants. The distribution of smokers, ex-smokers and nonsmokers was studied in categories of determinants to explore the potential confounders. The outcome-exposure relationship was then studied among males and females by using t-test and simple linear regression, while not controlling for confounding [32].

Finally a "causal model" for the quantitative effect of cigarette smoking on FEV_1 was fitted according to principles presented by MIETTINEN [28]. Firstly, a full multivariate linear regression model including exposure represented by quantitative cigarette-years and indicator variates of ex-smoking and other smoking and all potential confounders and nonconfounding determinants of outcome was fitted. The question of sensitivity to the effects of cigarette smoking was then addressed by studying modification in the additive model. The following variates were considered as potential modifiers: gender, wheezing, atopy, asthma, childhood respiratory illness and exposure to ETS during the growth period. With all the potential confounders in the model, modification of the effect of exposure was studied by introducing covariate-exposure product terms one by one and retaining them in the final model according to the statistical significance of the regression coefficients ($p<0.05$).

Results

Study population

The study population consisted of 418 men (40%) and 626 women (60%), aged 15–40 yrs. The overall mean age of the study population was 25 yrs (SD 5.8), 26 yrs (SD 6.0) in men and 24 yrs (SD 5.4) in women. The mean FEV_1 was 4.49 *l* (SD 0.64) in males and 3.21 *l* (SD 0.45) in females. Smoking characteristics of the study population are shown in table 1. The overall prevalence of current smoking was 39%, 28% in men and 46% in women. There were in all 16% ex-smokers, 22% in men and 13% in women. Table 1 also presents the quality and quantity of smoking and the distributions of the potential confounders in the study population.

Bivariate analyses

The mean FEV_1 among current cigarette smokers was lower than the mean of lifelong nonsmokers in both males and females (table 2). The mean FEV_1 was also studied in categories of the number of cigarette-years to describe the unadjusted relationships between FEV_1 and smoking habits in the study population (table 2).

The association between wheezing and the amount smoked is shown in table 3 for both men and women. The proportion of wheezers was 21% in men and 24% in women who had never smoked, both of which are statistically significantly lower than the proportion among current cigarette smokers (42% in men and 55% in women, $p<0.01$). In male smokers the proportion of wheezers did not differ essentially in different categories of cigarette-years. In female smokers with exposure to over 300 cigarette-years the proportion of wheezers was greater than in lighter smokers. There was no clear linear dose-response pattern however, either among females or males.

Table 1. – Smoking characteristics and the potential confounders and modifiers of the outcome-exposure relationship in the study population.

	Males		Females		Total	
	n	%	n	%	n	%
Population n	418		626		1044	
Current smoker	115	28	288	46	403	39
cigarettes only	103	25	286	46	389	37
pipe and/or cigar	12	3	2	0	14	2
Ex-smoker	92	22	80	13	172	16
cigarettes only	68	16	78	13	146	14
pipe and/or cigar	24	6	2	0	26	2
Lifelong nonsmoker	211	50	258	41	469	45
Cigarette-years*†						
1–99	32	31**	123	43**	155	40**
100–199	20	19	67	23	87	22
200–299	19	18	44	15	63	16
300–399	11	11	23	8	34	9
400–499	12	12	13	5	25	6
500–799	6	6	8	3	14	4
Age						
15–25 yrs	180	43	378	60	558	53
26–40 yrs	238	57	248	40	486	47
Wheezing	117	28	248	40	365	35
Atopy	145	35	260	42	405	39
Asthma	22	5	38	6	60	6
Childhood respiratory illness	9	2	12	2	21	2
Regular exercise	302	72	397	63	699	67
Exposure to ETS during growth	333	80	502	80	835	80
Exposure to dust	45	11	25	4	70	7
Exposure to chemical fumes	16	4	12	2	28	3

*: calculated by the average cigarette smoking rate × the duration of smoking; **: % of smokers of cigarettes only; †: 3 males (3%) and 8 females (3%) had missing values; ETS: environmental tobacco smoke.

Multivariate analysis

There was a significant linear relationship between smoking in cigarette-years and level of FEV_1 ($p=0.023$) (table 4). The estimated average reduction of FEV_1 level for 100 cigarette-years (corresponding to smoking of ten

Table 2. – The effect of smoking on FEV_1 among males and females (bivariate analysis)

	Males		Females		Total	
	Mean *l*	SE	Mean *l*	SE	Mean *l*	SE
Current smoker cigarettes only	4.48	0.06	3.15	0.03	3.50	0.04
Ex-smoker cigarettes only	4.48	0.08	3.33	0.06	3.86	0.07
Lifelong nonsmoker	4.52	0.04	3.25	0.03	3.82	0.04
Cigarette-years*						
1–99	4.46	0.12	3.22	0.04	3.47	0.06
100–199	4.67	0.17	3.18	0.05	3.52	0.09
200–299	4.31	0.14	3.07	0.06	3.44	0.09
300–399	4.60	0.18	2.96	0.09	3.49	0.16
400–499	4.46	0.14	2.81	0.12	3.60	0.19
500–	4.24	0.17	3.29	0.16	3.69	0.17

See table 1 for numbers of subjects in each category. *: calculated by the average cigarette smoking rate × the duration of smoking. FEV_1: forced expiratory volume in one second.

Table 3. – The proportion of subjects who reported wheezing among lifelong nonsmokers and current smokers in different categories of cigarette-years

	Males			Females			Total		
	N	n	%*	N	n	%	N	n	%
Lifelong nonsmokers	211	44	21	258	62	24	469	106	23
Current cigarette smokers total	103	43	42	286	156	55	389	199	51
Cigarette-years**†									
1–99	32	15	47	123	61	50	155	76	49
100–199	20	7	35	67	38	57	87	45	52
200–299	19	10	53	44	23	52	63	33	52
300–399	11	4	36	23	19	83	34	23	68
400–	18	5	28	21	12	57	39	17	44

N: number of subjects in each category; n: number of subjects reporting wheezing; %*: n/N×100; **: 11 subjects altogether had missing values of cigarette-years (3 males and 8 females); †: 5 of the subjects with wheezing had missing values of cigarette-years (2 males and 3 females).

cigarettes per day for 10 yrs) was 35 ml. Ex-smoking of cigarettes showed no statistically significant relationship with FEV_1 level.

The mean FEV_1 was 63 ml lower in the age group 26–40 yrs compared to the younger age group (p=0.047). Subjects with wheezing as well as those with a history of atopy had significantly lower mean FEV_1 than those without, while the difference in average FEV_1 between subjects reporting asthma and those not was of borderline significance. The mean FEV_1 among subjects reporting early childhood respiratory illness was on average 206 ml lower than among subjects without such a history (p=0.041). Also height and Quetelet index had a significant association with FEV_1 as expected.

Introduction of interaction terms of smoking with gender, wheezing, atopy, asthma, childhood respiratory illness and exposure to ETS during growth, into the model one by one showed only wheezing to be a significant modifier of the effect of cigarette smoking on FEV_1 (p=0.013) (table 4). When the product term wheezing × smoking was introduced, the regression coefficient of smoking was reduced close to zero, indicating that practically all of the effect in the "main effects model" was due to the effect in the subgroup of wheezers. The mean FEV_1 among smokers without wheezing was only 2 ml lower for each 100 cigarette-years than that in lifelong nonsmokers. Also, the independent effect of the presence of wheezing was reduced to less than half of that in the "main effects model" after inclusion of the product term. This suggests that wheezing was associated with lower level of FEV_1 mainly in the subgroup of smokers. Among nonsmoking wheezers the FEV_1 level was on the average 27 ml lower compared to subjects without wheezing. The mean loss of FEV_1 level due to interaction between smoking and wheezing was 68 ml for each 100 cigarette-years. The mean reduction of FEV_1 level in smokers with wheezing was calculated by summing the independent effects and the effect due to interaction. Thus, in this

Table 4. – Linear regression model of the quantitative effect of cigarette smoking on FEV_1 (*l*); main effects model and modification by wheezing

	Main effects model		Final model	
	Beta (SE-Beta)	p	Beta (SE-Beta)	p
Quantitative cigarette smoking (cigarette-years)	-0.00035 (0.00015)	0.023	-0.00002 (0.00020)	0.918
Ex-cigarette smoking* 1=yes, 0=no	0.024 (0.0430)	0.574	0.025 (0.0429)	0.554
Other smoking** 1=yes, 0=no	-0.079 (0.0773)	0.308	-0.085 (0.0771)	0.270
Gender 1=male, 0=female	0.611 (0.0460)	0.0001	0.609 (0.0459)	0.0001
Age yrs 1=26–40, 0=15–25	-0.063 (0.0316)	0.047	-0.062 (0.0315)	0.049
Height	0.044 (0.0023)	0.0001	0.044 (0.0023)	0.0001
Quetelet index	2.069 (0.4636)	0.0001	2.085 (0.4624)	0.0001
Wheezing 1=yes, 0=no	-0.071 (0.0319)	0.026	-0.027 (0.0364)	0.459
Atopy 1=yes, 0=no	-0.061 (0.0302)	0.045	-0.065 (0.0302)	0.032
Asthma 1=yes, 0=no	-0.123 (0.0638)	0.054	-0.130 (0.0637)	0.042
Childhood resp. illness 1=yes, 0=no	-0.206 (0.1008)	0.041	-0.210 (0.1006)	0.037
Regular exercise 1=yes, 0=no	0.026 (0.0313)	0.404	0.024 (0.0313)	0.440
Exposure to ETS during growth 1=yes, 0=no	-0.014 (0.0356)	0.703	-0.015 (0.0356)	0.677
Occupational exposure to dust 1=yes, 0=no	0.035 (0.0597)	0.557	0.036 (0.0595)	0.540
Occupational exposure to chemical fumes 1=yes, 0=no	-0.033 (0.0907)	0.714	-0.033 (0.0905)	0.716
Cigarette smoking × wheezing			**-0.00068 (0.00027)**	**0.013**
Intercept	-4.255 (0.3876)		-4.231 (0.3867)	
	r^2=0.71		r^2=0.71	

*: ex-smoking of cigarettes only; **: current or ex-smoking of pipe or cigar; ETS: environmental tobacco smoke; FEV_1: forced expiratory volume in one second.

group the FEV_1 level was on average 97 ml (2 + 27 + 68 ml) lower than that in lifelong nonsmokers without wheezing for the first 100 cigarette-years, and there was a reduction of 70 ml (2 + 68 ml) for each additional 100 cigarette-years.

Discussion

In the cross-sectional study of young adults a significant linear relationship between quantity of smoking in cigarette-years and level of FEV_1 was found. The FEV_1 level was on average 35 ml lower per each 100 cigarette-years compared to that of lifelong nonsmokers.

Common use of pack-years (or more appropriately cigarette-years, because the size of the pack varies) assumes that the total number of cigarettes describes the exposure. The two dimensions of quantitative exposure are the number of cigarettes smoked daily and the duration of smoking. Although both components contain a considerable source of error, it was considered important to take into account in the regression analysis

a quantitative estimate of smoking (cumulative exposure) as opposed to using a qualitative classification of exposure (current, ex-, other or lifelong nonsmoker). This was especially pertinent in the age range of the study population with a large variation in the total amount of exposure.

The estimate of the average quantitative effect of cigarette smoking on FEV_1 obtained in this study is close to the estimated effect of cumulative cigarette smoking among males (7.4 ml per pack-year) in the Six Cities Study [11], if it is assumed that the pack size they used was 20 cigarettes. Then 100 cigarette-years would correspond to 5 pack-years and 5×7.4 ml=37 ml reduction compared to 35 ml in the present study. Considering the difference in the age range studied, as well as the differences in the approach to the analysis, it is interesting to find this degree of agreement in the estimates. The effect of cigarette smoking on FEV_1 level was not significantly modified by gender in the present study.

The main objective of the study was to identify subgroups sensitive to the effects of cigarette smoking on ventilatory lung function. This was carried out by studying modification in the additive linear regression model. Wheezing was found to be a significant modifier of the effect of smoking on ventilatory lung function. Introduction of interaction term smoking × wheezing into the model reduced the independent effect of smoking close to zero, suggesting that the effects of smoking in this age group are limited to subjects with wheezing. Current smokers who also reported wheezing had on average 70 ml lower FEV_1 level for each 100 cigarette-years in contrast to lifelong nonsmokers and an additional reduction of 27 ml due to the presence of wheezing. Neither cigarette smoking among nonwheezers nor wheezing among nonsmokers was significantly associated with FEV_1 level.

The presence of wheezing can be considered an indicator of bronchial hyperresponsiveness [26]. DALES *et al* [33] concluded that attention should be directed towards more objective measures of bronchial hyperresponsiveness than questionnaire information. However, wheezing was shown to have 35% positive predictive value of bronchial hyperresponsiveness verified in methacholine challenge (sensitivity 26%, specificity 87%, likelihood ratio 2.0). If wheezing is accepted as an approximation of bronchial hyperresponsiveness, the results are consistent with the hypothesis that subjects with hyperresponsiveness of their airways are more sensitive to the effects of smoking. Some longitudinal studies focused on middle-aged male populations have shown among smokers an association between bronchial hyperresponsiveness and an accelerated decline of FEV_1 over the preceding years [34–36]. A similar relationship has been demonstrated among current and ex-smokers in grain elevator workers [37]. These studies have not examined the possibility of modification of the effect of smoking on lung function by bronchial hyperresponsiveness. LEBOWITZ *et al.* [38] found that, in a follow-up study of children 5.5–15 yrs of age initially, those who both smoked and reported respiratory symptoms had the lowest end-point residuals (observed-predicted value) of FEV_1 and maximum expiratory flow at 50% vital capacity ($\dot{V}max_{50}$). The interaction between smoking (current, ex-, lifelong non-) and symptoms was significant for both lung function outcomes. In a longitudinal study of children aged 5–19 yrs at initial examination, TAGER *et al.* [22] found no significant interaction between wheezing and personal smoking in an autoregression model explaining the level of FEV_1. The population experience in this study came mainly from a younger age period, which may explain the inconsistency with our results. Also the power to detect a significant interaction was limited due to the small number of smokers with wheezing in the study population.

The cross-sectional design of the present study raises a question concerning the sequence of events. Does smoking have adverse effects on ventilatory lung function mainly in a subgroup of smokers who have had the symptom of wheezing before taking up the smoking habit? Or does wheezing actually develop as a consequence of smoking concurrently with the decline in ventilatory function? These questions cannot be answered in a cross-sectional study and longitudinal studies are needed to address this issue. However, the importance of the presence of wheezing as an indicator of sensitivity to the effects of tobacco smoke was demonstrated in the present study.

The mechanisms underlying this susceptibility are not known, but some speculations can be made. If wheezing precedes the development of ventilatory impairment caused by cigarette smoking, a defect underlying bronchial hyperresponsiveness may be the basis for the susceptibility associated with wheezing. It has been suggested that bronchial hyperresponsiveness may be accompanied by an abnormality of airway epithelium, which could increase vulnerability to the harmful effects of cigarette smoke [39]. If wheezing develops concurrently with ventilatory impairment, this may indicate that wheezing and ventilatory impairment are both related to airway inflammation caused by cigarette smoke. The observation that blood total leucocyte count is inversely related to level of pulmonary function in adult men has provided indirect evidence on the potential role of inflammation in ventilatory impairment [40]. Inflammation of the peripheral airways and alveoli is proposed to be the basis of the pathogenesis of chronic obstructive pulmonary disease according to protease-antiprotease hypothesis [41]. On the other hand, increased bronchial hyperresponsiveness has been shown to be related to airway inflammation in some animal models [42, 43] as well as in a human physiology-pathology correlation study [44]. It is also possible that the inflammatory process associated with cigarette smoking leads to reduced airway dimensions, which may be associated with bronchial hyperresponsiveness because of altered airway geometry, for example due to the relationship between conductance and the 4th power of airway radius, or due to more central deposition of inhaled aerosols, or due to direct amplification of the response of bronchial muscle because its bulk is increased [45]. If airway inflammation underlies the association of wheezing with ventilatory impairment among cigarette smokers, the next step in understanding the susceptibility to the adverse effect of smoking on

lung function would be to examine the basic mechanisms that control the severity of inflammatory response provoked by cigarette smoke.

The results of the present study suggest that, during early adulthood, cigarette smoking is associated with a low level of ventilatory lung function among a subgroup of subjects with wheezing. Among the majority of young adults, there seems to be no association between cigarette smoking and level of ventilatory function. With a cross-sectional design, a causal relationship cannot be definitely elaborated. However, it can be concluded that the presence of wheezing among cigarette smokers indicates higher risk for low level of ventilatory function.

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Fonction pulmonaire ventilatoire chez les jeunes fumeurs de cigarette: étude des variations de sensibilité. M.S. Jaakkola, J.J.K. Jaakkola, P. Ernst, M.R. Becklace.

RÉSUMÉ: Le but de cette étude est d'estimer l'effet de la cigarette sur la fonction pulmonaire ventilatoire d'adultes jeunes, en insistant sur la recherche de sous-groupes particulièrement sensibles. Dans une étude transversale de 1.044 adultes âgés de 15 à 40 ans, l'on a décelé une relation linéaire statistiquement significative entre le tabagisme quantifié en années-paquet, et le niveau du VEMS. Chez les fumeurs de cigarettes habituels, le niveau du VEMS est en moyenne de 35 ml inférieur pour chaque 100 cigarettes-année d'exposition (ce qui correspond à fumer 10 cigarettes par jour pendant 10 ans), lors d'une comparaison avec des sujets qui n'ont jamais fumé, dans une étude de régression linéaire ajustée pour les facteurs confondants. Des sous-groupes potentiellement sensibles ont été étudiés, en introduisant des termes d'interaction entre la quantité fumée et le sexe, les sifflements, l'atopie, l'asthme, les maladies respiratoires de l'enfance, et l'exposition au tabagisme passif pendant la période de croissance, d'autre part un modéle de régression linéaire additionnel expliquant le niveau de VEMS. Le sifflement modifie de façon significative les effets de la fumée: le niveau de VEMS est en moyenne de 68 ml inférieur pour chaque 100 cigarettes-année, par suite de l'interaction entre le tabagisme et les sifflements. L'introduction de ce terme d'interaction élimine l'effet indépendant du tabagisme.
Ces résultats suggérent que l'effet défavorable de la fumée sur le VEMS chez de jeunes adultes pourrait se limiter à des individus atteints de sifflements respiratoires. Donc, la présence de sifflements chez les fumeurs indique un risque plus élevé de faibles valeurs de fonction pulmonaire ventilatoire par comparaison aux fumeurs qui n'ont pas de sifflement.
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