ORIGINAL ARTICLE

Longitudinal decline in lung function in former asbestos exposed workers

Eduardo Algranti,[1] Elizabete Medina Coeli Mendonça,[1] Eva Hnizdo,[2] Eduardo Mello De Capitani,[3] Jefferson Benedito Pires Freitas,[4] Vilton Raile,[4] Marco A Bussacos[1]

[1]Division of Medicine, FUNDACENTRO, Sao Paulo, Brazil
[2]Division of Respiratory Disease Studies, National Institute for Occupational Safety and Health, Morgantown, West Virginia, USA
[3]Department of Medicine, Discipline of Pneumology, UNICAMP Medical School, Campinas, Brazil
[4]CEREST, Sao Paulo and Osasco Municipality, São Paulo, Brazil

Correspondence to
Dr Eduardo Algranti, Division of Medicine, FUNDACENTRO DMe/CST, R. Capote Valente 710, São Paulo, 05409-002, Brazil; eduardo@fundacentro.gov.br

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ABSTRACT

Background This study was designed to assess the effect of asbestos exposure on longitudinal lung function decline.

Methods A group of 502 former asbestos-cement workers with at least two spirometry tests 4 years apart. Repeated evaluations included respiratory symptoms questionnaire, spirometry and chest imaging. Asbestos exposure was ascertained as years of exposure, an index of cumulative exposure and latency time. The mixed effects model was used to evaluate the effect of exposure on the level and rate of change in forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC).

Results Mean age at entry was 51 (SD 9.9) years, mean latency time 25.6 (SD 10.0) years, mean follow-up time 9.1 (SD 2.8) years and mean number of spirometry tests 3.5. The FEV_1 level was significantly related to pack-years of smoking at entry and during the follow-up, the index of cumulative asbestos exposure at entry, and the presence of asbestosis at follow-up. The FVC level was significantly related to pack-years of smoking during the follow-up, cumulative asbestos exposure at entry, asbestosis and pleural thickening at follow-up, and body mass index at entry. Asbestos exposure was not associated with increasing rates of FEV_1 and FVC decline. However, FEV_1 regression slopes with age, estimated by terciles of cumulative exposure, showed significant differences. Combined effects of smoking and exposure conferred further acceleration in lung function decline.

Conclusions Occupational exposure in asbestos-cement industry was a risk factor for increased lung function decline. The effect seems to be mostly concentrated during the working period. Smoking and exposure had synergic effects.

What this paper adds

- There are histological and functional evidences that asbestos exposure damages bronchioles but very few studies addressed long term functional consequences.
- Exposure to asbestos (mainly chrysotile) was significantly associated with lower levels of lung function in a dose–response manner.
- The ill effects seem to concentrate mainly in the level of forced expiratory volume in 1 s and forced vital capacity, as compared with the rate of decline.
- In this asbestos-cement workers' population, smoking had a stronger effect in decreasing lung function and its effect was potentiated by asbestos exposure.

INTRODUCTION

Asbestos exposure is associated with pleural and lung fibrosis, lung cancer and cancer of the cavity linings.[1] Recent studies found associations between asbestos and cancer of the larynx and ovary.[2] Because of its carcinogenic properties, focus on asbestos effects is mainly directed at cancer morbidity and mortality, overshadowing other related diseases. However, as a mineral dust, asbestos can affect the airways leading to structural changes with possible functional consequences.[3 4]

One of the first studies to analyse in detail lung function in 24 asbestos exposed workers found an increased elastic recoil, smaller vital capacities, ventilation inhomogeneity and larger mid-expiratory flows in the most exposed workers. In addition, they presented decreased peak-flows at any transpulmonary pressure level, suggesting that the primary lesion had a predominant peribronchiolar rather than alveolar location.[5] A larger study of asbestos-cement (A/C) workers demonstrated functional changes associated with cumulative exposure consistent with adverse effects on the airways.[6] In non-smokers, asbestos exposure was associated with decreased airflow when compared with a reference population.[7] A previous cross-sectional study involving A/C workers from the present study showed a significant reduction in %forced expiratory volume in 1 s (FEV_1) and %forced vital capacity (FVC) with increasing quartiles of exposure.[8] Autopsies done in chrysotile miners without asbestosis showed marked changes in small airways, including membranous bronchioles, when compared with non-exposed smoking controls.[3]

There are only a limited number of studies of longitudinal lung function changes in asbestos exposed workers. A/C workers showed an increase in FVC and FEV_1 decline in a 7-year follow-up in subjects with more than 15 years of latency from first exposure,[9] and significant accentuation of the FEV_1 decline in the higher exposure group.[10] A study from Chinese asbestos exposed workers showed excessive decline in

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FEV_1, a mean annual decline of 2.2% over a 10-year observation period.[11]

Recent development in the methodology of the longitudinal spirometry evaluation allow us to calculate the magnitude of detectable differences in FEV_1 slopes between groups and recommend the number of subjects needed,[12] evaluate data precision for the longitudinal set of data[13] and establish limits of normality for volume loss along time based on existing data precision.[14]

The objective of this report is to analyse the longitudinal decline in spirometric measurements in a group of former A/C workers, previously studied cross-sectionally for non-malignant respiratory effects of asbestos exposure.[8]

METHODS

Subjects

Subjects originated from a group of 947 former A/C workers employed at one plant, and first examined between 1995 and 2005. To date, new subjects are still being recruited to the group. The first examination consisted of a respiratory symptom questionnaire including smoking data, comprehensive occupational history, anthropometric data, chest auscultation, spirometry and chest image studies (x-rays and high resolution CT (HRCT) scans). The detailed description of the instruments is found elsewhere.[8] Subjects were invited to return for a re-evaluation every 2–3 years. At follow-up the same instruments were applied, except for occupational history and HRCT. The latter was repeated according to previous findings, physical examination and occupational and smoking history. Of the 947 subjects, 506 had at least two examinations 4 or more years apart.

The study methods were reviewed and approved by an ethical panel committee at the School of Public Health, University of São Paulo. At entry, subjects were told about the study instruments and gave their consent.

Spirometry

We restricted the analyses to workers who had at least 2 data points 4 or more years apart ending in May 2010. Four subjects were excluded for the following reasons: one for having spirometries done by another service, one for HIV infection with respiratory compromise, one for presenting congestive heart failure with chronic renal disease and one for having a lobectomy during follow-up, thus resulting in 502 eligible subjects.

Spirometry was performed using a bellows spirometer (Jones Pulmonaire, Oakbrook, Illinois, USA), calibrated daily with a 3 litre syringe. All curves were visually and numerically inspected for start and duration, according to the Brazilian Pneumology and Tisiology Society guidelines on spirometry.[15] To avoid censoring of spirometric data in workers with respiratory abnormalities, the lack of reproducibility was not a criterion for test exclusion provided that, at least, there was one acceptable curve. Throughout the study period, the 502 subjects have undergone on average 3.5 acceptable longitudinal spirometry tests, made using the same spirometer by the same technician. Predicted values were derived from reference equations for the Brazilian population.[16]

Data precision was calculated by uploading the longitudinal FEV_1 and FVC data into SPIROLA[i] software. The software calculates the absolute and relative within-person variation to indicate how precise are the longitudinal data.[17]

Pleural thickening and asbestosis

Subjects were screened with a PA chest x-ray and an HRCT on admission. A chest x-ray was made on every follow-up visit and, according to the occupational and smoking history and/or clinical symptoms and signs, an HRCT was repeated. Diagnosis of pleural thickening and asbestosis was made according to HRCT criteria described elsewhere.[8] Pleural thickening was categorised as 0 if absent, and in grades 1–3 according to a sum of the extension of the thickening, individually calculated for right and left chest wall and right and left diaphragm.[18]

Dust exposure

Chrysotile, either Brazilian or imported, was used during the whole period of the plant operation, from 1941 until 1992. Crocidolite was used in smaller amounts in the pipe production area until 1979. There were no routine fibre measurements in the industry before 1980. A semiquantitative index of dustiness ranging from 1 to 10 was developed, taking into consideration dustiness at various jobs, by a group of long tenure workers and a government inspector based on their work experience and plant knowledge. An individual index of cumulative exposure was then calculated by summing up the product of years spent in each job and the scale level. Years of exposure and latency time (years since first exposure) were also considered as surrogates of exposure. Changes in production methods and plant environment occurred over the years, particularly in the last 10 years of plant operation, but lacking objective data, these was not taken into account in the calculation of cumulative exposure. Individual exposures to A/C dusts were established at the baseline medical examination. Subjects could have been inadvertently exposed to asbestos after 1992, but none of them took further employment in a typical asbestos industry.

Data analysis

The data consisted of unbalanced repeated measurements of spirometry, chest imaging, smoking status and respiratory symptoms across follow-up time ranging from 4 to 14 years. Follow-up time of at least 4 years is needed to obtain sufficiently precise estimates of the rate of lung function change over time in individuals.[12 17]

To investigate the association between asbestos exposure and lung function, we first investigated the colinearity between exposure variables and FEV_1, using the PROC REG with the COLLIN option (SAS programme, V.9.2). No significant positive colinearity (variance inflation ≥ 10) was found. Models for FEV_1 as a dependent variable and age as an independent variable were tested for linear and non-linear transformations using SAS PROC TRANSREG with SPLINE option. The linear model showed R^2 of 0.3225. Both the quadratic and cubic polynomial splines with knots at 40, 50 and 60 years showed a minimum criterion change (<0.003 R^2). The linear mixed effects models were then used with FEV_1 or FVC as dependent variables. The following independent variables were included as fixed effects: baseline age, height, baseline body mass index (BMI), smoking status and pack-years, occupational exposure, asbestosis and pleural thickening. The effect of pack-years and change in weight between evaluations were then evaluated for each follow-up. Time of follow-up (years) at each examination was entered as a random effect variable. To determine the effect of occupational exposure on the longitudinal decline of FEV_1 and FVC (ie, slopes) during the follow-up, the interaction terms for

[i]Public domain software developed by NIOSH, Morgantown, West Virginia, USA, available at: http://www.cdc.gov/niosh/topics/spirometry/spirola-software.html

Table 1 Descriptive data of the studied former asbestos-cement workers (n=502), Brazil

Variable	At entry mean (SD)	At last follow-up mean (SD)
Mean age (year)	51.2 (9.9)	60.1 (10.3)
Mean follow-up time (year)		9.1 (2.8)
Mean latency time at entry into the study (year)	25.6 (10.0)	
Mean height (cm)	167 (68)	167 (68)
Mean weight (kg)	76.2 (12.7)	77.1 (13.5)
Mean BMI (kg/m^2)	27.1 (4.2)	27.5 (4.4)
Smoking status (n, %)		
Smokers	136 (27.1%)	92 (18.3%)
Ex-smokers	181 (36.1%)	229 (45.6%)
Non-smokers	185 (36.8%)	181 (36.1%)
Exposure		
Years of exposure	13.5 (9.0)	
Cumulative exposure	87.6 (71.6)	
Spirometry measurements		
FEV_1 (ml)	3142 (743.2)	2733 (766.1)
(% predicted)	94.0 (17.9)	88.5 (20.8)
FVC (ml)	4103 (830.7)	3606 (849.0)
(% predicted)	98.9 (15.4)	91.5 (17.1)
FEV_1 to FVC (%)	76.3 (8.7)	75.2 (10.5)
(% predicted)	95.1 (10.5)	95.5 (13.0)
Non-malignant asbestos diseases (n, %)		
Pleural thickening		170 (33.9%)
Asbestosis	43 (8.6%)	64 (12.7%)

BMI, body mass index; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.

time of follow-up and the explanatory variables of interest (index of cumulative asbestos exposure, smoking, asbestosis and pleural thickening) were also added to the models.

Independent variables presenting no significant association with FEV_1 or FVC ($p>0.05$) were deleted from the models in order to simplify results. In addition, we also estimated the mean FEV_1 rate of decline (ie, slope) for each individual using separate linear mixed effects models by terciles of cumulative exposure. The estimated regression parameters were then used to estimate FEV_1 change for age ranges 40–80 years, by terciles of cumulative exposure, standardised for other factors. Similar analyses were performed for three levels of pack-years (non-smokers as reference in the first level) within terciles of cumulative exposure. Statistical differences between slopes were calculated comparing the intercepts and parallelism of the slopes through variance and covariance analyses using SAS PROC REG ANOVA.

RESULTS

Table 1 shows the descriptive statistics for the demographic data, smoking and spirometry at first and last evaluations, and presence of asbestosis. The group's mean age at entry was 51 (SD 9.9) years. The mean follow-up time was 9.1 (SD 2.8) years with a reasonably long latency period. The prevalence of pleural thickening is quoted at last evaluation because the scoring of extent was determined only in the last available HRCT.

Of the 502 subjects, 412 (82%) had 3–7 data points and 90 (17.9%) had 2 data points; in total, 1778 spirometries and a mean number of measurements per subject of 3.5. Table 2 shows the number of subjects, the mean (SD) follow-up time, years of exposure, index of cumulative exposure and latency time by the number of examinations available for the 502 A/C workers. There was a trend for subjects with more longitudinal measurements to have longer and heavier exposure.

Table 2 The number of subjects, N (%), and the mean (SD) for time of follow-up, years of exposure, index of cumulative exposure and latency time by the number of examinations conducted on the 502 Brazilian former asbestos-cement workers

Number of exams	N (%)	Follow-up years (SD)	Exposure YE (SD)	Exposure CE (SD)	Exposure LT (SD)
2	90 (17.9)	8.0 (2.5)	9.7 (7.8)	54.2 (56.0)	22.4 (10.2)
3	191 (38.1)	7.8 (2.6)	13.0 (8.8)	84.3 (69.8)	24.7 (10.1)
4	137 (27.3)	10.1 (2.3)	14.3 (8.5)	91.0 (64.1)	26.7 (9.2)
5	42 (8.4)	10.8 (1.8)	17.3 (9.6)	120.5 (82.7)	29.5 (89.0)
6	37 (7.4)	11.9 (1.6)	18.9 (9.7)	130.5 (85.8)	29.2 (8.5)
7	5 (1.0)	12.8 (0.9)	18.4 (9.4)	147.1 (86.5)	34.4 (11.7)

CE, cumulative exposure; LT, latency time; YE, years of exposure.

Longitudinal FEV_1 data precision was assessed through the group average within-person variation estimated on pair-wise measurements repeated within 18 months on an individual, using SPIROLA software. For FEV_1, the group average absolute and relative within-person variations were 116 ml and 3.8%, respectively, indicating good longitudinal data precision.[17 19] The mean group slope was −38 ml/year.

Table 3 shows results from the mixed models for FEV_1 and FVC as dependent variables. For the FEV_1 model, the statistically significant ($p<0.05$) fixed independent variables were: age at entry, height and occupational exposure expressed as years of exposure or index of cumulative exposure, and pack-years at

Table 3 Results from the mixed effects model for dependent variables FEV_1 and FVC

Effect	FEV_1 (ml)* Estimate (SE)	FEV_1 (ml)* p Value	FVC (ml)* Estimate (SE)	FVC (ml)* p Value
Intercept	2594.60 (606.60)	<0.0001	2348.7 (855.91)	0.0063
Age at entry	−34.48 (2.92)	<0.0001	−32.70 (3.17)	<0.0001
Time of follow-up (y)	−41.26 (1.51)	<0.0001	−45.95 (1.87)	<0.0001
Height (m)	1448.6 (344.36)	<0.0001	2449.3 (483.55)	<0.0001
Pack-year	−6.04 (1.73)	0.0005	–	–
Pack-year between evaluations	−6.23 (1.72)	0.0003	−3.04 (0.59)	<0.0001
Cumulative exposure	−1.43 (0.42)	0.0008	−1.55 (0.45)	0.0006
Years of exposure	8.51 (3.95)	0.0315	10.32 (4.23)	0.0149
Asbestosis	−207.45 (81.07)	0.0107	−209.91 (83.43)	0.0121
Score of PT†	–	–	−82.25 (29.92)	0.0061
Body mass index	–	–	−23.07 (5.3)	<0.0001

Shown for each variable identified to be statistically significant ($p<0.05$) are the estimated parameter (SE) and p value. Estimates are based on 502 former Brazilian asbestos-cement workers.
*Mean FEV_1=3142 ml, mean FVC=4103 ml.
†Score of PT: score of pleural thickening ranging from 0 to 3.[18]
FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.

baseline. Of the repeated variables, pack-years through the follow-up and the presence of asbestosis through the follow-up were significantly associated with lower levels of FEV_1. The results for the FVC model is relatively similar (except for pack-years at entry not being significant) and the significant contributions of baseline BMI and increasing scores of pleural thickening, both contributing to lower levels FVC.

Excluding subjects who answered positively to the question 'Have you had an attack of wheezing with shortness of breath?' in both the first and last examinations (n=51) yielded similar results. Alternative models using height polynomials corrected FEV_1 and FVC yielded the same results and did not improve the model fit. The inclusion of baseline FEV_1 or FVC as independent variables in the models adjusted for the effects of exposure at baseline and yielded weaker models.

For the mean index of cumulative exposure in the cohort (87.6), there is an estimated loss of 125 and 136 ml in FEV_1 and FVC levels, respectively, compared with a loss of 121 ml in FEV_1 due to smoking 20 pack-years at entry. The mean additional loss of a subject who continued to smoke 1 pack/day for 9 years was approximately 55 ml. The presence of asbestosis conferred a loss of about 200 ml in FEV_1 and FVC levels. The presence of pleural thickening (score=1) and BMI (each kg/m^2 unit) further contributed a mean loss of 82.5 and 23 ml of FVC, respectively.

Of the interaction terms between time of follow-up and each of the significant variables shown in table 3, only the term for pack-years between evaluations was significant. Neither the interaction with index of cumulative exposure nor with the presence of asbestosis was significant. For the FVC, interaction with asbestosis approached significance (p=0.0693).

In addition, trends associated with increasing exposure were analysed using three separate mixed models, which included subjects classified according to terciles of index of cumulative exposure. The estimated FEV_1 decline with age (40–80 years) in each tercile is displayed in figure 1. The intercepts (not shown in figure 1) were 4940 (SE 33.3), 4990 (SE 39.2) and 4810 (SE 38.0) ml for increasing cumulative exposure terciles, respectively. Subjects in the higher exposure tercile started at a lower level of FEV_1. Annual FEV_1 decline rates for subjects in the first, second and third terciles were 37.2 (SE 0.63), 39.8 (SE 0.69) and 38.3 (SE 0.62) ml/year, respectively. An analysis of variance (ANOVA) comparing the slopes showed significant differences both for level and parallelism. Inclusion of interaction terms between index of cumulative exposure and time of follow-up was not significant in any tercile model, meaning that the rate of decline in FEV_1 was mildly affected by time.

When we stratified the analysis by smoking habits, non-smokers (n=190), smokers with ≤18 pack-years (n=167) and smokers with >18 pack-years (n=165), then the index of cumulative exposure was a significant term only for non-smokers. However, the model fitted better for the heavier smoking group suggesting that smoking effect better explains FEV_1 levels (results not shown).

The relationship among FEV_1 longitudinal decline, occupational exposure and smoking was also analysed in partitioned mixed models and graphically displayed in figure 2. The estimated mean FEV_1 decline in the extreme situations (non-smokers in the first tercile of cumulative exposure compared with heavier smokers in the third tercile of exposure) showed that smoking and heavier exposure was associated with significant differences in FEV_1 slope.

DISCUSSION

This set of data is unique in the sense that spirometry measurements were made by the same well-qualified technician, using the same instrument throughout the observation period. Evaluation of longitudinal data precision, with a relative within-person variation of 3.8%, indicates that the longitudinal spirometry has good precision.[17 19] We were able to confirm that exposure to dusts in the A/C industry is associated with lower levels of FEV_1 with a mild but significant trend with increased FEV_1 decline with increasing exposure. The effect of occupational exposure on the FEV_1 decline was weaker than the effect of smoking.

Subjects included in this report are part of a cohort of former A/C workers who had sufficient follow-up. Comparing with non-participating subjects who were only seen once or had less than 4 years between first and last evaluations, the participants were older, had higher exposure, and had higher prevalence of pleural thickening and asbestosis. In theory, the participants

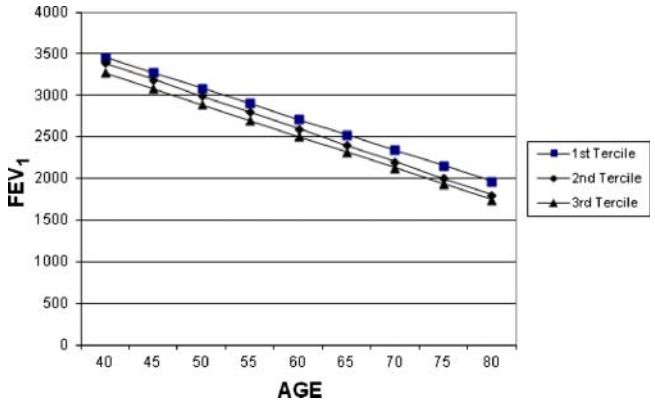

Figure 1 Estimated mean forced expiratory volume in 1 s (FEV_1) decline by the terciles of cumulative exposure for ages 40–80. At age 40, subjects in the second tercile of cumulative exposure compared with subjects in the first tercile have 70 ml less FEV_1 and subjects in the third tercile have 183 ml less. Former asbestos-cement workers, Brazil. *ANOVA: F=236.13, p<0.0001 for differences among slopes. This figure is only reproduced in colour in the online version.

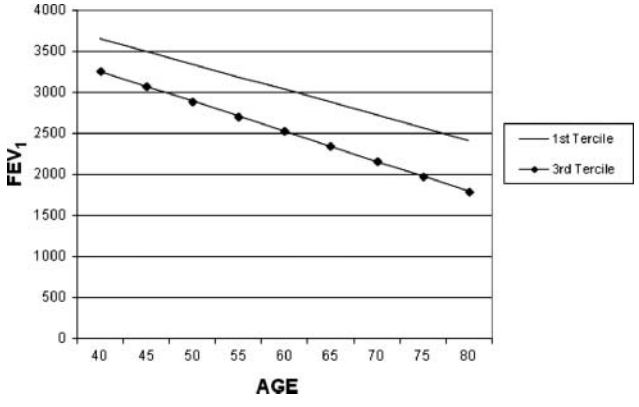

Figure 2 Estimated forced expiratory volume in 1 s (FEV_1) slopes in non-smokers in the first tercile of cumulative exposure compared with heavier smokers in the third tercile of exposure. Ages 40–80. At age 40, heavier smokers in the third tercile of occupational exposure started with lower FEV_1 by 396 ml and their decline was steeper. Former asbestos-cement workers, Brazil. *ANOVA: F=347.86, p<0.0001 for differences among slopes. This figure is only reproduced in colour in the online version.

should be prone to having lower levels of lung function and a faster decline in FEV_1 for having higher exposure. To overcome the potential bias due to non-participation, statistical analyses were stratified by different levels of exposure. Other possible bias was that the 502 subjects experienced further noxious exposures after leaving the A/C industry. At each visit, all subjects were questioned about further exposures and no censoring of data occurred because of that. To avoid bias related to lung function decline due to other causes we made exclusions of subjects that were submitted to lung resection and/or had had any other disease that affected the lungs, like HIV-related infections, chronic congestive heart failure and others. We kept 51 subjects with asthma-like symptoms in the modelling. Excluding them did not improve the model fit nor made differences in the findings in relation to occupational exposure. We also kept subjects unable to produce repeatable spirometric tracings who had at least one acceptable curve in order to avoid selection of fitter subjects in the group.[20]

A limitation of the study relates to exposure assessment. Lacking objective fibre measurements in the industry, we adopted a semiquantitative index as the main exposure metric. Jobs were classified into 10 groups reflecting their increasing exposure levels and increasing categorical weights were assigned in a linear manner to each group. In a previous report, index of cumulative dust exposure was significantly related to asbestosis,[8] which is an indication that the proposed metric reflects increasing dust exposure. To minimise this limitation, we conducted analyses by splitting the index of cumulative exposure in terciles.

A possible influence of concomitant exposure to cement dust may have also played a role in lung function decline. Recently, exposure to cement dust was associated with neutrophilic inflammation of the airways and increase in cytokine IL-1β levels,[21] but the evidence that cement dust affects lung function in the long term is conflicting. A second study showed small but significant decreases in cross-shift FEV_1, carbon monoxide diffusion (DLCO) and exhaled nitric oxide (NO) and an increase in leucocytes and fibrinogen counts.[22] Some of the cross-sectional studies found no difference in FEV_1 and FVC levels in exposed subjects and unexposed controls[23–25] and others reported lower levels of FEV_1 either in exposed compared with unexposed controls[26] or increasing exposure-related loss.[27 28] Also, a longitudinal study of lung function in cement workers did not show a significant difference in function loss compared with controls.[26] All studies indicating lower levels of lung function in cement workers came from developing countries. It might be that worse exposure conditions or other health determinants in the developing countries were responsible for the reported differences. Self-reported exposure to cement dust was a significant risk factor for chronic obstructive pulmonary disease (COPD) among department of energy workers in the USA.[29]

Lung function declines with age and the decline tends to accelerate in older subjects.[30] Statistical analysis allows us to choose between linear and non-linear modelling to best fit the observed data. Sherrill *et al*[31] described that the best fit for longitudinal FEV_1 and FVC data from healthy subjects, covering all age spans, was best described by four linear segments. Recently, McKay *et al*[32] reporting on a longitudinal study of more than a thousand refractory ceramic fibre workers showed that the fit for their spirometric data was best described by a cubic spline model with three knots. We did test our data with non-linear model fits using quadratic and cubic polynomial splines and found that they were no better than the linear modelling.

When data were modelled in terciles of cumulative exposure, FEV_1 decline showed significant differences between slopes, consistent with an exposure effect on starting levels (figure 1). From age 40–80, there was a loss of 1490, 1593 and 1534 ml of FEV_1 in increasing terciles of exposure, respectively. Despite the significant differences between slopes, visual inspection of figure 1 and yearly rates of change between the first and third terciles seem very close. Interaction terms between time of follow-up and index of cumulative exposure were not significant, suggesting a predominant exposure effect on FEV_1 and FVC levels. Longitudinal studies of pulmonary function in asbestos exposed groups showed a faster decline in FEV_1 compared with controls.[9] The same group was further analysed showing that even when exposure was discontinued it did not avoid FEV_1 accelerated decline and smoking brought an additive effect with exposure.[33] Ohlson *et al*[10] also demonstrated that smoking and asbestos exposure were more than additive in relation to accelerated FEV_1 decline. A 6-year follow-up study of 242 asbestos workers, exposed to low fibre levels, with at least 3 data points, showed that lung fibrosis was significantly related to FEV_1 slope, but neither exposure nor interaction terms between fibrosis and exposure were.[34] Lung fibrosis is closely associated with exposure and when modelled together one may overshadow the weaker variable. Table 3 showed that the index of cumulative exposure remained significant in a model adjusted for asbestosis. Statistical modelling with censoring of the 64 subjects diagnosed with asbestosis increased estimates of index of cumulative exposure (results not shown). Wang *et al*[11] showed that DLCO is the most rapidly declining functional parameter in a group of 125 asbestos workers in a 5-year follow-up study. We could not evaluate these latter findings for only a subset of our study group was submitted to routine DLCO evaluations. Glencross *et al* found that working as a sheet metal worker in shipyards was associated with accelerated loss of FEV_1 which was additive to the effect of smoking.[35] Figure 2 confirms that subjects in the upper tercile of exposure and smoking more than 18 pack-years had a significantly faster rate of decline.

Despite the difficulties of demonstrating causality between occupational exposures and COPD,[36] it is estimated that the population attributable fraction for occupational exposures approaches 20%.[37] These relationships are generally associated with an ample array of exposures. In our cohort, overall prevalence of FEV_1 to FVC below the LLN at last evaluation was 22.7%. Adopting the criteria of FEV_1 to FVC $< 70\%$ and $FEV_1 < 80\%$, which corresponds to GOLD stages II and more,[ii] the prevalence of abnormal findings was 13.9%, close to the prevalence of two definitions of COPD used by Dement *et al* among department of energy workers in the USA.[29] The US study showed a significant association between asbestos exposure and the prevalence of COPD and significant interaction terms between smoking and asbestos exposure, suggesting combined effects of both agents on the risk of COPD.

In contrast to FEV_1 results, FVC showed no association with the amount of smoking at baseline, but increasing score of pleural thickening was associated with decreased FVC. It is noteworthy that higher scores of pleural thickening conferred substantial losses of FVC, that is, 247 ml in subjects in score 3 (pleural thickening extent 3, affecting both chest walls plus both diaphragms). In a previous cross-sectional report of 828 former A/C workers, the presence of pleural thickening was significantly

[ii]Available at http://www.goldcopd.org/uploads/users/files/GOLD_Report_2011_Feb21.pdf

associated with lower levels of height-adjusted FVC.[38] This report also reinforced the detrimental association of higher BMI with lower levels of FVC. A large longitudinal study of risk factors for coronary arterial disease showed that weight gain in initially thin patients was associated with increasing spirometric indices till the age 38, but participants starting with BMI>26.4 experienced decreases in FEV_1 and FVC in 10 years of observation.[39] Weight gain was further associated with FVC losses in a dose–response manner. A longitudinal study of steel workers showed significant associations between weight gain and FEV_1 and FVC losses in a mean follow-up time of 6 years.[40] High BMI and weight gain were associated with increased functional losses in patients with COPD and asthma, respectively.[41 42] Therefore, obesity and weight gain are risk factors for decreased lung function, especially FVC.

The 502 subjects were mainly exposed to chrysotile. Amphiboles were used in small quantities until 1979 in the pipe production area. In subjects exposed to crocidolite, FEV_1 and FVC levels and slopes were significantly associated with cumulative exposure and the presence of asbestosis.[43] There is a lack of data on the relationship between fibre types and respiratory function impairment, in contrast with other asbestos-related diseases.

This report confirms findings from a previous cross-sectional analysis showing lower levels of FEV_1 and FVC with increasing exposure.[8] Increasing levels of cumulative exposure were significantly related to lower levels of FEV_1 in a dose–response manner, but we could not demonstrate a significant association with time of follow-up in FEV_1 slope, indicating that the effect of exposure on lung function was mostly concentrated during the working period. It also confirms that the combined effect of smoking and exposure in increasing the rates of FEV_1 declines along time.

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Eduardo Algranti, Elizabete Medina Coeli Mendonça, Eva Hnizdo, et al.

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