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Bronchial responsiveness and decline in FEV_1 in aluminium potroom workers

V. Søyseth*†, J. Kongerud†, H. Kjuus**, J. Boe†

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ABSTRACT: We have investigated the relationship between annual decline in forced expiratory volume in one second (ΔFEV_1) and bronchial responsiveness (BR) in aluminium potroom workers.

BR was measured in a cross-sectional study of 337 aluminium potroom workers half-way through a 6 yr follow-up study of lung function. A skin-prick test (SPT) was also performed. During follow-up the mean number of measurements of lung function (FEV_1) in each subject was 6.8.

Mean ΔFEV_1 was 21.3 ml·yr^{-1} (within subject SD=30.5 ml·yr^{-1}). Mean ΔFEV_1 was 57.0, 44.5 and 16.6 ml·yr^{-1} in subjects who had provocative concentration producing a 20% fall in FEV_1 (PC_{20}) ≤8.0, 8.1–32.0 and >32.0 mg·ml^{-1}, respectively. After adjustment for gender, atopy, smoking habit, FEV_1, age and familial asthma the association between BR and ΔFEV_1 was weakened, and was not statistically significant. A significantly accelerated decline in FEV_1 with age was found. The difference in ΔFEV_1 between smokers and nonsmokers was 39.3 ml·yr^{-1}, and between subjects who had a positive skin-prick test compared to subjects with a negative skin-prick test 39.6 ml·yr^{-1}. In subjects reporting work-related asthmatic symptoms the decline in FEV_1 was 43.2 ml·yr^{-1} greater than in asymptomatic subjects. In asymptomatic subjects, positive skin-prick test was also associated with increased ΔFEV_1.

These data indicate that a single measurement of BR is not a predictor of ΔFEV_1 in aluminium potroom workers. Smoking, work-related asthmatic symptoms, and positive reaction to skin-prick test in asymptomatic workers were risk factors of increased ΔFEV_1.

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*Hydro Aluminium, Årdal, Medical Dept, Årdal, Norway. †Dept of Thoracic Medicine, Rikshospitalet, University of Oslo, Norway. **Dept of Occupational Medicine, Telemark Central Hospital, Porsgrunn, Norway.

Correspondence: V. Søyseth
Hydro Aluminium, Ardal
Medical Department
PO Box 303
N-5870 Øvre Årdal
Norway

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In a cross-sectional study of a general population in western Norway, an increased prevalence of chronic obstructive disease was found in subjects who had worked in the aluminium industry [1]. KONGERUD and co-workers [2] found that the relative risk of airways obstruction increased with the duration of exposure in the potrooms. In another report, it was found that airflow limitation was closely related to increased bronchial responsiveness (BR)[3]. The association between decreased forced expiratory volume in one second (FEV_1) and BR has also been confirmed by other investigators [4, 5]. According to the "Dutch hypothesis" [6], smokers with chronic airflow limitation (CAL) may have an allergic constitution and increased nonspecific BR. This hypothesis has been supported by several reports [7–10]. However, in some of these studies, the adjustment for several potential confounders has been incomplete. Thus, the relationship between BR and annual decline in FEV_1 (ΔFEV_1) is incompletely understood.

Since increased BR seems to be a risk factor for the development of CAL, it is likely that BR could be a good predictor of ΔFEV_1. Moreover, as BR seems to decrease after removal from potroom exposure [11, 12], bronchial challenge testing could be a useful tool in the prevention of CAL under these settings. The aims of the present study were, thus, to investigate whether information from a cross-sectional survey could identify risk factors of increased ΔFEV_1, and therefore to: 1) examine whether BR is a predictor of ΔFEV_1 in aluminium potroom workers; and 2) compare bronchial challenge testing and a respiratory questionnaire as methods to identify workers with increased ΔFEV_1.

Methods

The study population was selected from a cross-sectional study of bronchial responsiveness in aluminium potroom workers in 1988, who participated in a follow-up study of lung function [3]. There were 380 workers employed in the potrooms, of whom 370 were available at the time of the examination by questionnaires and spirometry. Of these 370, four subjects were excluded from the methacholine challenge because they had FEV_1 <60% of predicted (obtained from a general asymptomatic urban population in Norway [13]), and 29

subjects refused to attend the bronchial challenge. Thus, 337 subjects gave their informed consent to participate in bronchial challenge testing: 38 females and 299 males, aged 18–67 yrs. Information about respiratory symptoms, smoking habits, familial asthma, and use of airway protection mask was obtained using a questionnaire [14]. Work-related asthmatic symptoms (WASTH) were defined as the combination of dyspnoea and wheezing, improving on days away from work, in subjects who had no asthma before employment. Details of the study population are described elsewhere [3].

Two dry bellow spirometers (Jones Pulmonaire, Jones Medical Instruments Co., Oak Brook, Illinois, USA) were used to measure FEV_1. Bronchial challenge to methacholine was performed in 337 workers using a shortened protocol of the COCKCROFT method [15, 3]. The response was expressed as the concentration of methacholine that could provoke a 20% decrease in FEV_1 from baseline (PC_{20}) [3]. BR was divided into three categories: bronchial hyperresponsiveness (BHR) (PC_{20} ≤8.0 $mg \cdot ml^{-1}$); minor responsiveness (PC_{20} 8.1–32.0 $mg \cdot ml^{-1}$); and normal responsiveness (PC_{20} >32.0 $mg \cdot ml^{-1}$) [3]. A skin-prick test (SPT) to five common aeroallergens was also performed [3], using allergen coated lancets (Phazet®, Pharmacia, Uppsala, Sweden). The test result was scored according to the largest weal to any of the five allergens: positive reaction if the largest weal was greater than the histamine reference; equivocal reaction if the largest weal was >1 mm and less or equal to the histamine reference; otherwise the test result was regarded as negative [3].

Lung function had been measured annually, during a 6 year follow-up from 1985 to 1991, by the same staff and spirometers. Some of the workers were tested more than once annually, due to temporary employment outside the potrooms, military service, or education. Some subjects started to work at the plant between 1985 and 1988, and some workers terminated their employment before 1991. Thus, the subjects had on unequal number of follow-ups. In 90% of the subjects, age at the cross-sectional survey deviated less than one year from age at the individual mean follow-up time.

Both spirometers were calibrated every half year with a 3 *l* syringe. At every visit, the subjects were asked to perform three expiratory manoeuvres: the best of two recordings should be reproducible within 100 ml or 5%, whichever was the largest. The lung volumes were converted to body temperature, pressure, and saturation (BTPS) values. All the recordings were obtained from the subjects in standing position, between 08.00 and 12.00 a.m.

Statistical analyses

Individual least-squares slopes of FEV_1 (b_i) *versus* time were calculated for each subject who had three or more recordings. These b_is were used as estimates of ΔFEV_1 and given as positive values if a decrease was estimated. In four of the 337 workers, only two recordings of FEV_1 were available. Thus, the analysis included the remaining 333 workers. A regression of b_is on

Table 1. – Weighted mean of annual decline in FEV_1 (ΔFEV_1 $ml \cdot yr^{-1}$) in 333 aluminium potroom workers at different levels of bronchial responsiveness stratified for gender, smoking habits, atopy, history of familial asthma, use of respiratory safety mask

	PC_{20} BHR ≤8.0 $mg \cdot ml^{-1}$	MR 8.1–32.0 $mg \cdot ml^{-1}$	NR >32.0 $mg \cdot ml^{-1}$	Mean	95% CI	
Gender						
Male	63.3 (12)	32.5 (18)	17.0 (265)	20.5	17.6 to 23.3	(295)
Female	40.1 (5)	87.3 (6)	12.5 (27)	28.1	20.0 to 36.2	(38)
Smoking						
Never	3.8 (2)	-134.1 (2)	-16.2 (78)	-19.5	-24.8 to -14.1	(82)
Former	100.3 (3)	30.0 (5)	2.5 (22)	17.6	9.4 to 25.9	(30)
Current	54.4 (12)	79.2 (17)	33.9 (192)	38.1	34.7 to 41.5	(221)
Skin test						
Negative	61.0 (13)	31.7 (17)	7.7 (218)	12.9	9.7 to 16.0	(248)
Equivocal	47.1 (2)	158.9 (1)	46.9 (38)	50.2	42.5 to 57.8	(41)
Positive	44.1 (2)	63.4 (6)	40.5 (36)	44.0	36.3 to 51.7	(44)
Familial asthma						
No	74.6 (12)	19.5 (15)	31.5 (204)	33.4	30.2 to 36.7	(231)
Yes	10.0 (4)	87.6 (9)	-33.7 (48)	-13.2	-19.2 to -7.9	(61)
Safety mask						
No	-2.2 (1)	3.8 (1)	-111.9 (29)	-102.4	-105.2 to -99.6	(31)
Yes	61.0 (16)	46.6 (23)	30.7 (263)	34.0	31.1 to 36.8	(302)
All	57.0 (17)	44.5 (24)	16.6 (292)	21.1	18.6 to 24.0	(333)
95% CI	46.2–67.7	34.8–54.2	13.7–19.5			

The inverse of the variance used in the weighted regression of ΔFEV_1 was used as weight. Results are ΔFEV_1 $ml \cdot yr^{-1}$, number of subjects in parenthesis. Negative values denote incline in FEV_1, positive values denote decline in FEV_1. BHR: bronchial hyperresponsiveness; MR: minor responsiveness; NR: normal responsiveness. 95% CI: 95% confidence interval of the mean; FEV_1: forced expiratory volume in one second; PC_{20}: provocative concentration producing a 20% fall in FEV_1.

the various covariates (listed in table 1) was calculated by a maximum likelihood weighted regression method (Appendix 1). The method is described as Method 1 by DIEM and LIUKKONEN [16]. The analyses were performed using the statistical package SYSTAT [17]. The maximum likelihood estimates of the coefficients of the covariates were obtained by defining the LOSS function [17] as the log-likelihood of the b_is [16]. The following covariates were included in the model: gender, atopy, age (continuous), smoking status, familial asthma, use of respiratory protection mask, and BR (Appendix 2). Lung function was expressed as standardized FEV_1 ($SFEV_1$, continuous), *i.e.* the difference between the observed and predicted value divided by residual standard deviation of the prediction lines [18]. As the relationship between ΔFEV_1 and $SFEV_1$ might depend on whether lung function was related to the time of inclusion in the study or to the end of follow-up, both these covariates were used in the analyses, as well as $SFEV_1$ at the cross-sectional survey. Age was expressed as the age at the cross-sectional survey. As lung function increases in the younger age groups [19], separate analyses were carried out in those younger than 25 yrs of age and in those who were 25 yrs or older.

The comparison between PC_{20} and respiratory symptoms as predictors of ΔFEV_1 was performed by stratified analysis [20], adjusting for smoking status using weights obtained from Step 1 of the weighted regression (smoking status was regarded as the main potential confounder). The stratified analysis was chosen because there were too few subjects to perform a full regression analysis in the different symptomatic subgroups. Similarly, a comparison between respiratory symptoms and response to the SPT was performed using the same method.

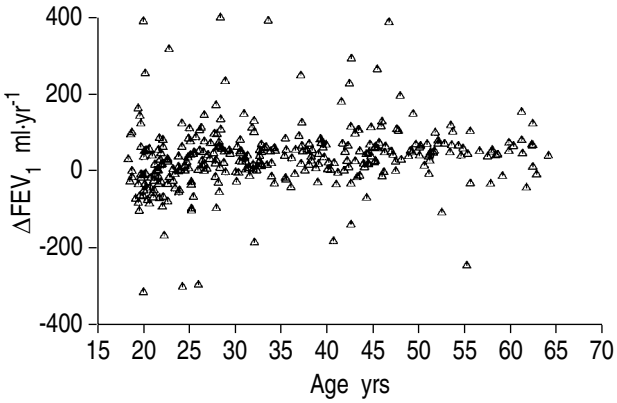

Fig. 1. – The relationship between annual change in forced expiratory volume in one second (ΔFEV_1) (ml·yr^{-1}) and age at the cross-sectional survey. Positive values of ΔFEV_1 denote decline in FEV_1.

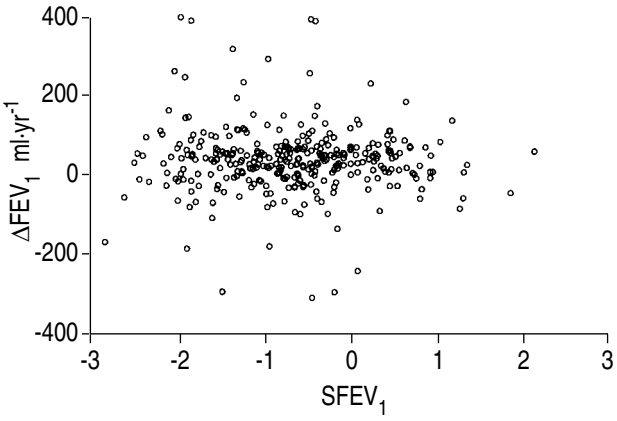

Fig. 2. – The relationship between annual change in forced expiratory volume in one second (ΔFEV_1) (ml·yr^{-1}) and $SFEV_1$ at the cross-sectional survey. Positive values of ΔFEV_1 denote decline in FEV_1. $SFEV_1$: standardized FEV_1.

Results

The total number of spirometric measurements was 2,206, in 333 subjects in whom more than two measurements were performed. The mean follow-up time and the mean number of spirometric measurements was 5.2 yrs (range 0.5–6.9 yrs) and 6.8 (range 3–14), respectively.

Mean decline in FEV_1

The weighted mean (using the inverse of the variance used in the maximum likelihood model as weights) of ΔFEV_1 was 21.2 ml·yr^{-1}. The mean standard deviation within subjects was 30.5 ml·yr^{-1}.

In table 1, weighted mean of ΔFEV_1 at different levels of BR stratified for gender, smoking status, atopy, familial asthma, and airway protection is shown. The weighted mean of ΔFEV_1 was 57.0 ml·yr^{-1} in those who had BHR, 44.5 ml·yr^{-1} in those who had minor responsiveness, and 16.6 mg·ml^{-1} in those who had normal responsiveness. In many of the strata a similar relationship between ΔFEV_1 and PC_{20} was not found (table 1). In subjects with positive or equivocal reaction to the SPT, ΔFEV_1 was 44.0 and 50.2 ml·yr^{-1}, respectively, compared to 12.9 ml·yr^{-1} in those who had a negative reaction. There was also evidence for increased ΔFEV_1 among smokers (38.1 ml·yr^{-1}) compared to past smokers (17.6 ml·yr^{-1}) and lifelong nonsmokers (-19.5 ml·yr^{-1}). A linear relationship between ΔFEV_1 and age was indicated (fig. 1), whereas, ΔFEV_1 seemed to be independent of $SFEV_1$ at the cross-sectional survey (fig. 2). A greater ΔFEV_1 was also found in those who used airways protection (34.0 ml·yr^{-1}) compared to those who reported no use of respiratory safety mask (-102.4 ml·yr^{-1}).

Factors influencing ΔFEV_1

Table 2 shows the results from the weighted regression analysis with ΔFEV_1 as the dependent variable and age, gender, smoking status, atopy, familial asthma, $SFEV_1$, use of respiratory safety mask and WASTH as independent variables. The adjusted ΔFEV_1 was significantly associated to age at the cross-sectional survey

Table 2. – Regression of annual decline (ΔFEV_1)(ml·yr^{-1}) on some characeristics of aluminium potroom workers, using a two-stage weighted regression

	β	SE	95% CI
Gender females *vs* males	-7.1	14.4	-35.4 to 21.2
Age continuous	1.9	0.4	1.1 to 2.6
Smoking status			
Ex *vs* nonsmoker	2.1	17.9	-33.0 to 37.2
Current *vs* nonsmoker	39.3	10.6	18.5 to 60.0
Skin test			
Equivocal *vs* negative	39.6	13.7	12.7 to 66.5
Positive *vs* equivocal	-3.6	17.7	-38.3 to 31.1
Familial asthma			
Present *vs* absent	-12.8	11.7	-35.8 to 10.1
$SFEV_1$ continuous	-7.4	5.4	-17.9 to 3.2
Safety mask			
Never *vs* occasional or always	-79.8	15.5	-110.2 to -49.5
WASTH yes *vs* asymptomatic	43.2	15.9	12.0 to 74.5
Bronchial responsiveness			
BHR *vs* MR	13.5	25.4	-36.9 to 63.2
Minor *vs* NR	0.2	18.4	-35.9 to 36.3

WASTH: work-related asthmatic symptoms; $SFEV_1$: standardized FEV_1. For further abbreviations see legend to table 1.

(1.9 ml·yr^{-1}). An overlap of the confidence intervals of the age effect was found between those who were 25 yrs or older and those who were younger than 25 yrs.

Current smokers had a significantly higher ΔFEV_1 (39.3 ml·yr^{-1}) than lifelong nonsmokers, whereas, there was no significant difference in ΔFEV_1 between ex-smokers and lifelong nonsmokers. Those who reported use of airway protection had a greater decline in FEV_1 than those who never used a safety mask (-79.8 ml·yr^{-1}).

There was no significant relationship between ΔFEV_1 and $SFEV_1$ at the cross-sectional survey or at inclusion to the study (-7.4 and 3.4 ml·yr^{-1}, respectively). The annual decline in FEV_1 was decreasing as $SFEV_1$ at the end of the follow-up increased (-11.5 ml·yr^{-1}; $p<0.01$): *i.e.* those who had the largest decline in FEV_1 had the lowest $SFEV_1$ at the end of the follow-up.

Whereas the crude rates indicated a progressive decline in FEV_1 with increasing BR, ΔFEV_1 was not significantly increased in subjects with BHR compared to subjects with minor responsiveness (13.5 ml·yr^{-1}), or subjects with minor responsiveness compared to subjects with normal responsiveness (0.2 ml·yr^{-1}). After deleting subjects with minor responsiveness from the model, there was no significant difference in ΔFEV_1 between subjects with BHR compared to subjects with normal responsiveness (20.2 ml·yr^{-1}). A continuous measure of BR was also used (slope of the dose-response curve (DRS)). No significant association, however was found between DRS and ΔFEV_1, and the use of DRS as a independent measure of BR caused no change between ΔFEV_1 and the other covariates in the model.

Different categories of respiratory symptoms were included in the model and the difference in ΔFEV_1 between those who reported respiratory symptoms and symptom-free subjects was estimated. The difference between those who reported dyspnoea, wheezing or cough and symptom-free subjects was 15.0, 16.9 and 24.5 ml·yr^{-1}, respectively. Only subjects with WASTH had a significantly increased ΔFEV_1 compared to symptom-free subjects.

Table 3. – Mean ΔFEV_1 (ml·yr^{-1}) according to different respiratory symptoms by degree of bronchial responsiveness

	BHR	MR	NR
No symptoms	28.3 (7)	-16.0 (13)	12.9 (219)
Dyspnoea	78.0 (10)	106.2 (8)	34.3 (52)
Wheezing	70.0 (8)	71.2 (9)	37.7 (44)
Cough	52.5 (6)	123.9 (5)	18.4 (32)
WASTH	66.8 (6)	81.0 (5)	69.2 (20)

Number of subjects in parenthesis. For abbreviations see legends to tables 1 and 2.

Table 4. – Difference in ΔFEV_1 (ml·yr^{-1}) between responders and nonresponders after stratification for smoking habits weighted by the inverse of the variance

	BHR - NR	MR - NR
No symptoms	4.3	28.2
Dyspnoea	31.6	37.9*
Wheezing	17.8	21.0
Cough	32.6	64.7*
WASTH	1.4	5.6

Results are differences in ΔFEV_1 between those who had BHR and NR and between those who had MR and NR. *: significantly different from zero, $p<0.05$. For abbreviations see legends to table 1.

ΔFEV_1, BR and respiratory symptoms

The relationship between ΔFEV_1 and BR in different categories of respiratory symptoms is shown in table 3. In subjects reporting WASTH, ΔFEV_1 seemed to be independent of PC_{20}. Only subjects with minor responsiveness reporting dyspnoea, wheezing or cough had an increased ΔFEV_1 compared to subjects with normal responsiveness (table 3). Thus, there was no evidence of increasing ΔFEV_1 with increasing BR in any of the symptom groups or in the asymptomatic subjects (table 4).

ΔFEV_1, BR and atopy

Similarly, the relationship between ΔFEV_1 and SPT reactivity was compared in subjects with different respiratory symptoms and asymptomatic subjects (table 5). As ΔFEV_1 was almost the same in subjects with equivocal and positive skin test reaction, subjects with more than 1 mm reaction to any of the allergens were pooled and compared with those who had a negative SPT. In asymptomatic subjects, the difference in ΔFEV_1 between those who had an equivocal or positive reaction to the

Table 5. – Weighted mean ΔFEV_1 ($ml \cdot yr^{-1}$) in subjects who had equivocal or positive reaction to the skin-prick test and subjects who had a negative reaction

Dependent variables	SPT negative	SPT positive or equivocal	p-value
No symptoms	-0.1 (179)	49.5 (60)	<0.01
Dyspnoea	50.0 (49)	54.4 (21)	NS
Wheezing	55.9 (42)	32.7 (19)	NS
Cough	30.2 (30)	59.8 (13)	NS
WASTH	84.3 (19)	48.7 (12)	NS

Number of subjects in parenthesis. NS: not significant; SPT: skin-prick test. For further abbreviations see legend to tables 1 and 2.

SPT and subjects with negative reaction to the SPT, was 53.5 $ml \cdot yr^{-1}$ ($p<0.01$). However, in subjects with respiratory symptoms, there was no significant association between the reaction to the SPT and ΔFEV_1. Thus, a positive or equivocal reaction to the SPT was a risk factor of accelerated decline in FEV_1 in asymptomatic subjects only.

Discussion

In this study, we have investigated the relationship between BR and annual decline in FEV_1. The unadjusted rates indicated that increased ΔFEV_1 was associated with increased BR. However, after adjustment for age, gender, smoking habits, use of safety mask, familial asthma, $SFEV_1$ and WASTH the difference in ΔFEV_1 between different categories of BR decreased and was not significant. We also found that ΔFEV_1 in those who reported WASTH was independent of the level of BR, and that WASTH was a significant predictor of ΔFEV_1. In asymptomatic subjects, the SPT was a significant predictor of ΔFEV_1.

The finding that ΔFEV_1 was unrelated to BR is apparently not in agreement with the "Dutch hypothesis" [6] and the findings by others [7–10]. However, in two of these studies [7, 9], bronchial challenge was performed at the end of follow-up and no adjustment was made for baseline FEV_1. As baseline FEV_1 and BR are highly correlated [3, 4], the observed association between ΔFEV_1 and BR could be a consequence of a decreased baseline FEV_1 rather than a cause of increased ΔFEV_1. Two other studies [8, 10] were restricted to patients with established CAL. Thus, the study populations in the latter two studies were not comparable to our subjects.

Although our data seem to reject the "Dutch hypothesis", some other factors must be considered. Whereas, ΔFEV_1 can be regarded as constant over the observation time (and should, therefore, be regarded as a valid estimator of the decline of lung function), it is questionable whether the measured PC_{20} could be regarded as constant during the observation time. In a 2 yr follow-up of workers reporting WASTH, with repeated measurements of BR, we found considerable variation of BR within subjects [21]. A similar observation has also been made in a group of asthmatics in a longitudinal study of repeated measurements of BR [22]. Thus, it is very likely that, in many of the subjects in the present study, BR has changed during the follow-up. As our classification of BR was based on only one measurement, a misclassification of the BR of subjects is likely to occur over a period of time. Moreover, such misclassification is probably independent of ΔFEV_1 and could, therefore, bias the association between BR and ΔFEV_1 toward zero [23]. Finally, in this young population, a relatively high proportion of the subjects had ΔFEV_1 close to zero, and this might decrease the probability of detecting any association between BR and ΔFEV_1. Nevertheless, our investigation shows that one measurement of BR cannot predict the ongoing ΔFEV_1 in aluminium potroom workers.

Those who reported WASTH had significantly increased ΔFEV_1 compared to symptom-free workers, and this relationship was independent of BR. In an earlier report concerning the same population we found that WASTH was strongly associated to occupational fluoride exposure [24]. Thus, it seems likely that WASTH is a good indicator of susceptibility to potroom fumes, as well as a sensitive risk factor of increased ΔFEV_1. We have also found that the majority of 26 workers reporting WASTH had BR in the normal range on at least one challenge during a 2 yr follow-up [21]. Nevertheless, the mean BR in these workers was markedly increased compared to a symptom-free reference group [21]. It is therefore possible that WASTH is a better indicator of the mean BR than one single measurement of PC_{20}. Thus, in this respect our results might be in agreement with the "Dutch hypothesis".

The relationship between a positive skin test and ΔFEV_1 is in agreement with the results from a study of ΔFEV_1 in shipyard workers [25]. A positive association between ΔFEV_1 and serum immunoglobulin (IgE), *i.e.* an index of atopy, has been reported by ANNESI *et al.* [26]. Since IgE and the reaction to the SPT are positively correlated [26], it is likely that allergy - as expressed by a positive SPT - may be associated with increased risk of developing CAL.

The relationship between ΔFEV_1 and current smoking has been found by others [27–29], and seems to apply to aluminium potroom workers as well. However, the difference in ΔFEV_1 between smokers and nonsmokers was higher in our study than in these studies, mainly because of a lower ΔFEV_1 in nonsmokers. A linear relationship between ΔFEV_1 and age was indicated, *i.e.* age can be treated as a continuous covariate in studies of ΔFEV_1 in adults. The finding that ΔFEV_1 increased with age at the cross-sectional survey is in agreement with JAAKKOLA and co-workers [30]. Our estimate of the relationship between age and ΔFEV_1 is the mean of the estimates found by others [27, 29].

The relationship between ΔFEV_1 and lung function was dependent on whether $SFEV_1$ at inclusion, at the cross-sectional survey or at the end of the follow-up was used. Those who had the lowest $SFEV_1$ at the end of the follow-up also had the largest decline in FEV_1, in accordance with the "horse-racing effect" [31].

The observation that those who never use airway protection have less decline in lung function is apparently surprising, and needs some comment. Firstly, after adjusting for confounding factors, such as age, smoking habit, symptoms, *etc*., the difference between the users and nonusers decreased. Nevertheless, a significant difference in ΔFEV_1 between these two groups remains, and we believe that the nonusers have decreased susceptibility for the development of respiratory disorders. These workers also had less symptoms [24], and were less reactive [3], than those who reported use of respiratory mask. Secondly, as information on use of safety mask was related to the cross-sectional study, they might have used airway protection during follow-up. Alternatively, this finding could indicate technical problems with the measurements. However, the SD of ΔFEV_1 was not larger in the mask-users than in nonusers, indicating that the observed difference between these groups was not due to technical problems in performing spirometry. Finally, it is unlikely that technical problems could cause systematically increased values in the nonusers.

In conclusion, a respiratory questionnaire seems to be a better screening tool for detection of increased ΔFEV_1 in aluminium potroom workers than a single bronchial provocation test with methacholine.

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Appendix 1

Maximum likelihood estimation of regression coefficients.

We wish to estimate the coefficients in:

$$\beta_i = \alpha + \sum_{j=1}^{13} \gamma_j \chi_{ij} + \varepsilon_i \qquad (1)$$

β_i=ΔFEV_1 of the *i*th individual calculated by least square regression of FEV_1 by time and χ_{ij} is the *j*th covariate of the *i*th individual. Let b_i denote the estimate of β_i. Now the log-likelihood of the b_is is:

$$-\frac{333}{2}\ln(2\pi) - \frac{1}{2}\sum_{i=1}^{333}\ln(\sigma^2+\tau^2/\kappa_i) - \frac{\sum_{i=1}^{333}(b_i-\alpha-\sum_{j=1}^{13}\gamma_j\chi_{ij})^2}{2(\sigma^2+\tau^2/\kappa_i)} \qquad (2)$$

where σ^2 is the variance of β_i not accounted for by the covariates χ_{i1}, ..., χ_{i13}, τ^2 is the residual variance about an individual participant's regression line; and τ^2/κ_i is the variance of the estimation error associated with the observed slope b_i. $\kappa_i = \sum_{j=1}^{m} (t_{ij}-\bar{t}_i)^2$, *i.e*. the sum of squared deviation from the mean follow-up time in the *i*th individual.

The NONLIN module of SYSTAT offers an algorithm that can estimate the γ_js:

Step 1

Specify the model (Equation (1)):

$$BI=C0+C1\times X1+C2\times X2+C3\times X3+C4\times X4+ C5\times X5+C6\times X6+C7\times X7+C8\times X8+C9\times X9+ C10\times X10+C11\times X11+C12\times X12+C13\times X13 \qquad (3)$$

BI=b_i; C0, C(1–13) estimates of α, γ_j, respectively; X(1–13)=χ_j of the *i*th participant. (Regarding definition of the Cs, see Appendix 2).

Step 2

Specify the LOSS-function (Equation (2)):

$$LOSS=LOG(VARIANCE+VARBI)+(1/(VARIANCE+VARBI)) \times(BI-ESTIMATE)\hat{}2 \qquad (4)$$

where VARIANCE=σ^2 is estimated by SYSTAT in the computation of the LOSS-function, VARBI=τ^2/κ_i and BI=b_i are stored on the file in each subject. ESTIMATE=$(\Delta FEV_1)_i$ in each individual estimated from Equation (3). Then the LOSS statement is evaluated in each case using the estimate from the model statement. The LOSS is summed over all cases, and this procedure is repeated until the tolerance criterion is obtained, or maximum iteration limit is reached.

Note: the constant terms (Equation (2)) do not have to be included when formulating the LOSS function, as they do not make any difference when the LOSS is minimized.

Appendix 2

Classification of covariates in the model.

Let χ_{i1}, ..., χ_{i12} denote the covariates for the *i*th participant: GENDER: FEMALE χ_{i1}=1, MALE χ_{i1}=0; χ_{i2}=AGE; SMOKING STATUS: CURRENT SMOKERS χ_{i3}=1, χ_{i4}=0, EX-SMOKERS χ_{i3}=0, χ_{i4}=1, LIFELONG NONSMOKERS χ_{i3}=χ_{i4}=0; SPT: POSITIVE RESPONSE. χ_{i5}=χ_{i6}=1, EQUIVOCAL RESPONSE χ_{i5}=0, χ_{i6}=1, NEGATIVE RESPONSE χ_{i5}=χ_{i6}=0; FAMILIAL ASTHMA: YES χ_{i7}=1, NO χ_{i7}=0; χ_{i8}=$SFEV_1$; USE OF RESPIRATORY MASK: YES χ_{i9}=1, NO χ_{i9}=0; RESPIRATORY SYMPTOMS: SYMPTOM-FREE χ_{i10}=χ_{i11}=0, WASTH χ_{i10}=1, χ_{i11}=0, OTHER SYMPTOMS χ_{i10}=0, χ_{i11}=1; BRONCHIAL RESPONSIVENESS: BHR χ_{i12}=χ_{i13}=1, MINOR RESPONSIVENESS χ_{i12}=0, χ_{i13}=1, NORMAL χ_{i12}=χ_{i13}=0.

For definition of abbreviations see text.

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