

## Longitudinal methods for describing the relationship between pulmonary function, respiratory symptoms and smoking in elderly subjects: The Tucson Study

D.L. Sherrill, M.D. Lebowitz, R.J. Knudson, B. Burrows

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**ABSTRACT:** In this study recently developed longitudinal techniques are used to examine the relationship between respiratory symptoms, smoking and pulmonary function measures in elderly subjects.

The subjects were participants in the Tucson Epidemiological Study of Airways Obstructive Disease, aged  $\geq 55$  yrs at the first survey 1972-1973, who had received pulmonary function testing and completed questionnaires in at least one of the six selected surveys. There were 633 males and 891 females, with up to 14 yrs follow-up included in the analysis. Based on their questionnaire responses, subjects were classified according to their respiratory symptoms and smoking habits at each survey. The pulmonary function testing included forced vital capacity (FVC), forced expiratory volume in one second ( $FEV_1$ ), and their ratio ( $FEV_1/FVC$ ). The pulmonary function data were analysed gender specific, with and without stratifying on vital status.

The results indicate that respiratory symptoms are generally associated with lower levels of lung function, and that the impairment associated with chronic cough was observed predominantly in male subjects. The negative association of smoking was apparent in most measures, but was largest and most progressive in the  $FEV_1/FVC$  ratios. Ex-smokers, in all cases, had better lung function values than current smokers, but their mean curves were always significantly below the values of nonsmokers.

*Eur Respir J., 1993, 6, 342-348.*

It is well-established that pulmonary function values decrease with ageing in normal adult subjects [1, 2], and that respiratory illnesses and smoking can increase this natural time course of decline. A number of studies have examined the relationship between symptoms, smoking and pulmonary function measures in adults [3-19], but only a few studies have looked at these associations specifically in elderly subjects [20-24]. In addition, other investigators have shown pulmonary function measures to be significant predictors of mortality [25-29], suggesting that longitudinal analyses of pulmonary function in an elderly population should examine the effects of vital status.

In this report we demonstrate how a mixed longitudinal or random effects model (REM) can be used to examine the association between respiratory symptoms and smoking and the level and rate of decline of pulmonary function in elderly subjects [30, 31]. This procedure is useful when subjects have an unequal number of observations, that are taken at unequal time intervals. The pulmonary function measures are analysed stratified by gender, and gender and vital status, and with adjustments for height.

Respiratory Sciences Center (Westend Research Laboratories), University of Arizona College of Medicine, Tucson, AZ 85724, USA.

Correspondence: D.L. Sherrill  
Respiratory Sciences Center  
University of Arizona College of  
Medicine  
Tucson  
Arizona 85724 USA

Keywords: Chronic cough  
cigarette smokers  
dyspnoea  
epidemiology  
forced vital capacity  
geriatric  
wheeze

Received: February 6 1992  
Accepted after revision November 8 1992

### Methods

#### *Study population*

Subjects were white, non-Mexican American participants in the Tucson Epidemiological Study of Airways Obstructive Disease aged  $\geq 55$  yrs at the first survey 1972-1973. The detailed description of the design and methods of data collection have been reported previously [32]. A total of 1,655 households, containing 3,805 individuals, were in the initial sample (1972), which included over 200 participants over 75 yrs of age.

For this analysis, data were available until the tenth survey, spanning a period of up to 14 yrs. Pulmonary function testing was performed at all surveys except the fourth, and self administered questionnaires were completed at intervals of, on average 1.5 yrs. Questions concerning smoking status and respiratory symptoms were asked in similar ways in all but the third, sixth and seventh surveys. Since different wording resulted in different response rates, the current analysis excludes these surveys, leaving a maximum of six possible surveys

where pulmonary function measures were made and consistent information on smoking status and respiratory symptoms was collected.

Subjects were classified at each survey as having chronic cough, exertional dyspnoea, or wheeze, if they responded positively to any of the following questions:

- 1) Do you cough on most days for as much as 3 months of the year?
- 2) Do you get short of breath walking with other people of your own age on level ground?
- 3) Does your chest ever sound wheezy or whistling, apart from colds?

Subjects were considered to be current smokers at any survey where they reported smoking one or more cigarettes per day regularly, and as ex-smokers if they had previously reported smoking, but had since stopped or had only reported smoking in the past. Vital status was obtained by trained nurse interviewers for any subject not continuing participation in the study [33]. Deaths were assessed until 1988 at the completion of Survey 10. Families, contacts listed on the initial questionnaire, neighbours, newspaper clippings, and obituaries were all utilized to ascertain vital status. Death certificates were sought as confirmation every time a subject was deceased or likely to be.

Spirometric tests were performed with a pneumotachograph, using standard American Thoracic Society criteria [34]. The following pulmonary function indices were included in the analysis: forced vital capacity (FVC), forced expiratory volume in one second ( $FEV_1$ ), and the ratio  $FEV_1/FVC$ . Percentage predicted values were computed using previously published reference equations [35, 36].

#### Statistical methods

Methods available for analysing longitudinal data when observations are missing and unequally spaced are limited. One approach reported by ROSNER *et al.* [37], used an autoregressive model, which could be easily implemented using ordinary least squares software. However, this procedure has been demonstrated to yield potentially false associations when both exposure and outcome are related to time [38]. More recent models, reported by VONESH and CARTER [39], describe how efficient estimators can be obtained without the need for the more computer-intensive iterative techniques. This approach does require assumptions concerning the within-subject error structure. A good discussion of linear longitudinal models is provided by WARE [40]. For the current study, a two stage random effect model was used, as originally described by HARVILLE [41], with modifications described by JONES and BOADI-BOATENG [30, 31]. The model included a first order autoregressive error structure, to account for serial correlation within subjects. The random effects model fits a polynomial to all the data, and simultaneously fits a polynomial to each individual's deviation from the population curve. The coefficients estimated for each individual's deviations are randomly distributed with zero means. The basic model is described briefly in the Appendix.

In this analysis, the best fitting population curves and the within-subject curves were always linear. Selection of the best fitting models was based on maximum likelihood and Akaike's Information Criterion (AIC) [30, 31]. The complete model included mean height and binary survey indicator variables as constant covariates, and chronic cough, wheeze, dyspnoea and smoking status as time-dependent covariates. The one binary indicator variable per survey served to correct for differences between surveys that could result from changes in equipment or techniques, *etc.* Interaction terms in the REM analysis included all current smoking by symptoms categories. For numerical stability, age was centred by subtracting the mean age from each observed age. All hypothesis testing was performed at the  $p=0.05$  significance level.

#### Results

Table 1 shows the distribution of pulmonary function tests/observations stratified by gender. For males, there were 633 subjects, providing 1,601 pulmonary function observations. There were 143 males with at least 10 yrs of follow-up, who contributed 653 observations or 41% of the total observations for males. There were only 201 male subjects with single observations. Females had more long-term follow-up than males, with 290 having at least 10 yrs of follow-up, providing 1,316 of the total 2,482 observations or 53%. There were 248 females who had single observations, accounting for 10% of their total observations.

Table 1. - Number of pulmonary function test observations by gender

	Number of observations						Total
	1	2	3	4	5	6	
Males	201	163	118	66	54	31	633
Females	248	198	164	122	96	63	891

The prevalence rates of chronic cough and wheeze were evaluated in survivors (initially and in later surveys) and in those who died, by gender and smoking (table 2). Prevalence rates were higher in males and current or ex-smokers, and in those who died in almost all smoking categories. Symptom rates increased over time in those surviving in essentially all smoking categories of both genders. The proportion with low percentage predicted  $FEV_1$  ( $\%FEV_1 < 75\%$ ) at Survey 1 was also much higher in males, in current or ex-smokers, and in those who subsequently died. The rates of low function increased over time in those current smokers who survived, in both genders. Symptoms were correlated with low lung function in each gender over the course of the study; chronic cough was about two times more prevalent, and wheeze about five times more prevalent, in those with  $\%FEV_1 < 75\%$ , in both genders (not shown). These data imply the necessity of including symptoms and smoking as covariates in gender specific analysis of longitudinal lung function.

Table 2. — Prevalence rates (per 100) for symptoms\* and low percentage predicted FEV<sub>1</sub> (%FEV<sub>1</sub>)\*\* by survival status, smoking, gender for the initial and later surveys

Symptoms Smoking	% Chronic cough (n)			% Wheeze (n)			% Low FEV <sub>1</sub> (n)		
	Current	Ex	Non	Current	Ex	Non	Current	Ex	Non
<b>Males:</b>									
<b>Survey 1</b>									
Survivors	38.0 (121)	20.5 (122)	6.8 (73)	10.7 (121)	8.2 (122)	0.0† (73)	18.8 (96)	26.0 (104)	16.7 (54)
Non-survivors	40.7 (86)	31.3 (160)	10.1 (69)	17.4 (87)	20.0 (160)	2.9† (69)	47.6 (82)	52.5 (139)	25.4 (59)
<b>Survey 9 or 10</b>									
Survivors	60.6 (33)	22.0 (82)	20.0 (40)	42.4 (33)	9.8 (82)	10.0 (40)	36.4 (22)	13.8 (58)	8.0† (25)
<b>Females:</b>									
<b>Survey 1</b>									
Survivors	27.3 (161)	14.3 (147)	11.8 (263)	8.7 (161)	4.1 (147)	2.7 (262)	15.4 (136)	15.7 (121)	12.2 (230)
Non-survivors	35.3 (88)	18.8 (48)	11.2 (178)	8.0 (88)	6.3 (48)	6.2 (178)	24.7 (81)	36.4 (44)	29.6 (159)
<b>Survey 9 or 10</b>									
Survivors	50.0 (44)	17.2 (93)	20.6 (189)	11.4 (44)	5.4 (93)	5.3 (189)	29.6 (27)	17.9 (56)	5.9 (119)

\*: chronic cough and wheeze (apart from colds) as described in the text; \*\*: %FEV<sub>1</sub> <75%; †: number of cases ≤3. FEV<sub>1</sub>: forced expiratory volume in one second.

Table 3. — Estimated coefficients±standard error from the random effects model (REM) for subjects over 55 yrs of age

	FEV <sub>1</sub> /FVC %	FEV <sub>1</sub> l	FVC l
<b>Males:</b>			
Constant	109.8±11.04*	-2.207±0.718*	-4.637±0.797*
Age <sup>†</sup>	-0.287±0.043*	-0.030±0.002*	-0.027±0.003*
<b>Covariables</b>			
Height cm	-0.208±0.063*	0.028±0.004*	0.048±0.005*
Chronic cough	-1.412±0.499*	-0.080±0.022*	-0.091±0.038*
Wheeze	-2.783±0.694*	-0.104±0.031*	-0.126±0.052*
Wheeze×age <sup>†</sup>	0.136±0.082	0.0002±0.004	-0.006±0.006
Dyspnoea	-3.430±0.632*	-0.079±0.028*	-0.166±0.048*
Ex-smokers	-1.977±0.559*	-0.062±0.026*	-0.024±0.042
Current smokers	-3.387±0.798*	-0.066±0.037	0.043±0.068
Current smokers×age <sup>†</sup>	-0.138±0.077*	-0.007±0.003*	-0.004±0.008
<b>Females:</b>			
Constant	99.35±7.685*	-2.128±0.352*	-3.231±0.401*
Age <sup>†</sup>	-0.235±0.032*	-0.021±0.001*	-0.020±0.001*
<b>Covariables</b>			
Height cm	-0.141±0.048*	-0.026±0.002*	0.037±0.002*
Chronic cough	-0.775±0.875	-0.014±0.016	0.044±0.022*
Wheeze	-1.786±0.735*	-0.116±0.022*	-0.169±0.036*
Dyspnoea	-2.155±0.545*	-0.072±0.016*	-0.070±0.027*
Ex-smokers	-2.016±0.504*	-0.041±0.016*	-0.039±0.022*
Ex-smokers×age <sup>†</sup>	-0.097±0.054*	-0.001±0.002	-0.001±0.003
Current smokers	-4.101±0.649*	-0.071±0.021*	-0.012±0.035
Current smokers×age <sup>†</sup>	-0.081±0.066	-0.004±0.003	0.0001±0.004

\*: p≤0.05; †: age centred to mean age (66 yrs males; 68 yrs females). FEV<sub>1</sub>: forced expiratory volume in one second; FVC: forced vital capacity.

The results of fitting the REM to the longitudinal pulmonary function data are listed in table 3. The symptom and smoking parameter estimates represent deviations in either intercepts and/or slopes (*i.e.* interactions with age) from those of the reference population, which in this case included subjects who were nonsmokers, free of any respiratory symptoms. For example, in the first column

under FEV<sub>1</sub>/FVC for males, the parameter for "current smokers" indicates that their ratios are on the average 3.387% below those of the reference groups, at the mean age of 66 yrs. Likewise, the "current smokers × age" parameter estimate shows a decline of 0.138%·yr<sup>-1</sup>, which is in addition to the 0.287%·yr<sup>-1</sup> decline observed in the reference group (age coefficient). These coefficients can

also be expressed in the form of a regression equation for computing and plotting the mean curves. The equation for  $FEV_1/FVC$  for male current smokers is as follows:

$$FEV_1/FVC = 109.8 - 0.287 \times Age' - 0.208 \times Height + (-3.387) - 0.138 \times Age'$$

where  $Age' = Age - Mean\ Age$ .

No interaction terms between smoking and symptoms were statistically significant for any of the pulmonary function measures and, thus, are not included in table 3.

Figure 1 illustrates the mean  $FEV_1/FVC$  ratios for selected subgroups using the results of the REM procedure (table 3). Fig. 1a shows that the mean ratios in current and ex-smokers were significantly lower than the reference group even at the younger ages, and that subjects continuing to smoke experienced progressive decreases with age. Although ex-smokers remained below the reference population, they did not experience any progressive loss of function with age, illustrating the importance of smoking cessation. Fig. 1b shows that for males, chronic cough and dyspnoea were related to lower mean ratios, with no additional decrease with age, with

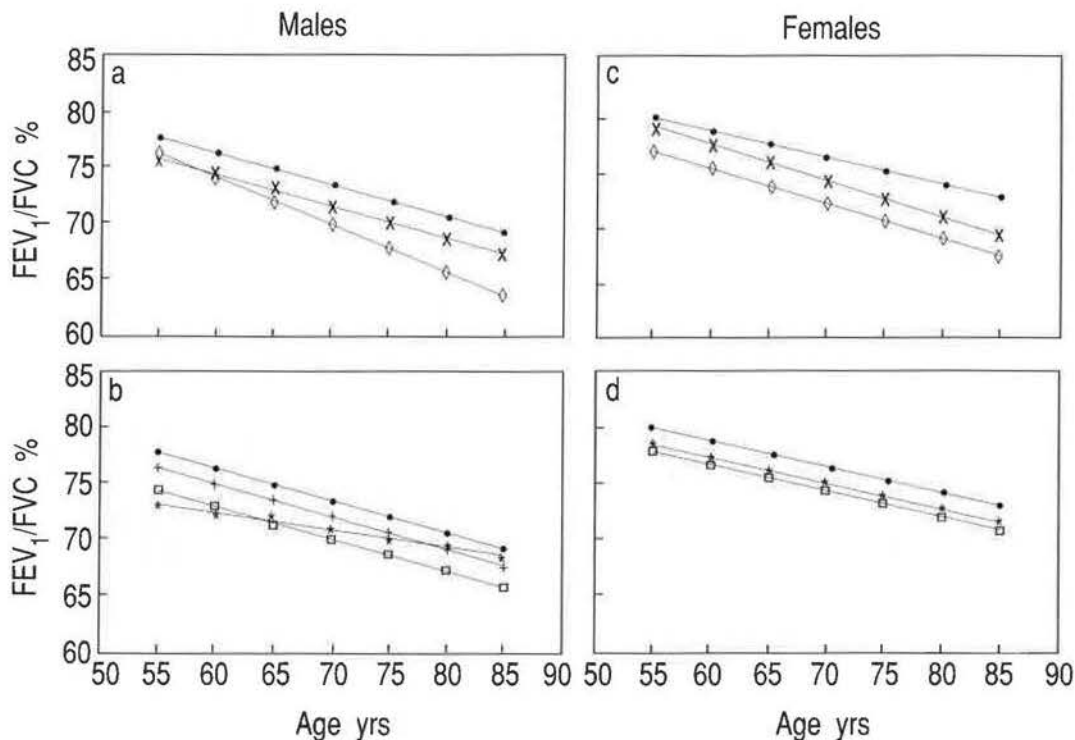


Fig. 1. — Mean  $FEV_1/FVC$  ratios versus age for male (a and b) and female (c and d) subjects, assessed at the mean height, using the results of the REM analysis (table 3). Plots a and c illustrate effects of smoking, both current and past on the temporal development of ratios. Plots b and d show the effects of respiratory symptoms on lung development. The reference subgroup is comprised of nonsmokers, who did not report having any respiratory symptoms (see methods). —•—: reference; —x—: ex-smokers; —◇—: current smokers; —+—: chronic cough; —\*—: wheeze; —□—: dyspnoea.  $FEV_1/FVC$ : forced expiratory volume in one second/forced vital capacity ratio; REM: random effects model.

#### Associations with $FEV_1/FVC$

The  $FEV_1/FVC$  ratios in the male reference population of asymptomatic nonsmokers, had an annual decrease of  $0.287\% \cdot yr^{-1}$ , as indicated by the negative age coefficient (table 3). Male subjects reporting chronic cough or dyspnoea had ratios that were lower than the reference values, by 1.412 and 3.430%, respectively, but that decreased with age at the same rate as the reference group. Lower ratio values were also estimated for current and ex-smokers, with current smokers decreasing more rapidly with age ( $0.138\% \cdot yr^{-1}$ ). Male wheezers also had lower ratios (2.783%) and a positive increase with age relative to the reference group, which was not statistically significant.

dyspnoea having the larger effect. Males reporting wheeze had quite different results. They had significantly lower ratios at the younger ages, but approached the reference group mean level of function by 80 yrs of age. This apparent improvement in function is a consequence of the positive interaction between wheeze and age.

In female reference subjects (table 3), the annual decrease with age in  $FEV_1/FVC$  was less than that observed in their male counterparts ( $0.235\% \cdot yr^{-1}$  compared to  $0.287\% \cdot yr^{-1}$  for males). The only respiratory symptoms associated with lower ratios in females were wheeze and dyspnoea, which were, respectively, 1.786 and 2.155% lower at the mean age than the reference group (fig. 1d), but not different from each other. Both current and ex-smokers had lower ratio estimates at the mean age, with

the largest negative associations being observed in current smokers (4.101%). Both smoking groups had progressive loss with age, but this was only statistically significant for ex-smokers. The association between smoking and  $FEV_1/FVC$  for females is illustrated in figure 1c. The magnitude of symptoms on  $FEV_1/FVC$  impairment were larger for males than females in all cases, with the detrimental association with current smoking also being more progressive with age.

#### *Associations with $FEV_1$ and FVC*

Symptomatic males had significantly lower  $FEV_1$  and FVC measures than the reference group. The largest impact on  $FEV_1$  was associated with reported wheeze. This subgroup had mean  $FEV_1$  values that were 104 ml lower than the reference group. The other symptom and smoking categories each had values around 80 ml lower. For FVC the largest reductions observed for males were associated with dyspnoea (166 ml) and wheeze (126 ml). The reduction in FVC relating to chronic cough was also significant, but the relationship with current or ex-smoking was not.

The primary associations between respiratory symptoms and  $FEV_1$  and FVC in females were with wheeze and dyspnoea, with only a small, but significant, 44 ml reduction in FVC being detected for chronic cough. The largest impairment was related to wheeze, which resulted in 116 ml and 169 ml reductions in  $FEV_1$  and FVC, respectively. Reported dyspnoea had a similar negative impact on  $FEV_1$  and FVC of around 70 ml. No symptom associations with  $FEV_1$  or FVC were progressive with age, in either males or females. Only small non-progressive changes were detected in  $FEV_1$  and FVC of female smokers. Ex-smokers were about 40 ml below the reference group at the mean age for both measures, and current smokers were 71 ml lower for  $FEV_1$ .

To examine the influence of those who died during follow-up on the time course of lung development, a second analysis was performed, also using the REM procedure, with participants stratified by gender and survival status. These results demonstrated that, for most symptoms, non-survivors had more impaired pulmonary function measures than survivors; hence, combining the two groups (table 3) yielded coefficients that are weighted averages of the two stratified coefficients. For example, male survivors ( $n=318$ ) reporting wheeze had  $FEV_1/FVC$  values that were 1.38% below the reference group at the mean age, while non-survivors ( $n=315$ ) were 5.71% lower. In the combined group analysis (table 3), male wheezers were 2.78% below the reference group, which is between the two stratified estimates. Likewise, in female wheezers, survivors had no significant reduction in  $FEV_1/FVC$  compared to the reference group, and non-survivors had a 5.94% reduction, which was statistically significant. This compares to the combined reduction of 1.79% (table 3), which was also significant. As expected, the results of smoking, both current and past, were also larger and more progressive in non-survivors. The  $FEV_1/FVC$  of male non-survivors who currently smoked de-

creased at a rate of  $0.34\% \cdot yr^{-1}$ , which is over twice that estimated in the combined group of current smokers ( $0.14\% \cdot yr^{-1}$ ) (table 3). The conclusions from these stratified analyses are that non-survivors do have a major influence on estimated associations between symptoms and smoking and pulmonary function measures.

#### *Gender differences*

To compare pulmonary function measures between genders, we did another REM analysis with males and females combined, and included a binary indicator variable (males=1, females=0) to estimate gender differences. The results showed that FVC and  $FEV_1$  were significantly higher in males by 535 ml and 341 ml, respectively, and that both measures declined at faster rates than those in females. In contrast, males had significantly lower  $FEV_1/FVC$  ratios (1.8%), which also declined at a more rapid rate ( $0.08\% \cdot yr^{-1}$ ) than that found in females.

### **Discussion**

In this study we have examined the association between respiratory symptoms and smoking and pulmonary function measures in a population sample of elderly subjects. We consider this study to be important because of the long-term follow-up of pulmonary function, up to 14 yrs, and the ages of the participants. It is unique in being able to use such a data set, with recently developed longitudinal techniques for analysis [31]. This longitudinal REM allowed us to include subjects with any number of observations, thus, increasing the power to detect important differences between subgroups.

To compare the sensitivity of the REM analysis to alternative approaches, we reanalysed the  $FEV_1$  data using slope estimates as the dependent variable in an analysis of covariance (ANCOVA). The same exact covariables that were used in the REM were included, except for the survey indicator variables. The results showed that a number of the symptom categories, that were significantly lower using the REM, were not significant using the ANCOVA. The differences between the two methods illustrate the importance of using true longitudinal techniques, particularly when the differences may be in the absolute level of pulmonary function, rather than in the rates of decline.

Since the REM procedure allows subjects to have an unequal number of data points, subjects with single observations were also included in the current analysis. In the REM analysis, the subjects with single observations cannot influence the slope estimates, since there is no slope information contained in a single observation, but they do contribute to the overall position of the fitted line. To determine the contribution of these single observations to the final results (table 3), we reanalysed the  $FEV_1/FVC$  data for the 432 males, excluding all subjects with only one observation (table 1). The results of this REM analysis showed no significant changes in the magnitudes of the estimated coefficients and only coefficients that were

of borderline significance in the original analysis became nonsignificant when single points were removed, indicating some loss of power due to the reduced sample size.

As mentioned in the methods section, indicator variables for each survey were included as constant covariables in the REM analysis, in order to adjust for possible differences between surveys. Such differences could be attributed to changes or improvements in flow measuring equipment, or recording devices used to perform the pulmonary function testing. In all of the REM results, there were surveys that differed significantly from the others; these results were not included in table 3. The significance of some of these variables does suggest that their inclusion was important in helping to ensure that reported differences were not inadvertently affected by survey biases.

The apparent improvement in  $FEV_1/FVC$  with age observed in male wheezers (fig. 1b) can probably be attributed to a survivor effect. Examination of their  $FEV_1/FVC$  raw data (not shown) showed a large number of subjects with extremely low ratios (<50%) in the <70 yr age group, and no subjects with ratios in this range >70 yr of age. This suggests that subjects with very low ratios do not live as long as those with higher ratios, and that it is those healthier subjects who survived beyond 70 yrs that caused the observed increases in  $FEV_1/FVC$  with age. Similar survival effects have previously been reported in this population [4].

Using the  $FEV_1/FVC$  ratio substantially reduces "regression toward the mean" [42]. However, one must be somewhat cautious in interpreting the  $FEV_1/FVC$  in the elderly, since effects of other diseases may have an impact. For example, there may be quite different FVCs and, thus, very different ratios, in heart disease or restrictive lung disease compared to airways obstructive disease (AOD) [5]. Likewise, one may underestimate declines in the ratio during age periods where the FVC is increasing while the  $FEV_1$  is declining in early AOD [1]. Nevertheless, the  $FEV_1/FVC$  is more specific for AOD, and is more likely to be less affected by the other problems that reduce both [42].

In summary, using longitudinal methods we have demonstrated that respiratory symptoms are generally associated with lower levels of lung function, and these differences are larger in subjects who subsequently die. The most pronounced and prevalent associations were found in the  $FEV_1/FVC$  ratios of both survivors and non-survivors. The observed association with chronic cough was predominately in male subjects, and was independent of survival status.

The negative impact of smoking was apparent in most measures, but was largest and most progressive in the  $FEV_1/FVC$  ratios. This was true in both genders. Ex-smokers in all cases had better lung function values than those subjects continuing to smoke, but they were always significantly below the reference group. Ex-smokers had similar rates of decline to nonsmokers, except for  $FEV_1/FVC$  in females which declined at a faster rate.

One important conclusion is that the risk factors for low and declining ventilatory function in the elderly are the same as those in the younger age groups. The same

factors affect ventilatory function over time, and the magnitudes of the effects are similar in those surviving the first peak of cardiopulmonary mortality.

## Appendix

The basic random effects model for the  $i$ th subject is:

$$y_i = X_i\beta + Z_i\tau_i + \varepsilon_i$$

where  $y_i$  is an  $n_i \times 1$  column vector of observations for subject  $i$ ,  $\beta$  is a  $p \times 1$  vector of coefficients representing the linear population parameters, and  $\tau_i$  is a  $q \times 1$  vector of coefficients, random across subjects, assumed to have a normal distribution with mean zero and covariance matrix  $D$ . The design matrices  $X_i$  ( $n_i \times p$ ) and  $Z_i$  ( $n_i \times q$ ) link  $\beta$  and  $\tau_i$ , respectively, to  $y_i$ . Both  $X_i$  and  $Z_i$  are known matrices, the elements of which are determined by the degree of polynomial selected for the population and within-subject models, respectively. Here,  $\varepsilon_i$  is assumed to be normally distributed with mean zero and covariance matrix  $V_i$ .

For our purposes, the vector  $y_i$  contains the values of pulmonary function indices for the  $i$ th subject, and  $n_i$  represents the number of surveys in which pulmonary function measures were taken ( $n_i = 1, 2, \dots, k$ ,  $k \leq 6$ ). The population design matrix  $X_i$  for the  $i$ th subject is linear, with a column of ones to estimate the intercept, and a column of ages to estimate the slope, and additional columns of  $X_i$  are generated based on the values of covariables in survey  $i$  for a given subject. The within-subject stage of the model was linear for all cases with the design matrix  $Z_i$  containing a column of ones to estimate each subject's deviation in intercept, and a column of ages, corresponding to the observed lung function measures, to estimate each subject's deviation in slope.

JONES and BOADI-BOATENG [30] describe a means of obtaining exact maximum likelihood estimates of the unknown parameters in matrix  $V_i$  by using the Kalman filter to calculate the likelihood function, and a nonlinear optimization programme to find the maximum likelihood estimates. The population parameters,  $\beta$ , are then estimated using weighted least squares. This analysis assumes that missing values are missing at random which, for this population, appears to be a valid assumption. Additional assumptions are that there is no cohort effect, not formerly tested.

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