Change in pulmonary diffusion capacity in a general population sample over 9 years

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Rationale: Data on the change in diffusion capacity of the lung for carbon monoxide (DL CO) over time are limited. We aimed to examine change in DL CO (ΔDLCO) over a 9-year period and its predictors.

Methods: A Norwegian community sample comprising 1,152 subjects aged 18–73 years was examined in 1987 and 1988. Of the 1,109 subjects still alive, 830 (75%) were re-examined in 1996/97. DL CO was measured with the single breath-holding technique. Covariables recorded at baseline included sex, age, height, weight, smoking status, pack years, occupational exposure, educational level, and spirometry. Generalized estimating equations analyses were performed to examine relations between ΔDLCO and the covariables.

Results: At baseline, mean [standard deviation (SD)] DL CO was 10.8 (2.4) and 7.8 (1.6) mmol min⁻¹ kPa⁻¹ in men and women, respectively. Mean (SD) ΔDLCO was –0.24 (1.31) mmol min⁻¹ kPa⁻¹. ΔDLCO was negatively related to baseline age, DL CO, current smoking, and pack years, and positively related to forced expiratory volume in 1 second (FEV₁) and weight. Sex, occupational exposure, and educational level were not related to ΔDLCO.

Conclusions: In a community sample, more rapid decline in DL CO during 9 years of observation time was related to higher age, baseline current smoking, more pack years, larger weight, and lower FEV₁.

Keywords: diffusion capacity for carbon monoxide; longitudinal change; occupational exposure; socioeconomic status; smoking

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findings in cross-sectional studies of this population sample (17, 23–26), we hypothesized that smoking habits, occupational airborne exposure, and SES were predictors of change in DLCO.

Methods

Study population

Details of the sampling and characterization of the study population have been given elsewhere (27, 28). Briefly, a stratified sample (n = 1,512) from the general population in Hordaland, Norway, aged 18–73 years was invited to a clinical and respiratory physiological examination in 1987/88. Altogether 1,275 (84%) attended. DLCO measurements were obtained from 1,152 (90%) of the 1,275 attendees.

All attendees from visit 1 were invited to a follow-up (visit 2) in 1996/97. From the 1,152 subjects with DLCO measurements at visit 1, 881 (76%) attended visit 2. Of those lost to follow-up, 43 were dead, 81 no longer lived in the study area, 63 did not wish to participate further, and 23 could not attend because of serious illness. We were not able to establish contact with 61 of the visit 1 attendees. We obtained DLCO measurements from 830 (94%) of the visit 2 attendees.

Questionnaires

At visit 1, data on smoking habits, educational level, and occupational airborne exposure were obtained through self-reported questionnaires (23, 29). Smoking habit was categorized into never smoking, ex-smoking, and current smoking. Pack years was calculated as average number of cigarettes smoked per day, divided by twenty and multiplied by total number of years of being a smoker. SES was assessed in terms of educational level which was categorized into primary school, secondary school, and higher education (17).

Occupational airborne exposure was based on the following data: self-reported past or present occupational exposure to dust or gas (24) and self-reported exposure to specific agents and work processes (asbestos, quartz, wood dust, welding, and soldering) (27).

Clinical examination and pulmonary function testing

Clinical examination included measurements of height and weight. Blood samples were analyzed for hemoglobin (Hb) concentration and fraction of carboxyhemoglobin (HbCO). Pulmonary function testing (PFT), including DLCO, and forced spirometry were performed in accordance with current guidelines at the time of examination (1, 30–32).

PFT at both visit 1 and visit 2 was performed using a SensorMedics Gould 2100 automated system (SensorMedics BV, Bilthoven, the Netherlands). The same instrument was used at both visits, with the same calibration procedure and biological control throughout the observation period by regular measurements of the technicians operating the instrument. Details of the standardization of measurements, calibration processes, and the results of repeated measurements in the biological controls are given in the Supplementary file. At both visits, DLCO, the alveolar volume (VA), and the ratio of DLCO to VA (KCO) were measured using the single breath-holding method, with a breath-holding time of 10 seconds, a washout volume of 0.75 L, and a sample volume of 0.75 L. VA was measured by helium dilution. The test gas was delivered and certified by Norsk Hydro A/S (Rjukan, Norway). The concentration of carbon monoxide was requested to be within 0.270 and 0.330% with an accuracy of 1%. The concentration of helium was requested to be within 9 and 11% with an accuracy of 1%. The mean of two measurements, with no more than 10% variability, is reported. The ATS/ERS guidelines require the DLCO measurement to be performed after the subject had achieved an inspiratory vital capacity (IVC) of at least 85% of his or her forced vital capacity (FVC) (27). Only 531 subjects (64%) met this criterion on both visits, while 750 subjects (90%) achieved an IVC/FVC ratio of at least 0.7. Excluding the subjects with an IVC/FVC ratio of less than 0.85 did not alter the study results overtly as compared to including them in the analyses (Tables E1 and E2). Hence, the data are presented including all subjects with an IVC/FVC ratio > 0.7. Predicted values for DLCO were calculated using the formula estimated by Cotes et al. (1). It was decided not to use Norwegian predicted values, as they are based on the sample population also used in this study.

Spirometry was performed as an inhalation from functional residual capacity to total lung capacity, followed by a maximal forced expiration to residual volume. For forced expiratory volume in 1 second (FEV1) and FVC, the highest value from three technically acceptable measurements, with variability between the two highest values within 300 mL, is reported. All subjects were shown how to perform the maneuvers before testing, using standardized instructions, for both forced spirometry and measurement of DLCO. Subjects were seated and wearing a nose-clip during all efforts. Reference values calculated from healthy Norwegian subjects were used for FEV1 (26).

Statistical methods

Descriptive statistics are presented using the mean and standard deviation (SD) for continuous variables and frequency and percentage for categorical variables. Comparisons of the study population and those lost to follow-up were performed using the independent samples t-test and the exact chi-squared test. Comparisons of means from baseline and follow-up were performed using paired samples t-test, testing for cohort effect was carried out using independent samples t-test, and modeling change in
DLCO as a function of age was performed using curve estimation. Testing for normal distribution was performed using the Kolmogorov-Smirnov and the Shapiro-Wilk tests. DLCO at first and follow-up survey 9 years later was analyzed in a multiple linear regression model and estimated with generalized estimating equations (GEE) to account for correlation between the two measures of DLCO in the same subject at the two surveys. In this model, time was given the values 0 and 9 (years), all other continuous explanatory variables were centered around their means, all categorical variables were represented by dummy variables, and all interactions between the explanatory variables (categorical and continuous) were included. From such a model, the estimated regression coefficients for the interactions give direct estimates of the average yearly change in DLCO from the first to the last visit (ΔDLCO) at the zero level for all explanatory variables (for continuous variables this is the mean value; for categorical variables it is the reference category), and for a value of 1 unit increase from 0 in each variable all others were fixed at 0. For the GEE estimation, an exchangeable correlation structure was assumed. Models with adjustments for change in Hb and HbCO were also made. Finally, we decided a priori to test the following interactions: age versus sex, age versus smoking habits, and sex versus smoking habits. A significance level of 5% was used for all analyses.

SPSS version 20 (IBM Corporation, New York, USA) was used for all analyses except for the GEE estimation for which Stata version 12 (StatCorp, College Station, Texas, USA) was applied.

**Results**

**Study population description**

The characteristics of those examined at baseline and at follow-up and those lost to follow-up are outlined in Table 1. Almost half of the sample was ever-smokers, and approximately one quarter of the subjects was current smokers. Those who were lost to follow-up were significantly older and had significantly lower lung function than those who remained in the study.

Analyses were performed to discover a cohort effect, if present, by comparing baseline FEV1 and DLCO values of those aged 40–44 years at baseline with the corresponding follow-up values of those aged 40–44 years at visit 2. Analyses were performed independently for men and women to adjust for difference in the ratio between the sexes in these sub-samples. There were no statistically significant differences in mean values of FEV1 and DLCO.

**Table 1.** Descriptive statistics for characteristics at baseline and follow-up of the stratified sample from the general population in Hordaland County, Norway, aged 18–73 years in 1987/88 with follow-up 9 years later

| Variable                              | Baseline n = 1,152 | Follow-up n = 830 | Lost to follow-up n = 322 |
|---------------------------------------|-------------------|-------------------|---------------------------|
| Sex (male), n (%)                     | 590 (51.2)        | 436 (52.5)        | 154 (47.8)                |
| Age (years), mean (SD)                | 41.6 (16.0)       | 49.8 (14.4)       | 44.4 (19.3)               |
| Height (cm), mean (SD)                | 171.8 (9.3)       | 172.1 (9.4)       | 170.1 (9.3)               |
| Weight (kg), mean (SD)                | 71.4 (12.8)       | 75.9 (13.9)       | 69.7 (12.1)               |
| Smoking habits, n (%)                 |                   |                   |                           |
| Daily smokers                         | 310 (26.9)        | 233 (24.7)        | 77 (23.9)                 |
| Ex-smokers                            | 207 (18.0)        | 149 (21.8)        | 58 (18.0)                 |
| Never smokers                         | 635 (55.1)        | 448 (53.5)        | 187 (58.1)                |
| Pack years smoked, a mean (SD)        | 12.7 (11.1)       | 16.1 (12.3)       | 13.7 (14.1)               |
| Occupational exposure, n (%)          | 337 (29.3)        | 259 (31.2)        | 78 (24.2)                 |
| Education level, n (%)                |                   |                   |                           |
| Primary school                        | 213 (18.5)        | 133 (16.0)        | 80 (24.8)                 |
| Secondary school                      | 714 (62.0)        | 532 (64.1)        | 182 (56.5)                |
| Higher education                      | 225 (19.5)        | 165 (19.9)        | 60 (18.6)                 |
| FEV1 (L), mean (SD)                   | 3.60 (1.02)       | 3.28 (0.96)       | 3.33 (1.12)               |
| FEV1 percent predicted, mean (SD)     | 95 (14)           | 92 (15)           | 92 (16)                   |
| DLCO (mmol min⁻¹ kPa⁻¹), mean (SD)    | 9.37 (2.53)       | 9.35 (2.61)       | 8.81 (2.67)               |
| DLCO percent predicted, mean (SD)     | 94 (15)           | 98 (18)           | 91 (17)                   |

SD, standard deviation; FEV1, forced expiratory volume in 1 second; DLCO, diffusing capacity of the lung for carbon monoxide.

*a*Non-smokers excluded.
Baseline DLCO
Mean DLCO at baseline for the entire cohort \((n = 1,152)\) was 9.37 mmol min\(^{-1}\) kPa\(^{-1}\) (SD: 2.53). Using multiple linear regression, we found that female sex, higher age, current smoking, ex-smoking, and increased pack years were associated with lower DLCO. Higher body height, larger weight, and higher FEV\(_1\) were significantly associated with higher baseline DLCO, as was higher education compared to secondary school. Occupational airborne exposure was not associated with baseline DLCO regardless of whether the exposure characterization was based on self-reported dust or gas or self-reported exposure to specific airborne agents (Table 2, and Tables E3 and E4).

Change in DLCO
Mean DLCO at follow-up \((n = 830)\) was 9.35 mmol min\(^{-1}\) kPa\(^{-1}\) (SD: 2.61). Baseline DLCO for the same 830 participants was 9.59 mmol min\(^{-1}\) kPa\(^{-1}\) (SD: 2.44). Mean \(\Delta DLCO\) between baseline and follow-up for those who attended both visits was \(-0.24\) mmol min\(^{-1}\) kPa\(^{-1}\) (95% CI: -0.33 to -0.15).

Mean change in DLCO percent of predicted values for those subjects who attended both visits was 3.0% (95% CI: 2.3 to 4.1). Mean change in FEV\(_1\) percent of predicted values for the same subjects was -3.0% (95% CI -3.9 to -2.7).

\(\Delta DLCO\) had a normal distribution, tested by both the Kolmogorov-Smirnov and the Shapiro-Wilk tests, with a large variation (Fig. 1). Approximately 40% had a decline of more than twice the average, while 5% had no change \((0 \pm 0.10\) mmol min\(^{-1}\) kPa\(^{-1}\)) and 38% had an increase \((>0.10\) mmol min\(^{-1}\) kPa\(^{-1}\)).

Univariate associations using GEE, adjusting only for baseline DLCO and change in Hb concentration and HbCO, were found for age, height, baseline FEV\(_1\), smoking habits, and pack years.

The multivariate analysis, including baseline DLCO, sex, age, baseline height, baseline weight, baseline FEV\(_1\), baseline smoking habits, pack years smoked before baseline, occupational exposure, and educational level, showed that higher baseline DLCO and age were associated with a more rapid decline in DLCO. Current smokers had a more rapid decline than never smokers, and increased pack years was associated with more rapid decline as well. Higher body height and weight, and higher FEV\(_1\) were associated with a lower rate of decline in DLCO. All the associations above persisted after adjusting for change in Hb and HbCO. Sex, occupational exposure to gas or dust, and level of education were not significantly associated with \(\Delta DLCO\) in the multivariate analyses (Table 3).

We found no interactions between age and sex, age and smoking habits, or sex and smoking habits on change in DLCO.

Mean alveolar volume (\(V_A\)) was 6.49 L (SD: 1.30) at baseline and 6.29 L (SD: 1.38) at follow-up. There was a significant reduction in \(V_A\) during the observation period. In a multivariate analysis, higher baseline \(V_A\) and female sex were significant predictors of a more rapid decline in \(V_A\) (Table E5).

Mean carbon monoxide diffusion coefficient (\(K_{CO}\)) at baseline was 1.48 mmol min\(^{-1}\) kPa\(^{-1}\) L\(^{-1}\) (SD: 0.25) and 1.49 mmol min\(^{-1}\) kPa\(^{-1}\) L\(^{-1}\) (SD: 0.32) at follow-up. When analyzing the values from only the participants who met the requirement of an IVC/FVC ratio of 0.85 or above, the corresponding means were 1.45 mmol min\(^{-1}\) kPa\(^{-1}\) L\(^{-1}\) (SD: 0.24) and 1.46 mmol min\(^{-1}\) kPa\(^{-1}\) L\(^{-1}\) (SD: 0.28), respectively. When analyzed in a multivariate model, we found that higher baseline \(K_{CO}\), male sex, higher age, lower baseline body weight, current smoking, higher number of pack years smoked, and lower level of education were significant predictors of a more rapid decline in \(K_{CO}\) (Table E6).

Discussion
In this 9-year follow-up study of a general population sample, we observed that the rate of decline in gas diffusion capacity was highly variable. Mean change in DLCO was \(-0.025\) mmol min\(^{-1}\) kPa\(^{-1}\) year\(^{-1}\). Current smoking was the strongest predictor for decline in DLCO. In addition, older age, higher cumulative smoking consumption in terms of pack years, lower level of FEV\(_1\), lower body weight, and shorter body height were independent predictors of increased DLCO loss. Sex, educational level, and occupational airborne exposure did not independently influence change in DLCO.

This is the first community study to show that current smoking status and previous smoking consumption in terms of pack years predict loss of DLCO. The study is also the first to examine the effect of educational level and occupational airborne exposure on change in gas diffusion capacity. Our study confirms the findings of others (18, 19) that the decline in DLCO becomes more rapid with higher age.

The magnitude of the decline in DLCO observed in our study is comparable to that found by Viegi et al. (19), while comparison to the decline found by Sherrill et al. (18) is more complicated because of differences in how the results are reported. Standard error of the mean of DLCO seems to be comparable between all three studies.

Current smoking was related to a reduced baseline DLCO and a larger subsequent decline in DLCO in the multivariate analyses. Adjusting for HbCO did not change this association. Hence, current smoking has an effect on level and decline of DLCO beyond that of previous exposure and that of HbCO. Smokers more often develop anemia that may impair gas diffusion (33). However, when change in Hb was added to the equation, the relationship between smoking and DLCO persisted. The study was not designed to investigate mechanisms by which tobacco smoke could alter the rate of change in DLCO.
Cumulative smoking exposure in terms of pack years was also an independent predictor of future decline in DL\textsubscript{CO} (Table 3). There may be several explanations for this finding. First, smoking exposure may cause airflow limitation and air trapping that lead to impaired gas diffusion capacity. However, the effect of pack years on DL\textsubscript{CO} decline persisted after taking baseline FEV\textsubscript{1} into account (Table 3). Second, we have recently shown in

### Table 2. Descriptive statistics for baseline DL\textsubscript{CO} in 1987/88 and average change per year during a 9-year follow-up, \(\Delta\text{DLCO}\), for 830 subjects from Hordaland County, Norway, according to baseline characteristics

| Characteristics at baseline | Baseline DL\textsubscript{CO} (mmol·min\textsuperscript{-1}·kPa\textsuperscript{-1}), mean (SD) | \(\Delta\text{DLCO}\) (mmol·min\textsuperscript{-1}·kPa\textsuperscript{-1}·year\textsuperscript{-1}), mean (SD) |
|-----------------------------|-------------------------------------------------|--------------------------------------------------|
| Sex                         |                                                 |                                                  |
| Male                        | 10.85 (2.38)                                   | −0.039 (0.161)                                   |
| Female                      | 7.83 (1.57)                                    | −0.010 (0.114)                                   |
| Age in years                |                                                 |                                                  |
| Up to 19                    | 10.60 (2.39)                                   | 0.003 (0.158)                                   |
| 20–29                       | 10.88 (2.49)                                   | −0.021 (0.150)                                  |
| 30–39                       | 10.00 (2.20)                                   | 0.001 (0.129)                                   |
| 40–49                       | 9.45 (2.10)                                    | −0.037 (0.163)                                  |
| 50–59                       | 8.23 (2.01)                                    | −0.032 (0.134)                                  |
| 60–69                       | 7.54 (1.69)                                    | −0.072 (0.103)                                  |
| 70–79                       | 6.02 (1.46)                                    | −0.050 (0.122)                                  |
| Height in cm                |                                                 |                                                  |
| 159 and below               | 6.55 (1.27)                                    | −0.023 (0.118)                                  |
| 160–169                     | 7.90 (1.61)                                    | −0.018 (0.103)                                  |
| 170–179                     | 9.93 (1.97)                                    | −0.030 (0.142)                                  |
| 180–189                     | 11.62 (2.31)                                   | −0.034 (0.192)                                  |
| 190 and above               | 12.84 (2.16)                                   | −0.005 (0.154)                                  |
| Weight in kg                |                                                 |                                                  |
| < 49                        | 6.08 (1.80)                                    | 0.001 (0.114)                                   |
| 50–59                       | 7.76 (1.64)                                    | −0.016 (0.111)                                  |
| 60–69                       | 8.83 (2.24)                                    | −0.026 (0.120)                                  |
| 70–79                       | 10.06 (2.54)                                   | −0.041 (0.156)                                  |
| 80–89                       | 10.48 (2.41)                                   | −0.001 (0.150)                                  |
| 90–99                       | 10.61 (2.44)                                   | −0.034 (0.207)                                  |
| 100                         | 10.78 (2.89)                                   | −0.049 (0.118)                                  |
| Smoking habits              |                                                 |                                                  |
| Never smoker                | 9.62 (2.62)                                    | −0.012 (0.144)                                  |
| Ex-smoker                   | 9.20 (2.31)                                    | −0.037 (0.119)                                  |
| Daily smoker                | 8.99 (2.43)                                    | −0.044 (0.148)                                  |
| Pack years smoked           |                                                 |                                                  |
| 0                           | 9.62 (2.62)                                    | −0.012 (0.144)                                  |
| 1–20                        | 9.23 (2.40)                                    | −0.031 (0.136)                                  |
| 21–40                       | 8.75 (2.19)                                    | −0.080 (0.137)                                  |
| > 40                        | 6.79 (1.92)                                    | −0.094 (0.125)                                  |
| Occupational exposure       |                                                 |                                                  |
| No                          | 9.08 (2.32)                                    | −0.019 (0.138)                                  |
| Yes                         | 10.12 (2.53)                                   | −0.029 (0.152)                                  |
| Education level             |                                                 |                                                  |
| Primary school              | 8.15 (2.22)                                    | −0.041 (0.131)                                  |
| Secondary school            | 9.43 (2.44)                                    | −0.023 (0.144)                                  |
| Higher education            | 10.37 (2.62)                                   | −0.020 (0.143)                                  |
| FEV\textsubscript{1} quartiles|                                 |                                                  |
| 2.89 L and below            | 6.87 (1.51)                                    | −0.031 (0.109)                                  |
| 2.90–3.55 L                 | 8.56 (1.27)                                    | −0.030 (0.125)                                  |
| 3.56–4.36 L                 | 9.95 (1.66)                                    | −0.014 (0.145)                                  |
| 4.37 and above              | 12.20 (1.95)                                   | −0.029 (0.174)                                  |

DL\textsubscript{CO}, diffusing capacity of the lung for carbon monoxide; FEV\textsubscript{1}, forced expiratory volume in 1 second; SD, standard deviation.
another data set that level of emphysema is related to DL<sub>CO</sub> after adjusting for FEV<sub>1</sub> (34). Hence, increased smoking consumption may cause decline in DL<sub>CO</sub> because of more emphysema.

Neither the Italian nor the American community study observed that current smoking or smoking consumption was related to decline in DL<sub>CO</sub> (18, 19). The follow-up rate in the Italian study was lower than that in the current study, and smokers tend to drop out more often than non-smokers in longitudinal surveys (35). The American study comprised only about half the number of subjects of our study and they had no subjects above the age of 59 years at baseline (18).

In line with others (18, 19), we observed that the DL<sub>CO</sub> decline becomes more rapid with increasing age. The best fit of the model was for age squared, adding further support to our finding that the decline accelerated with increasing age. In the multivariate analysis, this acceleration in the decline with increasing age was found to be independent of smoking, lung function, body height and weight, as well as occupational exposure and SES. Potential explanations might be age-related reduced alveolar ventilation, increased level of emphysema, increased pulmonary blood pressure, and impaired cardiac function (36).

When comparing DL<sub>CO</sub> with available European predicted values, we observed an increase in the percent predicted value while there was a decrease in the absolute value. These predicted values were based on a compilation of European cross-sectional studies, and the age coefficient may be overestimated because of a cohort effect and less precise characterization of the subjects with respect to symptoms, previous smoking, and occupational exposure. As for FEV<sub>1</sub>, the annual change in longitudinal studies is less than the estimated annual change from cross-sectional surveys.

The difference between cross-sectional and longitudinal estimates of annual change may also be influenced by regression to the mean. We included baseline DL<sub>CO</sub> in the model which will partially account for that phenomenon.

We did not observe that occupational airborne exposure influenced level of DL<sub>CO</sub> or decline of DL<sub>CO</sub> in this general population sample. This may imply that there is no impact of occupational exposure on gas diffusion capacity in a community setting, or that we have not been able to show it. Regarding the latter possibility, the exposure
Table 3. Adjusted yearly change in DLCO estimated by generalized estimating equations (GEE) of the stratified sample from the general population in Hordaland County, Norway, aged 18–73 years in 1987/88 with follow-up 9 years later

| Characteristic at baseline | Estimate | p     |
|---------------------------|----------|-------|
| DLCO at baseline          |          |       |
| At DLCO 9.6               | −0.0293  |       |
| Per 1 unit increase       | −0.0325  | <0.0001|
| Age at baseline           |          |       |
| At age 45 years           | −0.0293  |       |
| Per 10 years increase     | −0.0243  | <0.0001|
| Sex                       |          |       |
| Men                       | −0.0293  |       |
| Women                     | −0.0162  | 0.410 |
| Height at baseline        |          |       |
| At 170 cm                 | −0.0293  |       |
| Per 10 cm increase (at baseline) | 0.0240  | 0.013 |
| Weight at baseline        |          |       |
| At 70 kg                  | −0.0293  |       |
| Per 1 kg increase         | 0.0011   | 0.020 |
| Smoking at baseline       |          |       |
| Never                     | −0.0293  |       |
| Ex                        | −0.0238  | 0.700 |
| Current                   | −0.0738  | 0.002 |
| Pack years smoked before baseline |       |       |
| At 6 pack years           | −0.0293  |       |
| Per 10 pack years increase| −0.0196  | 0.003 |
| Occupational exposure     |          |       |
| No                        | −0.0293  |       |
| Yes                       | 0.0146   | 0.177 |
| Educational level         |          |       |
| Primary school            | −0.0293  |       |
| Secondary school          | −0.0443  | 0.270 |
| Higher education          | −0.0304  | 0.947 |
| FEV1 at baseline          |          |       |
| At FEV1 3.6 L             | −0.0293  |       |
| Per 1 L increase          | 0.0235   | 0.013 |

DLCO, diffusing capacity of the lung for carbon monoxide in mmol·min⁻¹·kPa⁻¹; FEV1, forced expiratory volume in 1 second.

We have previously shown in cross-sectional analyses in this population that lower SES in terms of educational achievement is independently related to reduced level of DLCO (17). However, we did not observe that SES predicted subsequent change in DLCO after adjusting for the other covariates. As people tend to stay in the socioeconomic class into which they are born, the effect of SES on DLCO may have been evident at an early stage in life after which the subsequent decline in DLCO is independent of SES. However, it should be noted that low as compared to high SES was an independent predictor of rapid decline in KCO (Table E6).

Strengths and limitations of the study
This study is based on a community survey with high response rates both at baseline and follow-up. The study sample is representative of the population at large with respect to sex, age, and smoking (25, 35). Except for the requirement of an IVC/FVC ratio above 0.85, the participants included in the analyses met the ATS-criteria for a satisfactory DLCO test (28). The same equipment for measuring DLCO was used at baseline and follow-up with the same technicians. The effect of smoking on change in DLCO was adjusted for by change in HbCO, and finally validated questions on occupational exposure were used.

There are also some limitations to the study. First, we had only two points of observations, rendering the study susceptible to regression towards the mean. On the other hand, we adjusted for baseline level of DLCO, which should at least partly take this bias into account. Second, we did not have data on menstrual cycle for female participants, and are therefore not able to adjust for the effects of the menstrual cycle on DLCO (39–41).

In conclusion, we have observed that in the population at large both current smoking and cumulative smoking exposure, reduced FEV1, and increasing age predict more rapid decline in gas diffusion capacity, while occupational exposure and SES do not. This knowledge may help physicians in their interpretation of DLCO measurements.

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