Study objective: Diffusing capacity of the lung for carbon monoxide (DLCO) is frequently assessed as part of a thorough pulmonary function assessment in patients with pulmonary or cardiopulmonary diseases. However, little information regarding the longitudinal trends of DLCO is available. In this study, we examined the temporal trends in DLCO to determine the effects of smoking and changes in smoking habits.

Design: A longitudinal study was recently conducted in the Po River Delta area of northern Italy, in which DLCO measurements were taken approximately 8 years apart in the same subjects; this offered the unique opportunity to assess the temporal changes in DLCO. The longitudinal DLCO data were analyzed independently in two age groups (20 to 40 years, and > 40 years) using a repeated-measures analysis.

Results: Included were 928 subjects > 20 years old who had DLCO assessments both at baseline and follow-up. Male subjects had higher mean levels of DLCO than female subjects in the older age group (≥ 40 years). Continuous smokers had significantly lower DLCO levels than “never-smokers,” but their changes in DLCO during follow-up were the same. This suggests that the lung damage due to smoking had occurred prior to DLCO testing. We also found that the annual decline in DLCO accelerated with age in adults ≥ 40 years old.

Conclusions: We conclude that in adults ≥ 40 years of age from the general population, DLCO accelerates downwards regardless of gender, smoking, and initial FEV1 level.

(CHEST 2001; 120:74–80)

Key words: age; diffusing capacity; gender; general population; lung function trends; spirometry

Abbreviations: ATS = American Thoracic Society; DLCO = diffusing capacity of the lung for carbon monoxide; ISA = internal surface area; REM = random effects model; VC = vital capacity

After a long period of low interest in diffusing capacity of the lung for carbon monoxide (DLCO),1 several investigators2–10 have published reports creating new interest in this simple but informative lung function test. The DLCO test is clinically useful for the early diagnosis of pulmonary vascular and interstitial lung disease and detecting emphysema in smokers with airways obstruction.2–4 Also, research on modification of the standard technique using mainly commercially available equipment has been published,9 along with an update of the official statement of the European Respiratory Society10 and the American Thoracic Society (ATS).11

However, little information on longitudinal trends of DLCO has been published. There are only few reports12–14 concerning clinical patients or occupational settings and one abstract15 on smokers from a general population. In 1999, Sherrill and coworkers16 reported the predictors of longitudinal change in DLCO over 8 years in a general population sample living in Arizona.

Our study design in the Po River Delta area (two surveys on the same subjects with an average interval...
of 8 years) offered the unique opportunity to assess the temporal changes of DLCO in a different environment on a broad age range, accounting for cigarette smoking. Using DLCO values for the initial survey, we have derived prediction equations for normal subjects and assessed the effects of respiratory symptoms and diseases and cigarette smoking, both current and lifetime, in this same population sample. The aims of the current report are to describe the age-specific longitudinal patterns of DLCO in a general population sample and to determine the effects of smoking and changes in smoking habits.

**Materials and Methods**

The Po River Delta Epidemiologic Study is a follow-up study on the natural history of COPD in a large population sample living in North Italy, near Venice. Population characteristics, sampling methodology, and main findings of the first cross-sectional investigation, including questionnaire and lung function, were previously reported. In particular, a detailed description of the method used to measure DLCO is reported in the articles describing the reference equations and the relationships of DLCO with respiratory symptoms. Briefly, the population sample (age range, 8 to 64 years) was a family-based, multistage, stratified cluster design. Data on the population were obtained from the last census before the study. Stratification was performed using two indexes of socioeconomic status: (1) "crowding," ie, subjects living in the house divided by the number of rooms; and (2) the percentage of heads of household in higher occupational activities according to the classification of the Italian National Statistics Institute. Based on the cumulative frequency distribution, each household was assigned to high, medium, or low socioeconomic status. Stratification was also performed on the basis of the age of heads of household (three categories). Households were constituted by one or more members.

A total of 3,284 subjects were investigated in the first cross-sectional survey (1980 to 1982), and 2,841 subjects participated in the second survey (1988 to 1991). Of those 2,841 subjects, 2,136 subjects also had participated in the first survey, yielding a follow-up of 65%.

The protocol of the second survey included the same questionnaire, a modified Italian version of the standard National Heart, Lung, and Blood Institute questionnaire, developed by the special Project on Chronic Obstructive Lung Disease of the Italian National Research Council (the CNR questionnaire). It was administered by trained interviewers who entered responses directly into a personal computer. The same lung function protocols for slow vital capacity (VC), FVC, and DLCO were used. In the follow-up survey, the single-breath nitrogen test was no longer performed, as it had been satisfactorily performed by a low percentage of subjects in the baseline survey. Further, in the follow-up survey, the methacholine challenge test, prick tests to common allergens, and measurement of total serum IgE were also included.

Subjects were tested with the same automated instrument (model 47804/S; Hewlett Packard; Waltham, MA) in both surveys at least 30 days after an infectious respiratory episode and, if they were current smokers, at least 1 h after the last cigarette smoked. Variable percentages of individuals were able to perform acceptable lung function tests: slow VC, from 94% in the first survey to 90% in the second survey; FVC and derived indexes, from 94 to 97%; and DLCO, from 80 to 76%. The CNR standardized lung function protocols are based essentially on the recommendations of the ATS with some exceptions: the inspired volume of DLCO had to be ≥ 85% of slow VC in order to be considered acceptable, and, for each subject, the higher DLCO value of the two acceptable measures was taken.

DLCO was computed by the method of Forster and Ogilvie, using the inspired volume at ambient temperature and pressure, dry, subsequently corrected to standard temperature and pressure, dry. Breath-holding time was computed from the moment when one half of the volume was inspired to the moment when dead space washout was completed and collection of alveolar gas was started, according to ATS recommendations valid at the start of the longitudinal survey. Corrections for carbon monoxide back pressure or hemoglobin or carbon dioxide or inspired volume dead space were not performed in the second survey in order to use the same formula for computing DLCO as in the first survey.

Cross-sectionally, nonsmokers were defined as those who had never smoked any kind of tobacco regularly. Smokers were those who were currently smoking at least one cigarette daily. Ex-smokers included those who had formerly smoked regularly until ≥ 6 months before the examination. Longitudinally, we defined those who did not change their status between the two studies as persistent nonsmokers, smokers, or ex-smokers, and those subjects who had stopped smoking or started smoking as quitters or new starters, respectively. Former smokers who had started smoking again during the 8 years of follow-up were classified as restarters.

The current analyses included only adult participants whose age at the initial survey was ≥ 20 years. This age cutoff was based on cross-sectional analysis of DLCO data from this same population, which showed that DLCO ceases to grow at approximately 18 years and 19 years in female and male subjects, respectively.

**Statistical Methods**

The longitudinal DLCO data were analyzed using a repeated-measures analysis that was used by Sherrill et al to describe longitudinal changes in DLCO among a random sample of adults in Arizona. Briefly, this procedure uses a "saturated" random effects model (REM) that fits polynomials that have order one less than the number of time points to each subgroup. For our data, this meant fitting a linear or first-order polynomial since there were two time points. A saturated model allows both time points for each subgroup to have a different mean estimate. For example, in this analysis, a given subgroup (eg, smokers) could differ from the reference group at both surveys, which would result in different slopes between them, or smokers could differ only by a constant amount at both surveys, and therefore smokers would have the same slope as the nonsmokers. The likelihood ratio test, which was calculated as the change in $-2\ln (likelihood)$ between nested models, was used to test for significant differences between groups.

In the REM analyses, FEV$_1$ (in liters), change in FEV$_1$, sex, weight, change in weight, initial age, pack-years, smoking status variables between surveys, and smoking status by age and gender interactions were all entered as fixed covariables. Pack-years was censored as a dichotomous indicator variable with 20 pack-years being set as a cutoff or threshold value. Two different forms of within-subject covariance structures were considered for each REM analysis: first-order autoregressive and uncorrelated or independent. The best fitting nonnested model was determined using Akaike Information Criteria with the model fully saturated for all covariables; for nested models, the best fitting model was determined using $-2\ln (likelihood)$ changes, which is equivalent

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to a likelihood ratio test. For all analyses, the uncorrelated covariance structure yielded the best overall fit.

Since we wanted an estimate of the true longitudinal slope between surveys, which based on plots of the raw data appeared to differ from the cross-sectional slope with age, we also included DLCO test dates as time-dependent variables. The initial test date was arbitrarily set to zero, and the follow-up test date was calculated as the change in time since the initial test. However, including initial age in the model allowed us to determine if the longitudinal slope estimates changed with age, an indication of acceleration in the DLCO growth curves. REM analyses were done independently in subjects whose initial age was < 40 years vs ≥ 40 years to assess differences in predictors related to age. Results from the REM analyses are presented as means and SEM, instead of as actual coefficients since these are not directly interpretable. Statistical hypothesis tests were two-tailed comparisons at the α = 0.05 significance level.

Results

Of the 2,136 subjects participating in both the baseline and follow-up surveys, 99 subjects at baseline had only questionnaire responses, 1 subject had only questionnaire responses and DLCO, and 253 subjects had only questionnaire responses and FEV1; at follow-up, 171 subjects had only questionnaire responses, 46 subjects had only questionnaire responses and DLCO, and 238 subjects had only questionnaire responses and FEV1. Thus, 1,328 subjects had all three criteria (questionnaire responses, DLCO, and FEV1) measured in both surveys. Of them, 400 subjects were < 20 years old and 928 subjects were ≥ 20 years old. The latter were retained in the analyses performed for this article.

Table 1 lists the basic descriptive statistics by age (including the distribution by 10-year age intervals) for the variables considered as predictors of DLCO. About half of the study participants in each group were men. The proportion of subjects who reported quitting smoking during the observation interval was similar in each age strata, however. The numbers of new smokers were not large enough to warrant inclusion in the primary analysis. The proportion of subjects with > 20 pack-years of smoking and the proportion of ex-smokers were significantly larger among the age ≥ 40 group, as expected. Older men and women were significantly heavier, shorter, and had lower FEV1 values.

The results of fitting the REM model to the longitudinal DLCO data are listed in Tables 2-5. All categories listed were statistically significant (p < 0.05). For the age ≥ 40 group, the following were significant predictors of DLCO: gender, age, current or ex-smoking, restarting smoking, pack-years of smoking, weight, change in weight, and initial FEV1. Table 2 shows the mean DLCO estimates for subjects ≥ 40 years old at each survey stratified by sex, smoking, and pack-year categories, adjusted for the other significant variables in the model (age, FEV1, weight, and change in weight). Men had statistically significantly higher mean levels of DLCO than women at both surveys in all subgroups. Subjects who were current smokers had significantly lower mean DLCO levels than “never-smokers,” which were even lower among smokers reporting > 20 pack-years of smoking. This was true for both male and female current smokers. Ex-smokers were the only group who improved their DLCO during the study observation interval. Their mean DLCO was significantly lower than never-smokers at the initial survey but did not differ at follow-up. Subjects who restarted the habit also had significantly lower DLCO levels when compared to never-smokers; however, the results for this subset may not be reliable because of the small sample size (n = 7).

The DLCO slopes for both sexes were steeper as age increased (Table 3). Figure 1 clearly illustrates an acceleration in DLCO decline with age, in this age group, with mean rates of decline in DLCO per year changing from −0.094 U/yr at age 40 years to −0.394 U/yr by age 70 years, for both men and women.
However, the slope of DLCO of Dlco and change in weight were also significant predictors.

Data are presented as mean (SEM); means calculated assuming age of 40 years, using sex-specific mean FEV1 and weight estimates and assuming no weight change.

**Table 2—Changes in DLCO (mL/min/mm Hg) Associated With Smoking Status and Gender for Participants ≥ 40 Years Old (n = 414)**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Initial DLCO</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never-smokers</td>
<td>Men</td>
<td>35.76 (0.73)</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>26.90 (0.52)</td>
</tr>
<tr>
<td>Current smokers</td>
<td>Men</td>
<td>32.28 (0.66)</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>31.13 (0.62)</td>
</tr>
<tr>
<td>Restarters</td>
<td>Men†</td>
<td>29.78 (2.52)</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>20.92 (2.51)</td>
</tr>
<tr>
<td>Ex-smokers</td>
<td>Men</td>
<td>34.58 (0.75)</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>25.73 (0.54)</td>
</tr>
</tbody>
</table>

*Data are presented as mean (SEM); means calculated assuming age of 40 years, using sex-specific mean FEV1 and weight estimates and assuming no weight change.
†Difference between initial and follow-up DLCO means not statistically significant (p < 0.05).

Table 3—Changes in DLCO for Never-Smokers by Age for Participants ≥ 40 Years Old (n = 158)

<table>
<thead>
<tr>
<th>Age†</th>
<th>Initial DLCO</th>
<th>Follow-up</th>
<th>Slope</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>35.72 (0.73)</td>
<td>34.97 (0.78)</td>
<td>−0.094</td>
</tr>
<tr>
<td>50</td>
<td>34.80 (0.64)</td>
<td>33.25 (0.66)</td>
<td>−0.194</td>
</tr>
<tr>
<td>60</td>
<td>33.88 (0.77)</td>
<td>31.53 (0.84)</td>
<td>−0.294</td>
</tr>
<tr>
<td>70</td>
<td>32.95 (1.05)</td>
<td>29.81 (1.19)</td>
<td>−0.394</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>26.86 (0.51)</td>
<td>26.12 (0.58)</td>
<td>−0.094</td>
</tr>
<tr>
<td>50</td>
<td>25.94 (0.36)</td>
<td>24.40 (0.40)</td>
<td>−0.194</td>
</tr>
<tr>
<td>60</td>
<td>25.02 (0.56)</td>
<td>22.67 (0.65)</td>
<td>−0.294</td>
</tr>
<tr>
<td>70</td>
<td>24.10 (0.90)</td>
<td>20.95 (1.06)</td>
<td>−0.394</td>
</tr>
</tbody>
</table>

*Data are presented as mean (SEM); means calculated for never-smokers assuming mean FEV1 of 3.35 L for men and 2.53 L for women, mean weight for men of 75 kg and mean weight for women of 63 kg, and no change in weight. Slopes calculated as the difference between survey means divided 8.0 years; unit of slope = mL/min/mm Hg per year.
†Represents each participants age at the time of the initial study.

**Table 4—Mean DLCO by Levels of FEV1 for Ages ≥ 40 and <40 Years**

<table>
<thead>
<tr>
<th>FEV1, L†</th>
<th>Initial DLCO</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 40 yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>2.20</td>
<td>32.00 (1.07)</td>
</tr>
<tr>
<td></td>
<td>3.35 (mean)</td>
<td>35.72 (0.73)</td>
</tr>
<tr>
<td></td>
<td>4.50</td>
<td>39.44 (0.79)</td>
</tr>
<tr>
<td>Women</td>
<td>1.83</td>
<td>24.54 (0.70)</td>
</tr>
<tr>
<td></td>
<td>2.53 (mean)</td>
<td>26.81 (0.51)</td>
</tr>
<tr>
<td></td>
<td>3.23</td>
<td>29.07 (0.55)</td>
</tr>
<tr>
<td>Age &lt; 40 yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>2.92</td>
<td>33.12 (0.48)</td>
</tr>
<tr>
<td></td>
<td>4.09 (mean)</td>
<td>34.88 (0.65)</td>
</tr>
<tr>
<td></td>
<td>5.25</td>
<td>36.63 (0.83)</td>
</tr>
<tr>
<td>Women</td>
<td>2.24</td>
<td>25.83 (0.45)</td>
</tr>
<tr>
<td></td>
<td>2.98 (mean)</td>
<td>27.77 (0.31)</td>
</tr>
<tr>
<td></td>
<td>3.72</td>
<td>29.71 (0.49)</td>
</tr>
</tbody>
</table>

*Data are presented as mean (SEM); means calculated assuming age of 20 years or 40 years, sex-specific mean weight, and no change in weight.
†Range of FEV1 values to illustrate this effect were selected to include 95% of observations.

DLCO was also significantly related to FEV1 in the older age group; subjects who had high levels of FEV1 also had higher mean DLCO values (Table 4). However, the slope of DLCO was the same at all levels of FEV1 and was independent of sex. Weight and change in weight were also significant predictors of DLCO with positive coefficients, for both sexes, suggesting that heavier subjects and those with an increase in weight would have higher levels of DLCO. Factors that were not statistically significant in the REM analyses for this age group included change in FEV1, quitting smoking (n = 65), interactions between smoking status and age, and interactions between smoking and gender.

For subjects aged 20 to 40 years, the same covariates were considered in the REM analyses; however, in this younger age group, only current smoking, weight, and FEV1 were statistically significant predictors of DLCO. The effects of current smoking on DLCO are listed in Table 5, which show that among both sexes current smokers had significantly lower mean DLCO levels than never-smokers. This effect was similar in magnitude to that found among the current smokers with a low smoking history (<20 pack-years) in the older age group. Similarly, subjects with higher levels of FEV1 also had higher mean DLCO values (Table 4). Although sex was not a

**Table 5—Changes in DLCO (mL/min/mm Hg) Associated With Smoking Status and Gender, Ages 20 to 40 Years (Young Adults; n = 514)**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Initial DLCO</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never-smokers</td>
<td>Men</td>
<td>36.27 (0.45)</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>27.77 (0.30)</td>
</tr>
<tr>
<td>Current smokers</td>
<td>Men</td>
<td>33.72 (0.49)</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>25.22 (0.41)</td>
</tr>
</tbody>
</table>

*Data presented as mean (SEM); means calculated using sex-specific weight and FEV1 mean estimates (Table 1).
significant factor in this REM analyses, the gender differences were reflected in the weight and FEV₁ coefficients.

**Discussion**

We have described the longitudinal trend of DLCO in a general population sample living in a rural area of northern Italy. To our knowledge, these data are only the second example of longitudinal DLCO in an epidemiologic general population study.

An analysis of the changes in prevalence rates of respiratory symptoms and diseases between the baseline and follow-up survey of the Po River Delta study (along with that between the baseline and follow-up survey of the analogous prospective Pisa study) has been recently published. In that analysis, participants in only the baseline survey of the Po River Delta study did not significantly differ from participants in both baseline and follow-up surveys with regard to baseline prevalence rates of respiratory symptoms and diseases. The only exception was a slight difference for baseline mean age in female subjects (35.5 ± 16.9 years vs 38.8 ± 15.7 years; p = 0.03).

In this analysis, we included the test dates as the time variable for predicting follow-up means and slopes. We chose to use this variable rather than the age at testing because inspection of the data plots suggested that rate of decline was increasing with age within subjects, yet because of "regression to the mean" this increasing rate of decline was not being detected. This is a common problem in longitudinal analysis when the duration of follow-up is short relative to the age span of the data. Inclusion of age as a fixed covariate allowed us to determine if the rate of decline was changing with age, which was true in the older subjects.

The mean interval between the two observations was 8 years, a period sufficient for the biological variation to overcome the variance due to technical errors. The same instrument was used, and the technicians, although different, followed the same protocol, which included the same formula for computing DLCO. Thus, the long-term reproducibility of the intraindividual DLCO measurements should have been good.

As mentioned in the "Material and Methods" section, corrections for carbon monoxide back pressure or hemoglobin or carbon dioxide or inspired volume dead space were not performed in both surveys. However, use of these four correction factors suggested by the ATS did not significantly change the uncorrected DLCO values in a large series of hospital patients, probably since the correction factors influence the formula in opposite directions. Indeed, part of the improvement in the DLCO seen in the former smokers may be due to a fall in their carboxyhemoglobin levels. Study participants had relatively low prevalence rates of respiratory symptoms, making the possibility for the existence of particular clinical conditions very unlikely. Comparability of cross-sectional and longitudinal data regarding the relationship of a functional parameter, mainly FEV₁, with age is still matter of debate; some authors have found a larger estimate of the age-regression coefficient cross-sectionally and others longitudinally between surveys. This discrepancy is also true for DLCO data; however, by including the test dates in the REM analyses, we estimated the "true" longitudinal DLCO slope between the two surveys.

Common predictors of DLCO in both age groups were current smoking, weight, and FEV₁. The effect of current smoking on DLCO in the younger age group was similar in magnitude to that found in the lighter smokers (< 20 pack-years) in the older age group. This finding is not surprising since there were very few current smokers in the younger age group with > 20 pack-years of smoking exposure. Two key differences between predictors of DLCO in the two age groups were age and change in weight. The lack of a significant age effect implies no acceleration in rates of decline with age among the younger adults between ages of 20 years and 40 years. This would suggest that the rate of decline in DLCO is rather constant until around 40 years of age, and thereafter it begins to accelerate downward. This acceleration was independent of smoking status. Further research needs to be done to investigate possible physiologic...
mechanisms related to this acceleration. The change in weight was likely not a significant predictor among the younger adults because they gained less weight during the follow-up period than the older adults.

The only data set to which we can compare our longitudinal data from a general population sample is the one obtained in Tucson, AZ, by Sherrill et al. Identical statistical procedures were used. The similarities are represented by the age effect: they found in the interval of 40 to 70 years an increase of the slope from $-0.43$ to $-0.63$ U/yr in men and from $-0.28$ to $-0.49$ U/yr in women. They also did not find an effect of lifetime cigarette consumption or pack-years on the DLCO slope. They reported that longitudinal changes in FEV$_1$ were significant predictors of DLCO slope, but in our cohort, FEV$_1$ was not a significant predictor of DLCO.

The Italian cohort was larger ($n = 928$ vs $n = 543$), was younger (38.4 years vs 49.4 years), had more male subjects (49% vs 41.3%), had more quitters (16.5% vs 6.3%), had more current smokers (29.9% vs 25.4%), had fewer ex-smokers (14.2% vs 29.5%), and had smoked much less (11.7 pack-years vs 36.8 pack-years for smokers, and 15.2 pack-years vs 26.2 pack-years for ex-smokers). These different factors and equipment differences may explain the lower mean values in Po River Delta, accompanied by more gradual change in DLCO, when compared to subjects in Tucson, AZ.

For the sake of consistency, it is important to comment the effect of age on the annual slope of DLCO, according to Hill’s criteria of causation. DLCO starts to decline early in life and accelerates markedly after age 40 years, unlike lung volumes and expiratory flows. This finding differs from cross-sectional observations of a linear association of DLCO with age $> 18$ to 20 years. For instance, the regression coefficients for age in the cross-sectional reference equation derived from normal subjects participating in the first Po River Delta survey was $-0.194$ mL/min/mm Hg for men and $-0.068$ mL/min/mm Hg for women $> 19$ years old.

However, the current finding strengthens the pathophysiologic explanation we hypothesized in our previous study. We concluded that the lung damage due to smoking occurred prior to the adult causes the mean linear intercept to increase, with a consequent decrease of gas-phase conductance in terminal airspaces.

Furthermore, our data confirm that results from general population samples cannot be predicted by results from employee cohorts. The results of Burgess et al, indicating a decrease in the decline of DLCO over time among Seattle firefighters, may have been influenced by the healthy worker effect or by effects due to older firefighters having less strenuous jobs with less smoke exposure than younger firefighters. Conversely, the much larger DLCO decline observed by Pham et al may be related to the heavy exposure to tobacco smoking and occupational toxicants by French steel workers during the 1970s.

With regard to smoking, we did not find any difference in the annual DLCO slope among the smoking categories, confirming in a larger database the findings of Sherrill et al. This occurred although the initial level of DLCO was higher in never-smokers, followed by restarters, current smokers of $< 20$ pack-years, and current smokers of $> 20$ pack-years, among the older age group. This suggests that the lung damage due to smoking occurred prior to DLCO testing. We did find that DLCO improved over the observation interval among ex-smokers. We conclude that in adults $\geq 40$ years of age from the general population, DLCO accelerates downwards regardless of gender, smoking, and initial FEV$_1$ level.

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